JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

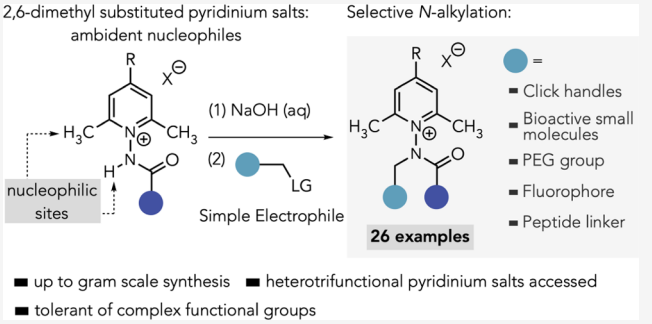
A Pyridinium Ylide-Alkylation Strategy for the Structural Diversification of *N*-Carbamoylpyridinium Salts

Akash M. Sarkar, Benjamin Gossett, and Michael T. Taylor*

Cite This: *J. Org. Chem.* 2024, 89, 17115−17121 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A pyridinium ylide-alkylation strategy has been developed for selectively accessing *N*,*N*-disubstituted pyridinium salts from monosubstituted pyridinium salts possessing ambident nucleophiles. The method was shown to be tolerant toward an array of different pyridinium scaffolds and common electrophiles, enabling access to structurally diverse pyridinium salts. The potential versatility of the approach was demonstrated through the synthesis of chemically complex, heterotrifunctional pyridinium salts containing a pyridinium warhead, a click chemistry handle, and a third, high-value, payload.



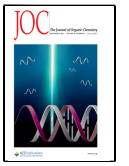
INTRODUCTION

Owing to their wide range of reactivity, *N*-substituted pyridinium salts have found myriad applications in organic synthesis. *N*-Substituted pyridinium salts can be leveraged to access to a wide array of oxidation states between pyridine- and piperidine-type structures, which is achieved by the addition of either nucleophiles or electrons into the electron-deficient aromatic ring.[1] Beyond redox cycling, the cationic charge on the pyridinium ring also imparts additional acidity to pendant functional groups, a property that makes these reagents ideally suited for generating ylides under mild conditions, and pyridinium ylides have found extensive use in cycloaddition chemistry.[2] The reactive properties of pyridinium salts are also becoming increasingly appreciated in chemical biology. We recently reported an optically triggered approach for tryptophan (Trp)-selective protein modification in which we exploit the inherent photolability of Trp by pairing Trp-containing biomolecules with *N*-carbamoylpyridinium salts that engage Trp in photoinduced electron transfer (PET) to yield a net carbamylation of the C2-position on the indole ring of Trp.[3] This ligation approach was found to be biocompatible and mechanistically tunable, traits which allowed us to exploit the mildness of this process to engage in live cell Trp-labeling.[3c]

As part of our program to expand the utility of this chemistry, we sought here to increase the generality of the approach by developing methods for structural diversification of *N*-carbamoylpyridinium salts that would ultimately enhance the scope of the incorporation of functionality into peptides and proteins. Additionally, *N*-carbamoylpyridinium salts and structurally analogous *N*-carbonylpyridinium salts have been shown by Studer and others to engage in photoredox-catalyzed C−N bond formation with small molecule aromatics, and therefore general approaches to increasing pyridinium molecular diversity could be applied in this context as well.[4]

Pyridinium salts that are used as radical reservoirs typically possess substitution at the 2,4, and 6 positions of the pyridinium ring in order to promote N−X bond fragmentation[5] and are typically synthesized by a condensation of a primary amine with a pyrylium salt to add the N−X bond that fragments[6] (Figure 1A). While primary amines are widely available with extensive structural diversity, these only enable access to *C*-centered radical reservoirs. Accessing *N*-centered radical reservoirs requires the condensation of a pyrylium salt with either substituted hydrazine or hydrazide precursors that may require multistep syntheses and extensive protecting group manipulations to access. We therefore considered a late-stage diversification strategy in which a single, monosubstituted hydrazide could be condensed onto the pyrylium salt, and then this structure could be derivatized by alkylation with exogenous electrophiles (Figure 1B). By virtue of being adjacent to a quaternized nitrogen, any X−H bonds on the atom adjacent increase notably in acidity and can thus be readily deprotonated under mild conditions to form pyridinium ylides. We sought to use pyridinium ylides as nucleophiles that could be alkylated with a wide range of electrophiles. While several groups have reported *N*-alkylation of amidopyridinium ylides, including a recent approach for

