Organic & Biomolecular Chemistry

PAPER

Transamidation of N-Acyl-Glutarimides with Amines

Yongmei Liu,[a,b,†] Marcel Achtenhagen,[b,†,§] Ruzhang Liu[a] and Michal Szostak[b,*]

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The development of new transamidation reactions for the synthesis of amides is an important and active area of research due to the central role of amide linkage in various fields of chemistry. Herein, we report a new method for transamidation of N-acyl-glutarimides with amines under mild, metal-free conditions that relies on amide bond twist to weaken amidic resonance. A wide range of amines and functional groups, including electrophilic substituents that would be problematic in metal-catalyzed protocols, are tolerated under the reaction conditions. Mechanistic experiments implicate the amide bond twist, thermodynamic stability of the tetrahedral intermediate and leaving group ability of glutarimide as factors controlling the reactivity of this process. The method further establishes the synthetic utility of N-acyl-glutarimides as bench-stable, twist-perpendicular, amide-based reagents in acyl-transfer reactions by a metal-free pathway. The origin of reactivity of N-acyl-glutarimides in metal-free and metal-catalyzed processes is discussed and compared.

1. Introduction

New methods for constructing amide bonds are of fundamental interest due to the central role of amide linkage in various fields of chemistry, including drug discovery, materials science and chemical manufacturing.[1–3] In this context, site-selective transamidation reactions under mild conditions represent one of the most useful transformations in organic synthesis (Fig. 1).[4,5] However, these broadly applicable processes suffer from the high stability of amide linkages due to amidic resonance (Er = 15-20 kcal/mol, $n_N \rightarrow \pi^*_{C=O}$ conjugation, planar amides),[6] and generally high temperatures, long reaction times and metal-promoters are necessary.[7]

From a practical standpoint, metal-free transamidations are vastly preferred due to high cost of metal catalysis, problems associated with removal of toxic metal waste and metal contamination of the amide products.[8] Furthermore, the development of chemoselective methods for amide formation has had a continuous impact on organic synthesis, especially in the context of pharmaceutical industry,[9] wherein a number of activating reagents and protocols for acylation of amines with carboxylic acids has been developed over the past decades (Fig. 2).[10]

Since the first report in 2015,[11] N-acyl-glutarimides have been established as the most reactive amide-based reagents in transition-metal-catalyzed amide N–C bond activation[12] owing to three synergistic factors (Fig. 3): (1) perpendicular twist of the amide bond (τ = 85.7°; χ_N = 5.6°);[13a,b] (2) high stability of the amide linkage under the reaction conditions; and (3) high selectivity for the acyl N–C cleavage imparted by the activating effect of the N-glutarimide substituent. Within this theme, our laboratory has introduced N-acyl-glutarimides to accomplish a range of acyl- and decarbonylative cross-coupling reactions with exquisite selectivity using Pd, Ni and Rh catalysis (Suzuki-Miyaura,[14] Negishi,[15] Heck,[16] biaryl Suzuki,[17] C–H arylation,[18] cyanation,[19] phosphorylation[20]) (Fig. 3). Mechanistic studies on the effect of amide bond distortion demonstrated that N-acyl-glutarimides contain the most distorted amide bond in any amide derivative to date.[13] More recently, Rueping et al. reported elegant methods for Ni-catalyzed decarbonylative amination,[21] reduction,[22] alkynylation,[23] cyanation,[24] silylation[25] and borylation[25] of N-acyl-glutarimides triggered by amide distortion. A complementary approach was reported by Han et al. on the Ni-catalyzed reductive coupling of N-acyl-glutarimides,[26] thus introducing the reductive manifold to the area of amide bond coupling.[27-29]

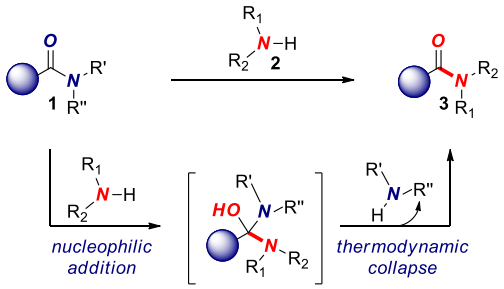


Fig. 1 Proposed mechanism for metal-free transamidation.

[a]*College of Chemistry and Chemical Engineering, Yangzhou University, 180 Siwangting Road, Yangzhou 225002, China.*
[b]*Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, USA. E-mail: michal.szostak@rutgers.edu.*
†These authors contributed equally.
§Present address: Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, USA.
†Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/x0xx00000x

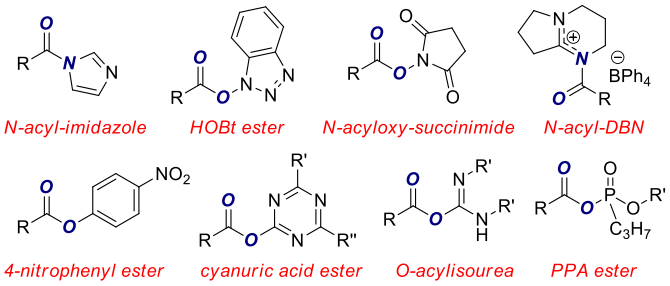


Fig. 2 Selected amide bond coupling reagents.