Received: June 4, 2024
Revised: August 16, 2024
Accepted: November 5, 2024
Published: November 20, 2024



https://doi.org/10.1021/acs.joc.4c01403
J. Org. Chem. 2024, 89, 17115−17121

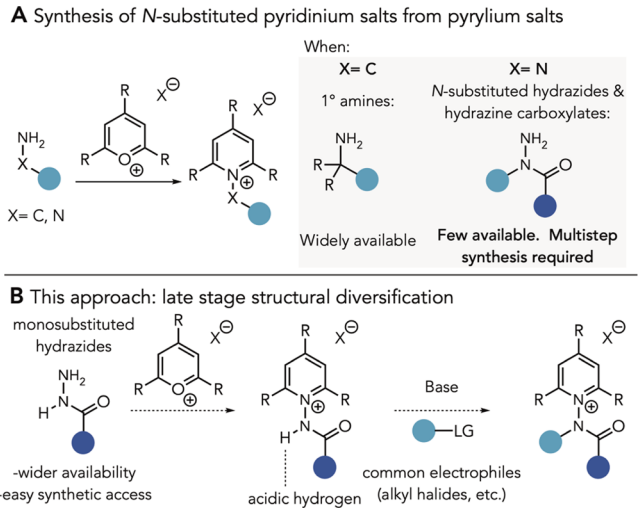


Figure 1. (A) Condensation of pyrylium salts with amine and hydrazides to form complex pyridinium salts. (B) This work: complex carbamoylpyridinium salt synthesis using a pyridinium ylide-alkylation strategy.

secondary amine synthesis,[7e] these reports use pyridinium ylides in which the pyridinium moiety lacks additional base-sensitive functional groups.[7]

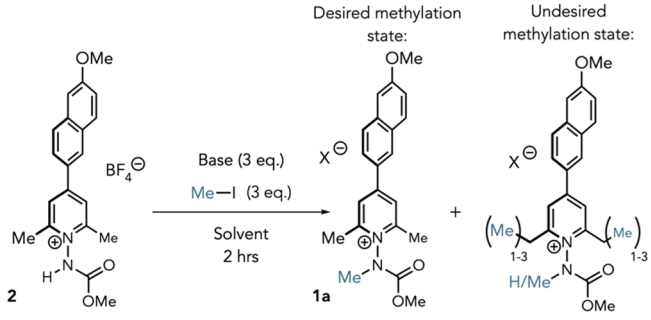
RESULTS AND DISCUSSION

By contrast, our recently reported salt **1a** features two benzylic methyl groups that flank the *N*-methyl-*N*-carbamoyl transferring group and are essential for the function and thermal stability of the salt in complex biological mixtures. When **1a** was incubated in buffered D_2O (ND_4^+-OAc) at 100 °C, we observed near-complete H/D exchange by LC/MS as evidenced by an increase of 6 *m*/*z* in the amount of **1a** (Figure 2A). When D_6-**1a** was incubated with phosphate-buffered saline (PBS) at 37 °C for 30 min, we observed D/H exchange to give a mixture of deuteration states of **1a**, ranging from +0 to +6 deuterium atoms. H/D exchange has been previously reported for pyrylium structures, and these results show that the same occurs with related pyridinium salts as expected.[6] Moreover, this experiment confirmed that **1a** and related pyridinium salts possessing benzylic methyl groups can exist as a mixture of pyridinium salt and nucleophilic 1,2-dihydropyridines through rapid and reversible protonation/deprotonation. Thus, **1a** and related pyridinium salts could potentially act as ambident nucleophiles (*N*-centered nucleophile vs *C*-centered dihydropyridine nucleophile) for a potential electrophile (Figure 2B).

We sought conditions that would select *N*-alkylation over *C*-alkylation by exploring the methylation of pyridinium salt **2** to give **1a**. Our studies commenced by exploring combinations of solvent, base (3 equiv), and methyl iodide as an electrophile (3 equiv). We opted to monitor these preliminary experiments using LC/MS as changes in the alkylation state could readily be detected and semiquantitated with this technique. Thus, the treatment of **2** with NaOH in either ethanol or water (Table 1, entries 1 and 2) gave only trace conversion. Higher conversion was observed in polar aprotic solvents such as acetonitrile and DMF. However, when Cs_2CO_3 was used as a base, we observed a wide distribution of alkylation products in both acetonitrile (Table 1, entry 3) and DMF (Table 1, entry 4) ranging from monomethylation to pentamethylation (entries 3 and 4) and with very little selectivity for monomethylation. These results confirmed that the benzylic methyl groups of **2** are reactive and viable nucleophiles under these conditions. The use of triethylamine in acetonitrile gave solely monomethylation (Table 1, entry 5) but only in modest conversion. Based on a report from Hong,[7d] in which monoalkylation of pyridinium ylides was observed in acetone, we attempted a one-pot alkylation of **2** using potassium *t*-butoxide as a base in acetone and observed moderate conversion and modest selectivity for monomethylation (Table 1, entry 6).

Given the inability to control alkylation states with one-pot conditions, we next considered a stepwise sequence featuring the generation and isolation of the pyridinium ylide followed by alkylation with an electrophile. Reports from Charette[7b] and

Table 1. Attempted Optimization of a One-Pot Alkylation



entry	base	solvent	% conversion[a]	ratio of methylation states (+1, +2, +3, +4, +5[b])
1	NaOH	EtOH	trace	not measured
2	NaOH	H_2O	trace	not measured
3	Cs_2CO_3	CH_3CN	46	1:1.8:1.8:1.7:1.3
4	Cs_2CO_3	DMF	60	2.1:1.5:1.4:1:0
5	TEA	CH_3CN	18	+1 observed only
6	kOtBu	acetone	65	32:17:11:4:1

[a]Conversions and alkylation ratios were estimated using total ion count (TIC) from LC/MS. [b]Methylation state refers to the number of methyl groups incorporated into **2** as assessed by mass spectrometry.