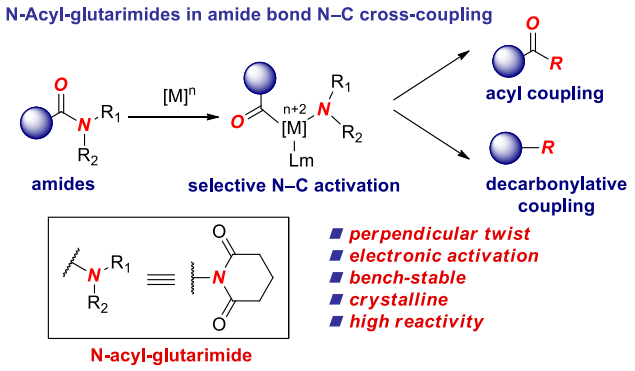


Fig. 3 N-Acyl-glutarimides in amide bond cross-coupling.

Important from the practical point of view, N-acyl-glutarimides are bench-stable, crystalline solids that can be routinely prepared from the corresponding acyl chlorides or carboxylic acids in >80% yields on a gram scale.[30] The high stability of N-acyl-glutarimides, resulting from delocalization of the NIp into the carbonyl groups in the glutarimide ring,[31] renders these reagents very attractive for applications in both transition-metal catalysis and metal-free reactions,[32] wherein the reactivity is controlled by amide bond twist.[33]

As part of our interest in amide bond N–C functionalization, herein, we describe a new method for transamidation of N-acyl-glutarimides with amines under mild, metal-free conditions that relies on amide bond twist to weaken amidic resonance. The following features of our findings are notable: (1) A wide range of amines and functional groups, including electrophilic substituents that would be problematic in metal-catalyzed protocols, are tolerated under the reaction conditions. (2) Mechanistic experiments implicate the amide bond twist, thermodynamic stability of the tetrahedral intermediate and leaving group ability of glutarimide as factors controlling the reactivity of this process. (3) The method further establishes the synthetic utility of N-acyl-glutarimides as bench-stable, twist-perpendicular, amide-based reagents in acyl-transfer reactions by metal-free pathway. *Most importantly, this approach provides direct access to a diverse range of amides by transamidation of readily available N-acyl-glutarimides as novel acyl-transfer reagents for amines in organic synthesis.*[1–7]

2. Results and discussion

Our laboratory has been interested in amide bond N–C functionalization due to the pivotal role of amide linkages in living organisms, and the untapped potential to exploit amide bond destabilization as an enabling feature in organic synthesis. We have demonstrated N-acyl-glutarimides in metal-free Friedel-Crafts arylation and tandem transacylation for the synthesis of anhydrides.[32] We hypothesized that N-acyl-glutarimides might be directly employed in synthetically valuable transamidation reactions via nucleophilic addition under mild, metal-free conditions that relies on twisting of the amide bond to weaken amidic resonance (Fig. 1).[35]

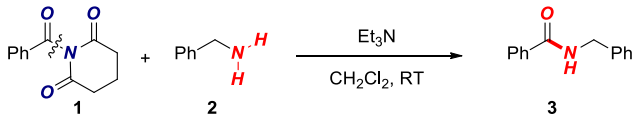
The desired transamidation reaction was initially optimized using N-benzoylglutarimide and benzylamine as model substrates (Tables 1-3). Throughout the manuscript the new amide bond formed is denoted in red colour, the N-acyl-glutarimide bond is denoted in blue. This is justified by vastly different properties of the amide bond in these compounds.

We determined that transamidation of N-benzoylglutarimide proceeds in excellent yield at room temperature (Table 1, entry 6: Et_3N, CH_2Cl_2, amine, 3.0 equiv). The effect of amine and triethylamine stoichiometry on the reaction is presented in Table 1. The stoichiometry of both amine and triethylamine could be decreased to close to equimolar ratio, however, at the expense of the reaction efficiency (entry 1), while increasing the stoichiometry improved the reactivity (entries 1-6). This is likely due to low stability of the acylammonium species under the reaction conditions. Importantly, the reaction showed good efficiency at various temperatures (entries 7-8). Furthermore, triethylamine could be omitted from the reaction set-up altogether, albeit the product was formed in lower yield (entry 9). We note that under the optimized conditions, opening of the glutarimide ring to give benzamide or the open-chain transamidation product was not observed.[10d]

The effect of solvent on the reaction is summarized in Table 2. While, dichloromethane proved to be optimal (entry 1), other solvents, such as DMF (entry 2), THF (entry 4) and DCE (entry 6), provided the transamidation product with promising efficiency. While low conversion was observed under aqueous conditions (entry 7), performing the reaction under high dilution conditions (entry 8) resulted in a good reactivity.[35]

Finally, among the bases tested, triethylamine was identified as the optimal base (Table 3, entry 1), while pyridine (entry 2), Hünig's base (entry 3) and $NaHCO_3$ gave lower conversions but still afforded the desired product (cf. background reaction, Table 1, entry 9).

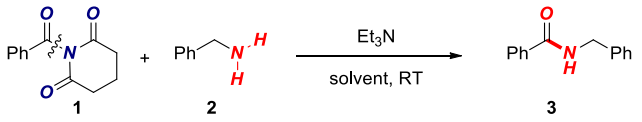
Table 1 Development of transamidation of N-acyl-glutarimides with amines: stoichiometry optimization[a]



Entry	Amine (x equiv)	Et_3N (y equiv)	Yield (%)[b]
1	1.1	1.0	61
2	1.1	3.0	63
3	1.5	2.0	69
4	1.5	3.0	72
5	2.0	2.0	75
6	3.0	3.0	91
7[c]	3.0	3.0	77
8[d]	3.0	3.0	86
9	3.0	-	53

[a]Conditions: amide (1.0 equiv), amine (x equiv), Et_3N (y equiv), CH_2Cl_2 (0.25 M), 23 °C, 15 h. [b]Determined by ^1H NMR and/or GC, internal standard, nitromethane. [c]0 to 23°C. [d]80°C.