https://doi.org/10.1021/acs.joc.4c01403
J. Org. Chem. 2024, 89, 17115−17121

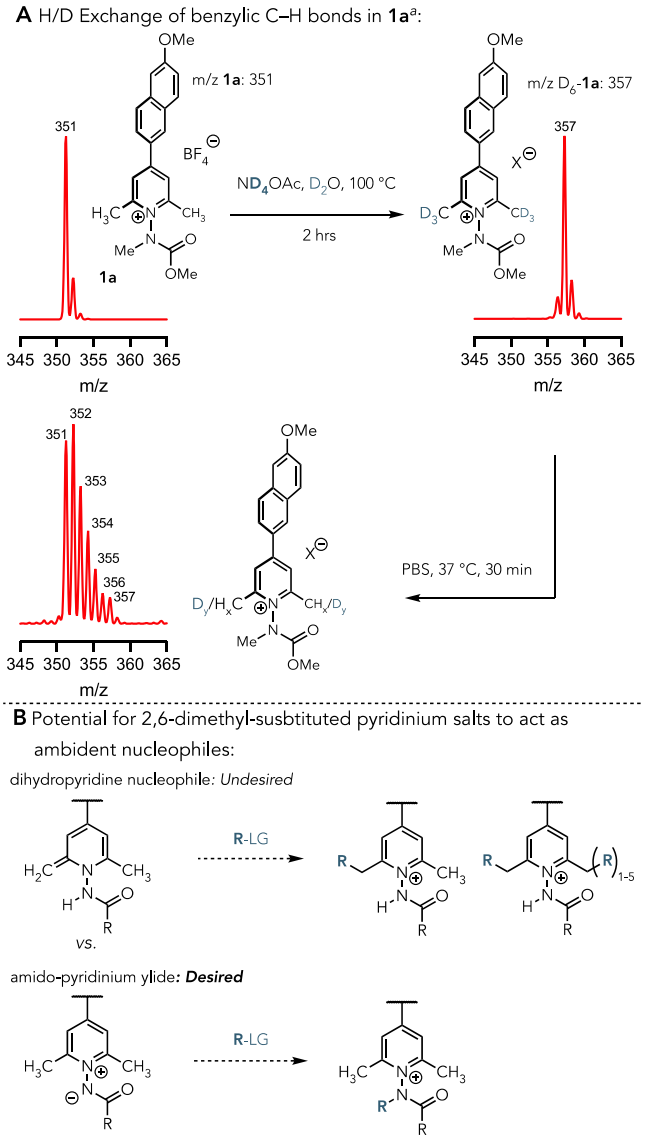
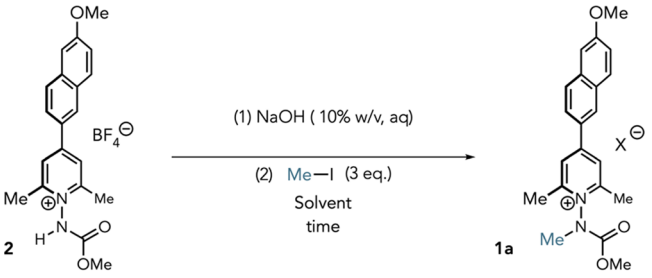


Figure 2. (A) H/D exchange of benzylic C−H bonds in **1a**. (B) Potential off-target alkylation of 2,6-dimethyl-substituted pyridinium salts. [a]H/D exchange was monitored by LC/MS. PBS, phosphate-buffered saline.

Davies,[8] in which simple *N*-benzyliminopyridinium ylides were isolated, suggested that our *N*-carbamoylpyridinium ylides may also be sufficiently stable for isolation. Thus, **2** was treated with a solution of NaOH (aq., 3 equiv) for 1 h, followed by extraction with CH_2Cl_2, removal of the organic solvent, and direct subjection of the crude residue to methyl iodide (3 equiv) (Table 2). Solvent and time conditions were varied as shown in Table 2, and results were assessed by LC/MS analysis of crude reaction mixtures. Under all solvent conditions tested, we observed significant conversion and with exclusive selectivity for monomethylation, confirming that ylide of **2** was formed under the employed conditions. We also acquired ^{1}H NMR data of the ylide of **2** in CD_3CN, which did not show any evidence of undesired dihydropyridine nucleophiles (Figure 2; see Supporting Information page S90 for the ^{1}H NMR spectrum). Between the solvents assayed, DMF gave the highest conversion within 2 h (>95%, entry 3) and CH_2Cl_2 gave the lowest (56%, entry 2), with CH_3CN and acetone giving moderate conversion (70 and 64%, respectively,

Table 2. Optimization of an Iterative Ylide Formation-Alkylation Procedure



entry	solvent	*t* (h)	% conversion[a]	alkylation distribution ratio: (+1, +2, +3, +4, +5)[a]
1	CH_2Cl_2	2	56	+1 observed only
2	CH_3CN	2	70	+1 observed only
3	DMF	2	>95	+1 observed only
4	acetone	2	64	+1 observed only
5	acetone	6	>95	+1 observed only

[a]Conversions and alkylation ratios were estimated using total ion count (TIC) from LC/MS.