Table 2 Development of transamidation of N-acyl-glutarimides with amines: solvent optimization[a]

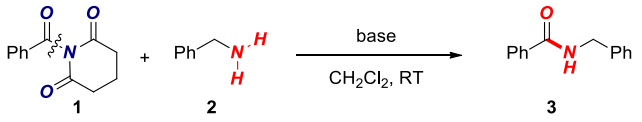


1 2 3

Entry	Solvent	Yield (%)[b]
1	CH_2Cl_2	91
2	DMF	47
3	MeOH	26
4	THF	52
5	DME	42
6	DCE	72
7[c]	$MeOH/H_2O$	<5
8[d]	CH_2Cl_2	73

[a]Amide (1.0 equiv), amine (3.0 equiv), Et_3N (3.0 equiv), solvent (0.25 M), 23 °C, 15 h. [b]Determined by ^1H NMR and/or GC, internal standard, nitromethane [c]1:1 v/vol. [d]0.025 M.

Table 3 Development of transamidation of N-acyl-glutarimides with amines: base optimization[a]



1 2 3

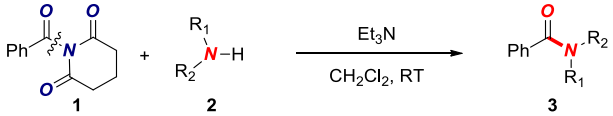
Entry	Base	Yield (%)[b]
1	Et_3N	91
2	Pyridine	60
3	DIPA	62
4	$NaHCO_3$	47

[a]Amide (1.0 equiv), amine (3.0 equiv), base (3.0 equiv), CH_2Cl_2 (0.25 M), 23 °C, 15 h. [b]Determined by ^1H NMR and/or GC, internal standard, nitromethane.

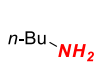
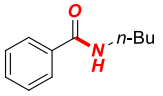
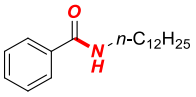
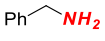
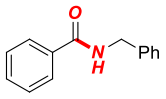
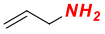
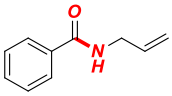
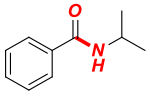
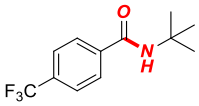
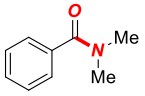
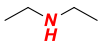
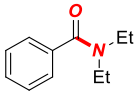
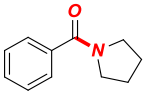
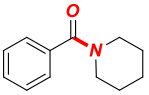
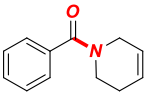
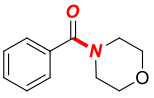
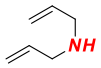
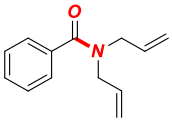
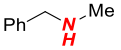
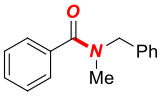
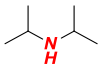
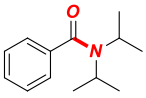
With the optimized conditions in hand, the scope and generality of this novel transamidation protocol was next explored (Tables 4-5). As shown, N-acyl-glutarimides react with a broad range of amines to afford synthetically valuable amides in good to excellent yields. Importantly, the transamidation accommodates simple alkyl (**3a**-**3b**), benzyl (**3c**), allyl (**3d**), sterically-hindered α-branched amines (**3d-3f**), and secondary amines (**3g-3n**) (Table 4). We determined that for more sterically-demanding amines (**3b**, **3m**) addition of catalytic DMAP (**3b**) to facilitate the formation of acylammonium,[10b] or increasing the reaction temperature to 80 °C (**3m**) gives optimum results, presumably to facilitate nucleophilic addition of the amine. Furthermore, while the very sterically-hindered *tert*-butylamine was ineffective under standard conditions, we found that the reactivity could be restored by increasing the electrophilicity of N-acyl-glutarimide (**3f**).[36] Finally, we note that the very sterically-hindered di-isopropylamine was unreactive under our reaction conditions (**3o**). In this case complete recovery of the staring material was observed, which should prove useful in selective transamidations with this class of amides.[37]

We next focused on the scope of N-acyl-glutarimides that can participate in this protocol (Table 5). As expected, the scope with respect to the amide substitution is also very broad. Electron-poor (**3p**) and electron-rich (**3q**) substituents on the aromatic ring are readily tolerated (see mechanistic studies, Fig. 4). Importantly, this metal-free method tolerates several functional groups that would be problematic using metal-catalysis, such as chloro (**3r**) and bromo (**3s**).[7c,d] Furthermore, fluorinated aromatics relevant from the medicinal chemistry standpoint are competent substrates for the reaction (**3t**).[38] Other electrophilic functional groups, such as esters (**3u**) are also tolerated on the amide component. Finally, we were pleased to find that transamidation of aliphatic N-acyl-glutarimides is also feasible (**3v-3w**).[39] Interestingly, N-acyl-glutarimides permit for selective transamidation of aliphatic amides bearing primary and secondary α-carbon substituents by N-acyl cleavage (**3v-3w**), while amides bearing α-carbon tertiary substituents such as **3x** are recovered unchanged from the reaction conditions. This unusual chemoselectivity (cf. Yamada amides)[40] may lead to chemoselective transamidations. Moreover, it should be noted that while the substrate scope of these mild metal-free conditions is broad, less nucleophilic amines, such as anilines, are incompatible with the reaction conditions. In contrast, anilines, including sterically-hindered examples, have been shown to participate in metal-catalyzed Buchwald-Hartwig acyl-type amination by N–C cleavage.[7a,b] This divergent selectivity opens the door for the development of chemoselective protocols for transamidation of non-planar amides.