entries 1 and 4). Extension of the reaction time in acetone to 6 h resulted in full conversion of **2** (>95%, entry 5). Performance of the ylide-alkylation sequence in acetone on a 0.1 mmol scale reaction enabled the isolation of **1a** in a 67% yield (Scheme 1). The spectral qualities of **1a** isolated from this experiment were in excellent agreement with samples synthesized via hydrazide condensation.[3c] While DMF gives complete conversion in a shorter time frame compared to acetone, we opted to use acetone as the solvent of choice for this process owing to its practical ease of use and its superior properties as a green solvent compared to DMF.[9]

With optimal conditions in hand, we next sought to explore the scope of electrophiles tolerated through this approach. Beyond Me-I, alkyl iodides are well tolerated for pyridinium alkylation and enabled perdeuteromethylation (**2a**, 82%), ethylation (**2b**, 44%), and acetamidylation (**2c**, 81%). Alkyl bromides also readily alkylate **2**, enabling benzylation (**2d**, 66%), propargylation (**2e**, 55%), and the addition of nitriles (**2f**, 76%) and acetyl groups (**2g**, 64%). α-Chloroacetates proved less reactive (19% conversion by LC/MS) and required the use of KI as an additive to achieve a competent yield (49% isolated yield). The ylide-alkylation method also tolerates carbamates that are frequently used as protecting groups, with boc-(**2j**) and cbz (**2k**) protecting groups tolerated in pyridinium ylide propargylation in 68 and 67%, respectively. Taken together, the diversity of tolerated electrophiles allowed for the potential incorporation of a wide array of functionality into the pyridinium scaffold. For example, perdeuteromethylation enables the synthesis of probes that are potentially useful for mass spectrometry-based workflows[10] and protein NMR spectroscopy,[11] while α-haloacetamides and α-haloacetates are very mild electrophiles that are compatible with sensitive structures such as drugs, drug fragments, peptides, and fluorophores. The method does have limitations, with unsuccessful electrophiles including dimethyl bromomalonate, 2,2,2-trifluoromethyl-1-iodo ethane, Umemoto's reagent, Togni's reagent, or the Ritter trifluoroiodomethane-TMG reagent. In these instances, no discernible alkylation or trifluoromethylation was observed.

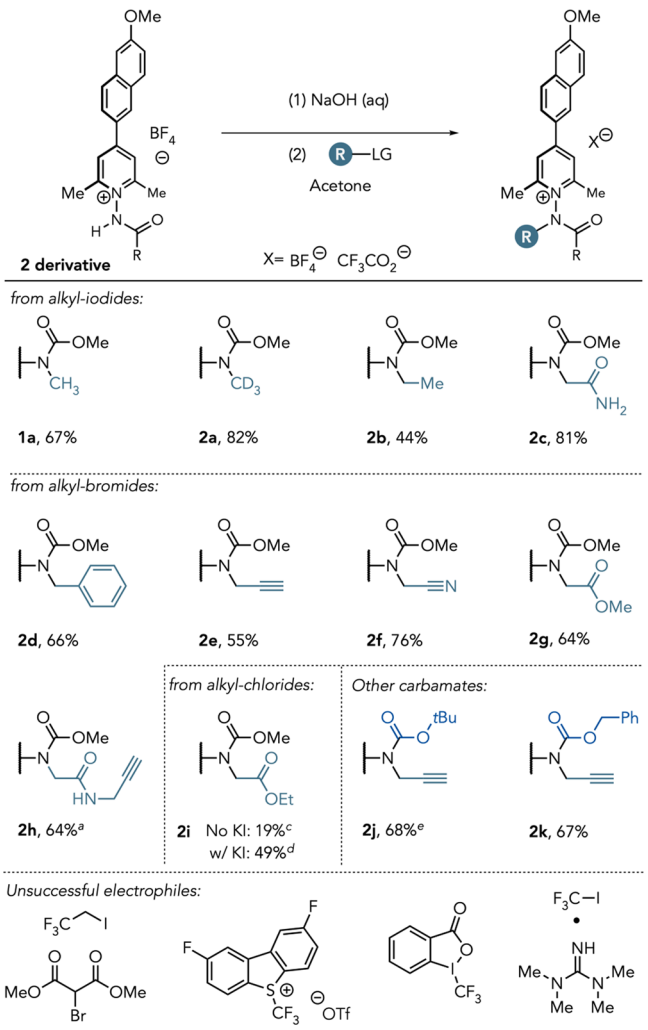
https://doi.org/10.1021/acs.joc.4c01403
J. Org. Chem. 2024, 89, 17115−17121

Table 3. Photophysical Properties of Pyridinium Salts 3−10[a]

compound	λ_{max}^{abs} (nm)	λ_{max}^{em} (nm)	Stokes shift (nm)	ε (L mol^{-1} cm^{-1})
3	268	409	141	3.4×10^4
4	273	393	120	1.0×10^5
5	350	441	91	2.0×10^4
6	345	449	104	1.4×10^4
7	362	504	142	6.9×10^3
8	376	523	147	3.6×10^4
9	387	447	60	6.3×10^3
10	321	386	65	2.0×10^4