Table 4 Transamidation of N-acyl-glutarimides with amines: amine scope[a]

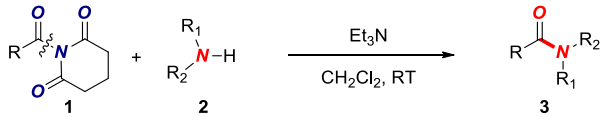


1 2 3

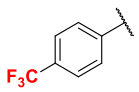
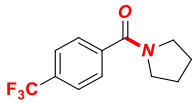
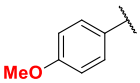
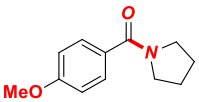
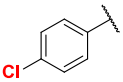
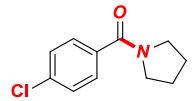
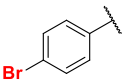
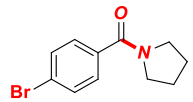
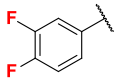
Entry	Amine	3	Product	Yield (%)[b]
1		**3a**		61
2[c]		**3b**		75
3		**3c**		91
4		**3d**		81
5		**3e**		63
6[d]		**3f**		78
7		**3g**		95
8		**3h**		91
9		**3i**		98
10		**3j**		90
11		**3k**		94
12		**3l**		95
13[e]		**3m**		90
14		**3n**		95
15		**3o**		<5

[a]Conditions: amide (1.0 equiv), amine (3.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2 (0.25 M), 23 °C, 15 h. [b]Isolated yields. [c]DMAP (0.20 equiv). [d]4-CF_3-C_6H_4 amide. DMAP (1.0 equiv). [e]DCE, 80 °C.

Table 5 Transamidation of N-acyl-glutarimides with amines: amide scope[a]



1 2 3

Entry	Amide (R)	3	Product	Yield (%)[b]
1		**3p**		66
2		**3q**		80
3		**3r**		88
4		**3s**		94
5		**3t**		84
6		**3u**		86
7		**3v**		80
8		**3w**		79
9		**3x**		<5

[a]Conditions: amide (1.0 equiv), amine (3.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2 (0.25 M), 23 °C, 15 h. [b]Isolated yields. See ESI for details.

A series of studies was performed to provide insight into the reaction mechanism. Specifically, we sought to address the role of amide bond twist in N-acyl-glutarimides as the driving force for metal-free transamidation.

(1) A Hammett correlation study, employing transamidation of differently substituted aromatic amides with benzylamine, showed a large positive Hammett-Brown ρ^+-value of 1.43 (R^2 = 0.94) (Fig. 4), which can be compared with the ρ-value of 2.01 (R^2 = 0.74). This suggests that resonance effects are involved in stabilization of the reactive center, and that electron-deficient arenes are inherently more reactive substrates, consistent with the relative electrophilicity of the amide bond.

(2) During the reaction development, we observed that the reactivity was strongly dependent on the amine used. A series of competition studies established the following relative order of reactivity: pyrrolidine > *n*-$BuNH_2$ > $BnNH_2$ > Et_2NH ≈ *i*-$PrNH_2$

> anisidine >> *t*-BuNH$_2$ (Table 6). The observed reactivity is consistent with the relative basicity[41] and steric hindrance of amine nucleophiles used in the reaction.

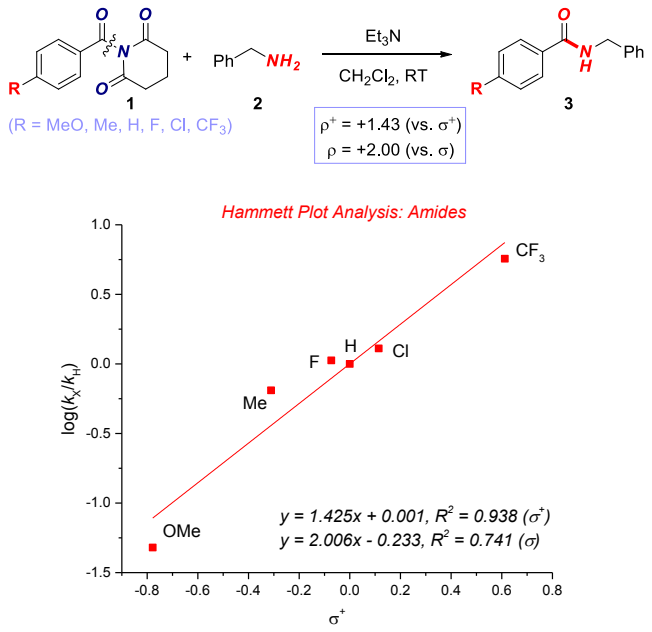
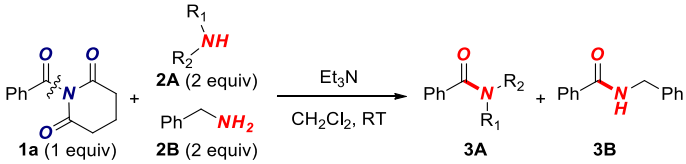


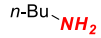
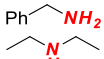
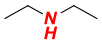
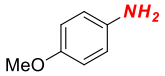
Fig. 4 Plot of log *k* vs. σ$^+$ for transamidation of N-acyl-glutarimides with PhCH$_2$NH$_2$: effects of substituents on aryl amide.

(3) Hitchcock et al. reported an elegant study on the synthesis and transamidation of N-acyl-succinimides.[10c] These five-membered analogues of N-acyl-glutarimides contain much less distorted amide bond (τ = 46.1°; χ_N = 9.5°), as a result of decreased steric interactions between exo- and endo-cyclic oxygens in the five-membered framework.[13] As a consequence, while N-acyl-succinimides have been routinely tested as substrates in all N–C cross-coupling reactions, the reactivity of these half-twisted amides is inferior to N-acyl-glutarimides in metal-catalyzed protocols.[11,12] However, succinimide is a much better leaving group than glutarimide (pK_a = 9.5 vs. pK_a = 11.4, also note phthalimide, pK_a = 8.3).[42] To address the role of twist vs. leaving group ability, we established the relative order of amine reactivity in transamidation using N-benzoyl-succinimde as the electrophilic component (Table 7). Interestingly, we found an excellent correlation between the reactivity of N-acyl-glutarimides and N-acyl-succinimides. Furthermore, a plot of log of relative reactivity of N-acyl-glutarimides vs. log of relative reactivity of N-acyl-succinimides gave a linear correlation with a slope of 0.93 (R^2 = 0.99) (Fig. 5).

(4) To further explore the effect of twist on the transamidation reactivity in N-acyl-glutarimides vs. N-acyl-succinimides, a series of competition studies was conducted (Table 8). As shown, we found that N-acyl-glutarimides are significantly more selective acylating reagents than N-acyl-succinimides, and this reactivity is consistent with the leaving group ability in the transamidation reaction.[43] It may be thus expected that they are more selective for certain applications. Thus, on the basis of these results and the well-established reactivity of N-acyl-glutarimides in metal-catalyzed N–C cross-coupling,[11-26] we conclude that the present metal-free transamidation is controlled mainly by the thermodynamic collapse of the tetrahedral intermediate (vs. kinetic activation of the amide bond by twist and Nlp to glutarimide conjugation).

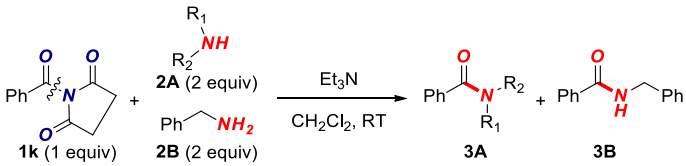
Table 6 Transamidation of N-acyl-glutarimides with amines: selectivity studies – effect of amines[a]

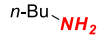
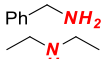
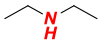
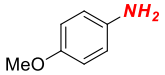


Entry	Amine	3	RV[b]	pK_{BH+}
1		**3i**	3.71	11.3
2		**3a**	2.50	10.6
3		**3c**	1.0	9.3
4		**3h**	0.38	11.0
5		**3y**	0.05	5.4
6		**3f**	0.004	10.7
7		**3e**	0.39	10.7

[a]Conditions: amide (1.0 equiv), amine (3.0 equiv), Et$_3$N (3.0 equiv), CH$_2$Cl$_2$ (0.25 M), 23 °C, 15 h. [b]Relative reactivity values determined from product distribution by ^{1}H NMR and/or GC of crude reaction mixtures. RV = reactivity values vs. the corresponding *N*-benzylbenzamide are shown.

Table 7 Transamidation of N-acyl-succinimides with amines: selectivity studies – effect of amines[a]



Entry	Amine	3	RV[b]	pK_{BH+}
1		**3i**	6.81	11.3
2		**3a**	2.90	10.6
3		**3c**	1.0	9.3
4		**3h**	0.34	11.0
5		**3y**	0.05	5.4
6		**3f**	0.003	10.7
7		**3e**	0.36	10.7

[a]Conditions: amide (1.0 equiv), amine (3.0 equiv), Et$_3$N (3.0 equiv), CH$_2$Cl$_2$ (0.25 M), 23 °C, 15 h. [b]Relative reactivity values

determined from product distribution by ^{1}H NMR and/or GC of crude reaction mixtures. RV = reactivity values vs. the corresponding *N*-benzylbenzamide are shown.

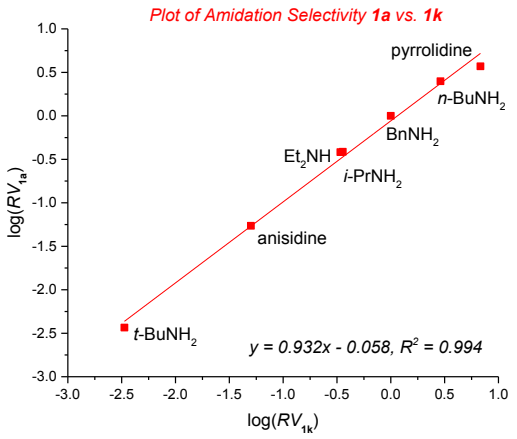
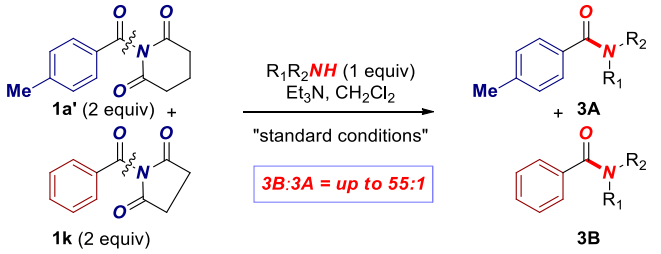
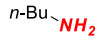
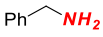
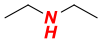
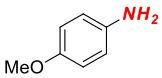


Fig. 5 Plot of log RV-glutarimide (Table 6) vs. log RV-succinimide (Table 7) for transamidation with amines: effects of amines.