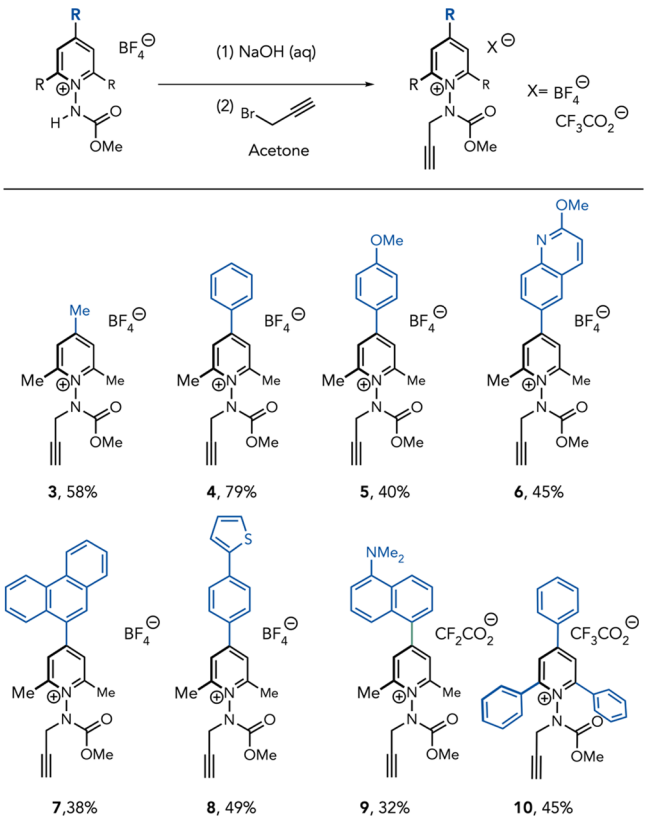
[a]Data acquired in 20 mM NH_4OAc (pH 6.9) buffer.

Scheme 1. Electrophile and *N*-Substituent Substrate Scope[a,b]



[c]Conversion assessed by LC-MS. [d]1:1 KI:electrophile ratio. [e]Isolated with bromide counterion. [a]Reaction conditions: ylide formation: **2** derivative (1 equiv), NaOH (aq) (3−10 equiv). Ylide-alkylation: electrophile (2−4 equiv), acetone ([ylide] = 0.3 M). [b]Yields are averages of two experiments.

Scheme 2. Pyridinium Substrate Scope[a,b]