Table 8 Selectivity studies in the transamidation of N-acyl-glutarimides and N-acyl-succinimides: effect of amines[a]



Entry	Amine	3	3B:3A[b]	pK_{BH+}
1		**3i**	54.7	11.3
2		**3a**	22.5	10.6
3		**3c**	8.7	9.3
4		**3h**	30.5	11.0
5		**3y**	11.0	5.4
6		**3f**	33.5	10.7

[a]Conditions: amide (2.0 equiv), amine (1.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2 (0.25 M), 23 °C, 15 h. [b]Relative reactivity values determined from product distribution by ^{1}H NMR and/or GC of crude reaction mixtures.

(5) Moreover, we found that O-nucleophiles such as alcohols and water are ineffective as nucleophiles with both N-acyl-glutarimides and N-acyl-succinimdes under the developed conditions (Fig. 6). In this case, full recovery of amide starting materials was observed. In contrast, bridged lactams, another class of non-planar amides, are notorious to suffer from rapid hydrolysis/alcoholysis.[34] Thus, it is clear that despite the significant twist, N-acyl-glutarimides (τ = 85.7°) and N-acyl-succinimides (τ = 46.1°)[13] are sufficiently robust for general applications in metal-free transformations. Furthermore, our results support amine nucleophilicity as the driving force for nucleophilic addition to the weakened amide bond. In both cases, amide bond destabilization occurs by amide bond twist and electronic $n_N \rightarrow \pi^*_{C=O}$ conjugation into the carbonyl groups of the activating ring.

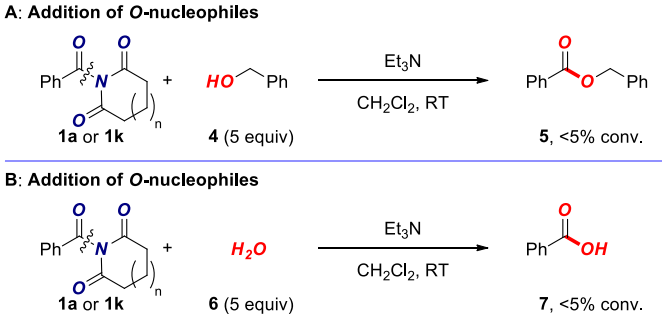


Fig. 6 Selectivity studies in transamidation of N-acyl-glutarimides and N-acyl-succinimides.

3. Conclusions

In summary, through exploiting amide bond twist and electronic activation, we have developed a new method for transamidation of N-acyl-glutarimides with amines under mild, metal-free conditions. The method tolerates a wide range of amides and functional groups, including electrophilic substituents that would be problematic in metal-catalyzed protocols, delivering important amide products in good to excellent yields. The high reactivity of N-acyl-glutarimides relies on weakening of amidic resonance through steric and electronic activation of the amide bond. Mechanistic studies demonstrated amide bond weakening and thermodynamic collapse of the tetrahedral intermediate as decisive factors controlling the reactivity of this process. In a broader context, the method further establishes the utility of N-acyl-glutarimides as bench-stable, twist-perpendicular, amide-based reagents in acyl-transfer reactions by a metal-free pathway.

In the last two years, N-acyl-glutarimides have spearheaded the development of novel metal-catalyzed acyl and decarbonylative cross-coupling reactions by N–C activation.[11–26] The high stability, ready availability and distortion-tuneable reactivity of perpendicularly twisted N-acyl-glutarimides should enable the development of practical protocols for other metal-free functionalizations in organic synthesis. Studies in this direction are underway and will be reported in due course.

Acknowledgements

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(21472161). M.A. thanks the Chemistry Department (Rutgers University) for a Summer Undergraduate Fellowship. The Bruker 500 MHz spectrometer used in this study was supported by NSF-MRI (CHE-1229030).

Notes and references

1 A. Greenberg, C. M. Breneman and J. F. Liebman, *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, Wiley, 2000.

2 Reviews: (*a*) R. Marcia de Figueiredo, J. S. Suppo and J. M. Campagne, *Chem. Rev.*, 2016, **116**, 12029. (*b*) A. Ojeda-Porras and D. Gamba-Sanchez, *J. Org. Chem.*, 2016, **81**, 11548; (*c*) J. R. Dunetz, J. Magano and G. A. Weisenburger, *Org. Process Res. Dev.*, 2016, **20**, 140; (*d*) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405; (*e*) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606; (*f*) C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827; For a review on electrophilic activation of amides: (*g*) D. Kaiser and N. Maulide, *J. Org. Chem.*, 2016, **81**, 4421; For an excellent overview of amide coupling, see: (*h*) S. A. Ruider and N. Maulide, *Angew. Chem. Int. Ed.*, 2015, **54**, 13856

3 Selected recent reports on amide bonds: (*a*) N. Caldwell, C. Jamieson, I. Simpson and A. J. B. Watson, *Chem. Commun.*, 2015, **51**, 9495; (*b*) R. Y. Zhu, M. E. Farmer, Y. Q. Chen and J. Q. Yu, *Angew. Chem. Int. Ed.*, 2016, **55**, 10578; (*c*) S. L. Zultanski, J. Zhao and S. S. Stahl, *J. Am. Chem. Soc.*, 2016, **138**, 6416; (*d*) W. S. Bechara, G. Pelletier and A. B. Charette, *Nat. Chem.*, 2012, **4**, 228; (*e*) S. Das, D. Addis, S. Zhou, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 1770.

4 For reviews, see: (*a*) W. D. Loomis and P. K. Stumpf, Transamination and Transamidation In *Nitrogen Metabolism*; E. K. Allen, Ed.; Springer, 1958; (*b*) M. E. Gonzalez-Rosende, E. Castillo, J. Lasri and J. Sepulveda-Arques, *Prog. React. Kinet.*, 2004, **29**, 311; For selected examples, see: (c) T. A. Dineen, M. A. Zajac and A. G. Myers, *J. Am. Chem. Soc.*, 2006, **128**, 16406; (*d*) A. C. Allen, B. N. Atkinson and J. M. Williams, *Angew. Chem. Int. Ed.*, 2012, **51**, 1383; (*e*) E. Bon, D. C. H. Bigg and G. Bertrand, *J. Org. Chem.*, 1994, **59**, 4035; (*f*) S. E. Eldred, D. A. Stone, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2003, **125**, 3422; (*g*) T. B. Nguyen, J. Sorres, M. Q. Tran, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2012, **14**, 3202; (*h*) N. A. Stephenson, J. Zhu, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2009, **131**, 10003; (*i*) S. N. Rao, D. C. Mohan and S. Adimurthy, *Org. Lett.*, 2013, **15**, 1496.

5 For enzymatic methods, see: M. V. Sergeeva, V. V. Mozhaev, J. O. Rich and Y. L. Khmelnitsky, *Biotechnol. Lett.*, 2000, **22**, 1419.

6 K. Eisenberg, *Proc Natl. Acad. Sci. U.S.A.*, 2003, **100**, 11207.

7 For selected examples, see: Pd catalysis (acyl-Buchwald-Hartwig reaction): (*a*) G. Meng, P. Lei and M. Szostak, *Org. Lett.*, 2017, **19**, 2158; (*b*) S. Shi and M. Szostak, Chem. *Commun.*, 2017, **53**, 10584; Ni catalysis: (*c*) E. L. Baker, M. M. Yamano, Y. Zhou, S. M. Anthony and N. K. Garg, *Nat. Commun.* 2016, **7**, 11554; (*d*) J. E. Dander, E. L. Baker and N. K. Garg, *Chem. Sci.*, 2017, **8**, 6433; (*e*) C. W. Cheung, M. L. Ploeger and X. Hu, *ACS Catal.*, 2017, **7**, 7092.

8 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leaser, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.

9 (*a*) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471; (*b*) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451; A recent survey indicates that amide bond formation is the most common reaction in medicinal chemistry: (*c*) D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443.

10 For excellent reviews, see: (*a*) Ref. 1c and 1f. For selected examples, see: (*b*) Y. Liu, S. Shi, M. Achtenhagen, R. Liu and M. Szostak, *Org. Lett.*, 2017, **19**, 1614; For an elegant study on using N-acylsuccinimides, see: (*c*) C. A. Goodman, J. B. Eagles, L. Rudahindwa, C. G. Hamaker and S. R. Hitchcock, *Synt. Commun.*, 2013, **43**, 2155; See, also: (*d*) C. A. Goodman, C. G. Hamaker and S. R. Hitchcock, *Tetrahedron Lett.*, 2013, **54**, 6012; (*e*) C. A. Goodman, E. M. Janci, O. Onwodi, C. C. Simpson, C. G. Hamaker and S. R. Hitchcock, *Tetrahedron Lett.*, 2015, **56**, 4468; (*f*) J. E. Taylor, M. D. Jones, J. M. J. Williams and S. D. Bull, *J. Org. Chem.*, 2012, **77**, 2808, and references cited therein.

11 (*a*) G. Meng and M. Szostak, *Org. Lett.*, 2015, **17**, 4364; (*b*) G. Meng and M. Szostak, *Org. Biomol. Chem.*, 2016, **14**, 5690.

12 Reviews: (*a*) R. Takise, K. Muto and J. Yamaguchi, *Chem. Soc. Rev.*, 2017, **46**, 5864; (*b*) G. Meng, S. Shi and M. Szostak, *Synlett*, 2016, **27**, 2530; (*c*) C. Liu and M. Szostak, *Chem. Eur. J.*, 2017, **23**, 7157; (d) Y. Gao, C. L. Ji and X. Hong, *Sci. China Chem.,* 2017, **60**, 1413.

13 (*a*) V. Pace, W. Holzer, G. Meng, S. Shi, R. Lalancette, R. Szostak and M. Szostak, *Chem. Eur. J.*, 2016, **22**, 14494; (*b*) Winkler-Dunitz distortion parameters: τ (twist angle), χ_N (pyramidalization at N) and χ_C (pyramidalization at C) describe the magnitude of rotation around the N–C(O) bond, pyramidalization at N and C; τ is 0° for planar amide bonds and 90° for fully orthogonal bonds; χ_N and χ_C are 0° for planar bonds, and 60° for fully pyramidalized amide bonds.

14 (*a*) See, Ref. 11. (*b*) P. Lei, G. Meng and M. Szostak, *ACS Catal.*, 2017, **7**, 1960; (*c*) P. Lei, G. Meng, Y. Ling, J. An and M. Szostak, *J. Org. Chem.*, 2017, **82**, 6638.