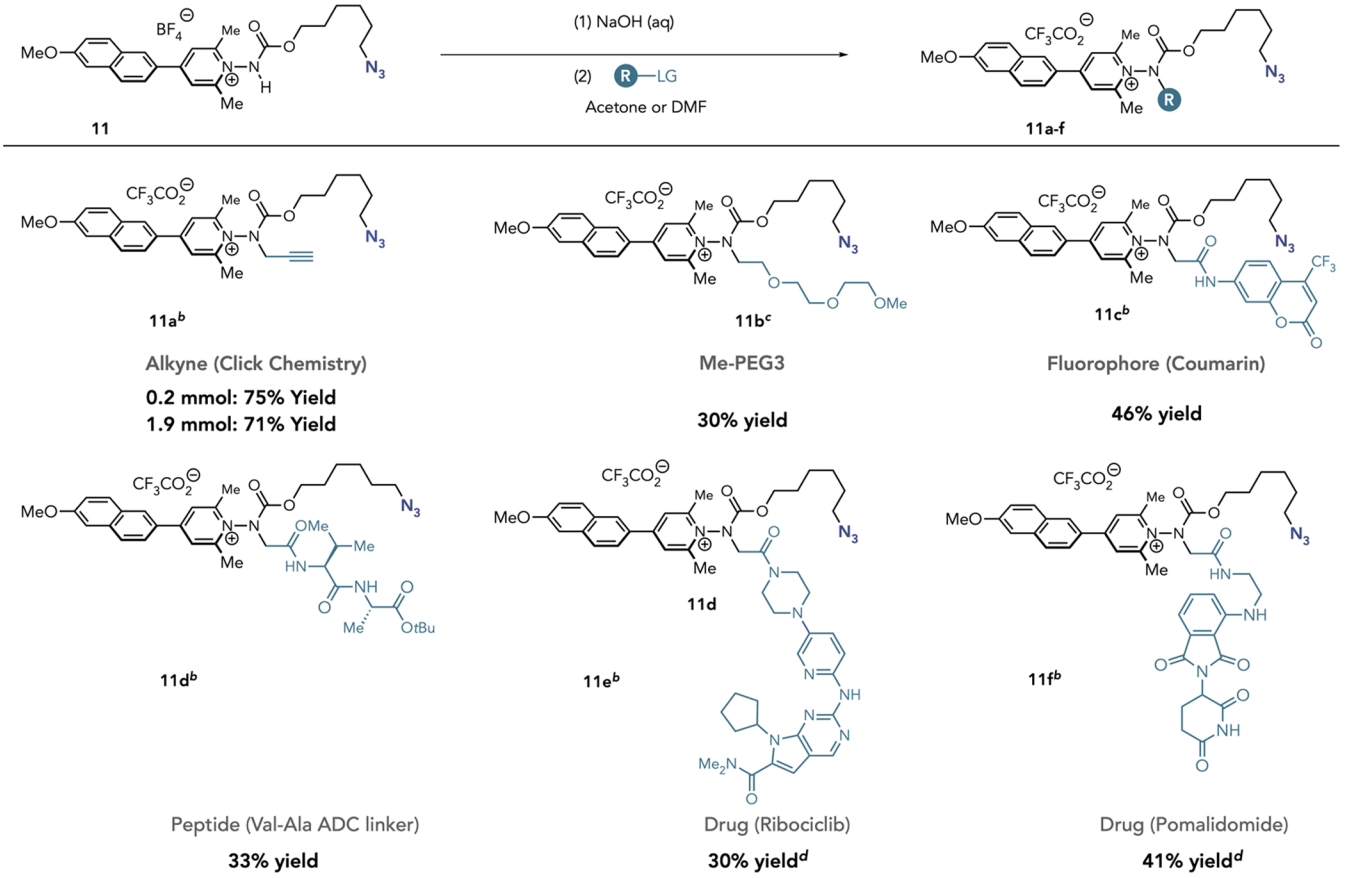


[a]Reaction conditions: ylide formation: pyridinium derivative (1 equiv), NaOH (aq) (3 equiv). Ylide-alkylation: propargyl bromide (1.7−4.3 equiv), acetone ([ylide] = 0.3 M). [b]Yields are averages of two experiments.

Next, we explored the scope of pyridinium salt structures that would be compatible with this chemistry by synthesizing a small battery of *N*-carbamoylpyridinium salts and studying their propargylation under our ylide conditions (Scheme 2). Analogs of our first-generation pyridinium salts were readily propargylated to yield trimethylpyridinium salt **3** (58%) and phenylpyridinium salt **4** (79%) in good yields. Biarylpyridinium salts containing diverse functionality are well tolerated by this process. *p*-Methoxyphenyl-substituted salt **5** was readily propargylated in a 45% yield, while 2-methoxyquinoline-substituted **6** was accessed in a 40% yield. Anthracenyl-substituted **7** was synthesized in a 38% yield, while 4-thiophenyl−phenyl-substituted salt **8** was accessed in a 49% yield. 5-Dimethylamino naphthyl-substituted salt was accessed in a 32% yield, a salt that bears structural/electronic similarities to dansyl-based fluorophores. Finally, 2,4,6-aryl-substituted pyridinium salts have become essential radical reservoirs in small molecule organic synthesis, and we show that this motif is well tolerated with our ylide-alkylation sequence by accessing salt **10** in a reasonable yield (45%).

https://doi.org/10.1021/acs.joc.4c01403
J. Org. Chem. 2024, 89, 17115−17121

Scheme 3. Synthesis of Heterotrifunctional Pyridinium Salts[a]



[b]Acetone used as a solvent. [c]DMF used as a solvent. [d]Reactions were quenched with excess benzyl bromide. [a]Yields are averages of two experiments.

Pyridinium salts **3**–**10** vary substantially in their substitution patterns, which can have a marked effect on the photophysical properties. Photophysical data are provided in Table 3 and show that these salts vary in their absorption maxima from Uv-B (**3**,**4**) to the Uv-A region (**5**–**10**) and significant absorption into violet/blue spectrum (**8**, **9**) (see the Supporting Information for full spectra). As observed previously,[2b] biarylpyridinium salts display large Stokes shifts (>100 nm for **4** and **6** and >140 nm for **7** and **8**). Notably, **9** displays a comparatively modest Stokes shift, likely due to the steric hindrance of the bulky 5-dimethylamino-naphthyl group causing hindered rotation about the biaryl bond.

Encouraged by the general nature of the alkylation procedure, we then sought to apply this approach to generate heterotrifunctional pyridinium salts. Reagents of this class, which contain multiple functionalizable handles that are chemically orthogonal to each other, are appreciated as they provide platforms in which several different functionalities/capabilities can be incorporated into peptides and proteins in a single reaction and have found application in assembling theranostic-type compounds.[12] To achieve this, we selected heterobifunctional ylide precursor **11** as a suitable substrate (Scheme 3). **11** features two unique chemical warheads: the pyridinium warhead as well as the azide click handle. Thus, the treatment of **11** with NaOH (aq), followed by alkynylation with propargyl bromide, yielded heterotrifunctional pyridinium salt **11a** in a 75% isolated yield. We then performed this reaction on a 1 g scale (1.9 mmol), yielding **11a** in a 71% yield. This result hints at the potential to perform a larger-scale probe synthesis. Encouraged by these results, we next sought to alkylate **11** with complex electrophiles to create highly bespoke pyridinium probes. Thus, the alkylation of **11** with Me-PEG-3-Br in DMF and with 3 equiv of potassium iodide yielded pegylated **11b** in a useful 30% yield. Our data in Scheme 2 clearly indicates that α-haloacetates and acetamides are competent electrophiles for this process. A key advantage of these electrophiles is the ease with which they can be incorporated into many types of structures in a single step from simple α-haloacetyl halides and an appropriate amine or alcohol nucleophile. Using this simple approach, we prepared an α-bromoacetylated coumarin analog **SI29**. Treatment of **11** with **SI29** resulted in highly substituted **11c** in a 46% isolated yield. We then extended this demonstration to peptides, showing that ADC linker Val–Ala[13] could readily be incorporated into the **11** scaffold in a 33% isolated yield (**11d**). Next, we synthesized α-bromoacetylated analog (**SI27**) of kinase inhibitor Ribociclib.[14] Treatment of **11** with **SI27** enabled access to **11e** in a 30% yield. Finally, α-bromoacetylated pomalidomide analog **SI38** reacted smoothly with ylide **11** to yield **11f** in a 40% isolated yield. While each of the **11** analogs was purified by reverse phase chromatography, analogs **11e,f** each possessed identical retention times to **11**. Thus, to separate alkylated products from unreacted **11**, we quenched the alkylation reactions with benzyl bromide, which converted unreacted ylide to compound **2d**, which has a