15 S. Shi and M. Szostak, *Chem. Eur. J.*, 2016, **22**, 10420.

16 G. Meng and M. Szostak, *Angew. Chem. Int. Ed.*, 2015, **54**, 14518.

17 S. Shi, G. Meng and M. Szostak, *Angew. Chem. Int. Ed.*, 2016, **55**, 6959.

18 G. Meng and M. Szostak, *Org. Lett.*, 2016, **18**, 796.

19 S. Shi and M. Szostak, *Org. Lett.*, 2017, **19**, 3095.

20 C. Liu and M. Szostak, *Angew. Chem. Int. Ed.*, 2017, **56**, 12718.

21 H. Yue, L. Guo, H. H. Liao, Y. Cai, C. Zhu and M. Rueping, *Angew. Chem. Int. Ed.*, 2017, **56**, 4282.

22 H. Yue, L. Guo, S. C. Lee, X. Liu and M. Rueping, *Angew. Chem. Int. Ed.*, 2017, **56**, 3972.

23 W. Srimontree, A. Chatupheeraphat, H. H. Liao and M. Rueping, *Org. Lett.*, 2017, **19**, 3091.

24 A. Chatupheeraphat, H. H. Liao, S. C. Lee and M. Rueping, *Org. Lett.*, 2017, **19**, 4255.

25 S. C. Lee, L. Guo, H. Yue, H. H. Liao and M. Rueping, *Synlett*, 2017, DOI: 10.1055/s-0036-1591495.

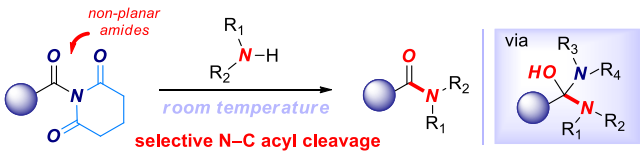
26 S. Ni, W. Zhang, H. Mei, J. Han and Y. Pan, *Org. Lett.*, 2017, **19**, 2536.

27 For a relevant use of N-acylsuccinimides in Ni/Ir-catalyzed acyl transfer, see: J. Amani, R.; Alam, S.; Badir and G. A. Molander, *Org. Lett.*, 2017, **19**, 2426.

28 For an excellent mechanistic study on Ni-catalyzed Suzuki biaryl coupling of N-acyl-glutarimides, see: C. L. Ji and X. Hong, *J. Am. Chem. Soc.*, 2017, **139**, 15522.

29 For other select examples of amide cross-coupling by N–C activation, see: (*a*) L. Hie, N. F. F. Nathel, T. K. Shah, E. L. Baker, X. Hong, Y. F. Yang, P. Liu, K. N. Houk and N. K. Garg, *Nature*, 2015, **524**, 79; (*b*) J. A. Walker, K. L. Vickerman, J. N. Humke and L. M. Stanley, *J. Am. Chem. Soc.* **2017**, *139*, 10228; (*c*) Dey, S. Sasmai, K. Seth, G. K. Lahiri and D. Maiti, *ACS Catal.*, 2017, **7**, 433; (*d*) H. Liu, H. Yue, J. Jia, L. Guo and M. Rueping, *Chem. Eur. J.*, 2017, **23**, 11771; (*e*) Y. Bourne-Branchu, C. Gosmini and G. Danoun, *Chem. Eur. J.*, 2017, **23**, 10043.

30 *N*-Acyl-glutarimides are bench-stable, crystalline solids with no decomposition observed while storing in ambient conditions on a bench-top over 24 months.
31 For relevant studies on amide bond destabilization in cross-coupling, see: (*a*) R. Szostak, S. Shi, G. Meng, R. Lalancette and M. Szostak, *J. Org. Chem.*, 2016, **81**, 8091; (*b*) R. Szostak, G. Meng and M. Szostak, M., *J. Org. Chem.*, 2017, **82**, 6373. (*c*) See, ref. 13.
32 (*a*) Y. Liu, G. Meng, R. Liu and M. Szostak, *Chem. Commun.*, 2016, **52**, 6841; (*b*) Y. Liu, R. Liu and M. Szostak, *Org. Biomol. Chem.*, 2017, **15**, 1780.
33 Half-twist of N-acyl-succinimides has been utilized in cross-coupling. See, Y. Osumi, C. Liu and M. Szostak, *Org. Biomol. Chem.*, 2017, **15**, 8867, and references cited therein.
34 For leading references on amide bond destabilization, see: (*a*) K. Tani and B. M Stoltz, *Nature*, 2006, **441**, 731; (*b*) A. Greenberg and C. A. Venanzi, *J. Am. Chem. Soc.*, 1993, **115**, 6951; (*c*) J. Aubé, *Angew. Chem. Int. Ed.*, 2012, **51**, 3063.
35 G. W. Anderson, J. E. Zimmerman and F. M. Callahan, *J. Am. Chem. Soc.*, 1964, **86**, 1839.
36 S. K. Davidsen, P. D. May and J. B. Summers, *J. Org. Chem.*, 1991, **56**, 5482.
37 (*a*) T. Oshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama and K. Mashima, *J. Am. Chem. Soc.*, 2008, **130**, 2944; (*b*) Y. Shimizu, H. Morimoto, M. Zhang and T. Ohshima, *Angew. Chem. Int. Ed.*, 2012, **51**, 8564.
38 T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2013, **52**, 8214.
39 Transamidation of aliphatic amides using metal-catalysis represents a major challenge and often requires extensive ligand optimization. See, ref. 7d for details.
40 S. Yamada, *J. Org. Chem.*, 1992, **57**, 1591.
41 C. Laurence, K. A. Brameld, J. Graton, J. Y. Le Questel and E. Renault, *J. Med. Chem.*, 2009, **52**, 4073.
42 N-acyl-phthalimides typically react with amines via cleavage of the endocyclic N–C bond. See, ref. 10d for details. Note that N-acyl-phthalimides are incompetent substrates in metal-catalyzed N–C cross-coupling. See, ref. 33 for details.
43 For a lead reference on reactivity-selectivity principle, see: E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, 2005.



■ *Metal-Free Transamidation of N-Acyl-Glutarimides at RT*