https://doi.org/10.1021/acs.joc.4c01403
J. Org. Chem. 2024, 89, 17115–17121

sufficiently different polarity to enable facile purification by reverse phase chromatography.

In summary, we have developed a pyridinium ylide-alkylation approach that enables the assemblage of functionally diverse and, in some cases, highly complex pyridinium salts. We anticipate that this method will enable the synthesis of a wide array of radical precursors and functional probes that can be applied to both small molecule synthesis and protein ligation.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01403.

General considerations, experimental procedures, photophysical data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Michael T. Taylor − *Department of Chemistry & Biochemistry, University of Arizona, Tucson, Arizona 85721, United States;* orcid.org/0000-0002-7655-7222; Email: mtaylor6@arizona.edu

Authors

Akash M. Sarkar − *Department of Chemistry & Biochemistry, University of Arizona, Tucson, Arizona 85721, United States*

Benjamin Gossett − *Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.4c01403

Author Contributions

A.M.S.: designed, performed, and analyzed experiments and contributed to writing the manuscript and associated documents. B.G.: designed, performed, and analyzed experiments. M.T.T.: conceived the project, designed and analyzed experiments, and contributed to writing the manuscript and associated documents.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Science Foundation, Division of Chemistry, Chemistry Life Processes Institute, for generous support of this work (CHE-2302483). B.G. thanks the NSF REU program (CHE-2051148) for support. The authors acknowledge the W. M. Keck Center for Nano-Scale Imaging (RRID:SCR_022884) and the Nuclear Magnetic Resonance Facility (RRID:SCR_012716) at the University of Arizona Department of Chemistry and Biochemistry for instrumentation support. The authors also thank NSF (Grant Nos. 1920234, 840336, 9214383, 9729350) for additional instrumentation support and the University of Arizona for startup funds.

■ REFERENCES

(1) (a) He, F.-S.; Ye, S.; Wu, J. Recent Advances in Pyridinium Salts as Radical Reservoirs in Organic Synthesis. *ACS Catal.* **2019**, *9*, 8943−8960. (b) Madaan, P.; Tyagi, V. K. Quaternary Pyridinium Salts: A Review. *J. Oleo Sci.* **2008**, *57*, 197−215. (c) Zou, J.; Mariano, P. S. The synthetic potential of pyridinium salt photochemistry. *Photochem. Photobiol. Sci.* **2008**, *7*, 393−404. (d) Kim, M.; Koo, Y.; Hong, S. *N*-Functionalized Pyridinium Salts: A New Chapter for Site-Selective Pyridine C−H Functionaliation via Radical-Based Processes under Visible Light Irradiation. *Acc. Chem. Res.* **2022**, *55*, 3043−3056. (e) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. Synthesis of Pyridine and Dihydropyridine Derivatives by Regio- and Stereoselective Addition to *N*-Activated Pyridines. *Chem. Rev.* **2012**, *112*, 2642−2713.

(2) (a) Dong, S.; Fu, X.; Xu, X. [3 + 2]-Cycloaddition of Catalytically Generated Pyridinium Ylide: A General Access to Indolizine Derivatives. *Asian J. Org. Chem.* **2020**, *9*, 1133−1143. (b) Qiu, G.; Kuang, Y.; Wu, J. *N*-Imide Ylide-Based Reactions: C-H Functionalization, Nucleophilic Addition and Cycloaddition. *Adv. Synth. Catal.* **2014**, *356*, 3483−3504. (c) Sowmiah, S.; Eperança, J. M. S. S.; Rebelo, L. P. N.; Afonso, C. A. M. Pyridinium salts: from synthesis to reactivity and applications. *Org. Chem. Front.* **2018**, *5*, 453−493.

(3) (a) Tower, S. J.; Hetcher, W. J.; Myers, T. E.; Kuehl, N. J.; Taylor, M. T. Selective Modification of Tryptophan Residues in Peptides and Proteins Using a Biomimetic Electron Transfer Process. *J. Am. Chem. Soc.* **2020**, *142*, 9112−9118. (b) Orellana, N. V.; Taylor, M. T. Targeting Tryptophan for Tagging through Photoinduced Electron Transfer. *Synlett* **2021**, *32*, 1371−1378. (c) Hoopes, C. R.; Garcia, F. J.; Sarkar, A. M.; Kuehl, N. J.; Barkan, D. T.; Collins, N. L.; Meister, G. E.; Bramhall, T. R.; Hsu, C.-H.; Jones, M. D.; Schirle, M.; Taylor, M. T. Donor-Acceptor Pyridinim Salts for Photo-Induced Electron-Transfer-Driven Modification of Tryptophan in Peptides, Proteins, and Proteomes Using Visible Light. *J. Am. Chem. Soc.* **2022**, *144*, 6227−6236.

(4) (a) Greulich, T. W.; Daniliuc, C. G.; Studer, A. *N*-Amino-pyridinium Salts as Precrurors for N-Centered Radicals − Direct Amidation of Arenes and Heteroarenes. *Org. Lett.* **2015**, *17*, 254−257. (b) Moon, Y.; Park, B.; Kim, I.; Kang, G.; Shin, S.; Kang, D.; Baik, M.-H.; Hong, S. Visible Light Induced Alkene Aminopyridylation Using N-Aminopyridinium Salts as Bifunctional Reagents. *Nat.Commun.* **2019**, *10*, No. 4117.

(5) Tcyrulnikov, S.; Cai, Q.; Twitty, J. C.; Xu, J.; Atifi, A.; Bercher, O. P.; Yap, G. P. A.; Rosenthal, J.; Watson, M. P.; Kozlowski, M. C. Dissection of Alkylpyridinium Structures to Understand Deamination Reactions. *ACS Catal.* **2021**, *11*, 8456.

(6) Balaban, T. S.; Balaban, A. T. Product Class 1: Pyrylium Salts. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2003; Vol. *14*, pp 11−200.

(7) (a) Kakehi, A.; Ito, S.; Konno, Y.; Maeda, T. Synthesis Using Pyridinium N-Ylides. I. Synthesis of and Some Reactions of Substituted 1-(Acetylimino)pyridinium Ylides. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 251−256. (b) Larivée, A.; Mousseau, J. J.; Charette, A. J. Palladium-Catalyzed Direct C-H Arylation of *N*-iminopyridinium Ylides: Application to the Synthesis of (±)-Anabasine. *J. Am. Chem. Soc.* **2008**, *130*, 52−54. (c) Molina, A.; de las Heras, M. A.; Martinez, Y.; Vaquero, J. J.; Navio, J. L. G.; Alvarez-Builla, J.; Gomez-Sal, P.; Torres, R. Synthesis and structure of complexes of acyl N-aminides with zinc(II) salts. *Tetrahedron* **1997**, *53*, 6411−6420. (d) Kim, N.; Lee, C.; Kim, T.; Hong, S. Visible-Light-Induced Remote C(sp^3)−H Pyridylation of Sulfonamides with Carboxamides. *Org. Lett.* **2019**, *21*, 9719−9723. (e) Roychowdhury, P.; Waheed, S.; Sengupta, U.; Herrera, R. G.; Powers, D. C. Synthesis of Secondary Amines via Self-Limiting Alkylation. *Org. Lett.* **2024**, *26*, 4926−4931.

(8) Chatzopoulou, E.; Davies, P. W. Highly regioselective synthesis of 2,4,5-(hetero)aryl substituted oxazoles by intermolecular [3 + 2]-cycloaddition of unsymmetrical internal alkynes. *Chem. Commun.* **2013**, *49*, 8617−8619.

(9) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; McElroy, R.; Sherwood, J. Tools and techniques for solvent selection: green solvent selection guides. *Sustainable Chem. Processes* **2016**, *4*, No. 7.

(10) Lehmann, W. D. A timeline of stable isotopes and mass spectrometry in the life sciences. *Mass Spectrom. Rev.* **2017**, *36*, 58−85.
(11) Sattler, M.; Fesik, S. W. Use of deuterium labeling in NMR: overcoming a sizeable problem. *Structure* **1996**, *4*, 1245−1249.
(12) Sharma, A.; Verwilst, P.; Li, M.; Ma, D.; Singh, N.; Yoo, J.; Kim, Y.; Yang, Y.; Zhu, J.-H.; Huang, H.; Hu, X.-L.; He, X.-P.; Zeng, L.; James, T. D.; Peng, X.; Sessler, J. L.; Kim, J. S. Theranostic Fluorescent Probes. *Chem. Rev.* **2024**, *124*, 2699−2804.
(13) Su, Z.; Xiao, D.; Xie, F.; Liu, L.; Wang, Y.; Fan, S.; Zhou, X.; Li, S. Antibody-drug conjugates: Recent advances in linker chemistry. *Acta Pharm. Sin. B* **2021**, *11*, 3889−3907.
(14) Chen, P.; Lee, N. V.; Hu, W.; Xu, M.; Ferre, R. A.; Lam, H.; Bergqvist, S.; Solowiej; Diehl, W.; He, Y.-A.; Yu, X.; Nagata, A.; VanArsdale, T.; Murray, B. W. Spectrum and Degree of CDK Drug Interactions Predicts Clinical Performance. *Mol. Cancer Ther.* **2016**, *15*, 2273−2281.

https://doi.org/10.1021/acs.joc.4c01403
J. Org. Chem. 2024, 89, 17115−17121