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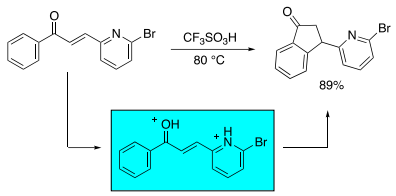

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ABSTRACT

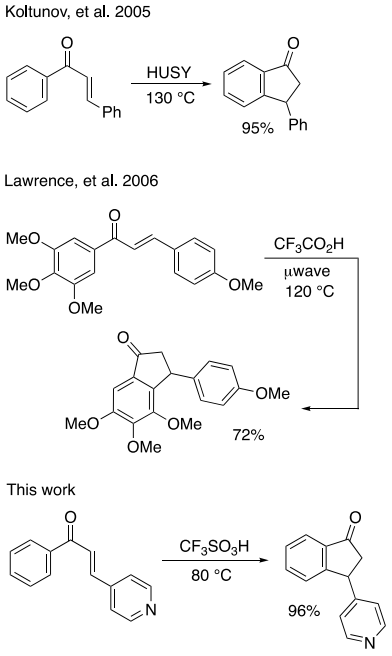
A series of Nazarov cyclizations has been studied involving *N*-heterocyclic-substituted 1-arylprop-2-en-1-one derivatives (aza-chalcones). Superacid catalyzed reactions of these derivatives provide good yields of heterocyclic-substituted 1-indanones. A mechanism is proposed involving diprotonated, superelectrophilic intermediates.

1. Introduction

Olah and coworkers first recognized the concept of superelectrophilic activation.[1] It was proposed that monocationic electrophiles, such as nitronium (NO_2^+) and acetyl (CH_3CO^+) cations, could undergo further protonation in sufficiently acidic media and the resulting species should exhibit enhanced electrophilic reactivities.[2] This concept has been confirmed by numerous experimental studies with these multiply charged intermediates, or superelectrophiles.[2] As a result of the high reactivities of superelectrophiles, they have been used in many novel synthetic methods.[2,3] In previous studies, we and others have demonstrated that stable cationic charges - from protonated *N*-heterocyclic rings – have a profound activating effect in electrophilic reactions.[4] These *N*-heterocycle-based systems often have reactivities similar to Olah's superelectrophiles.

A number of recent studies have shown that strongly acidic media may be used to promote the Nazarov cyclization of chalcone derivatives to provide functionalized indanones.[5] For example, Koltunov and coworkers utilized zeolite and solid acid catalysts to convert chalcone to 3-phenyl-1-indanone (Scheme 1).[6] A diprotonated superelectrophile was proposed as the possible intermediate leading to cyclization. Others have accomplished this transformation using forcing conditions and excess acids such as $AlCl_3$.[7] Several other reports describe chalcone cyclizations involving primarily electron rich aryl rings,[8] such as Lawrence's microwave-assisted synthesis of potential tubulin-binding agents.[8a] In the following manuscript, we describe the use of protonated *N*-heterocyclic rings to facilitate the Nazarov reaction and provide functionalized 1-indanone products in good yields.

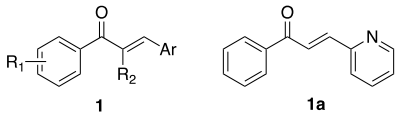
Scheme 1.



2. Results and Discussion

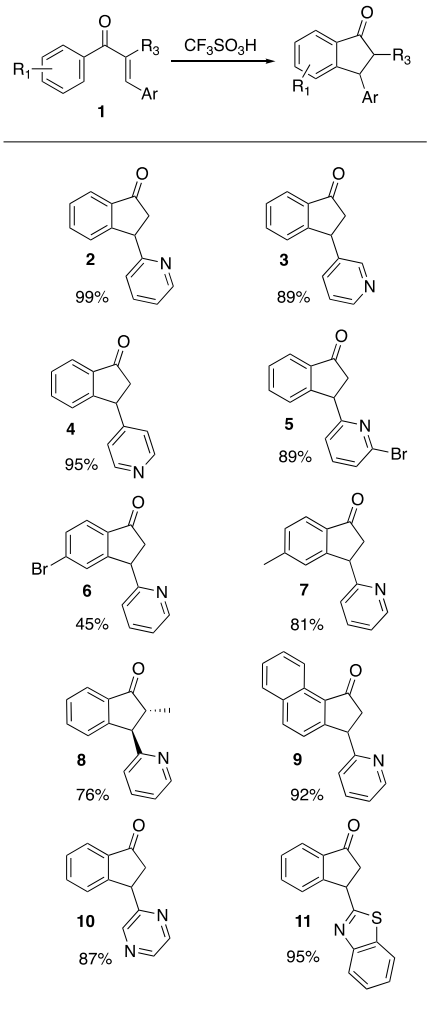
In previous studies from our group, protonated *N*-heterocyclic rings have been shown to enhance the reactivities of carboxonium ion and carbenium ion electrophiles.[4b,c,d] Likewise, the presence of

monocationic or dicationic protonated *N*-heterocyclic rings activated Diels-Alder dienes for cycloaddition reactions with ethylene.[9] In order to probe the effects of *N*-heterocyclic rings on the Nazarov reaction, a series of 1-arylprop-2-en-1-one derivatives (**1**) were prepared.[10] Derivatives of compound **1** were typically



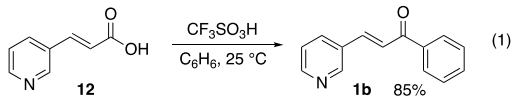
prepared using condensation chemistry, for example acetophenone reacts with 2-pyridinecarboxaldehyde to give 1-phenyl-3-(pyridin-2-yl)prop-2-en-1-one (**1a**, see Experimental Section). Upon treatment with excess superacid, CF_3SO_3H, substrate **1a** provides the functionalized indanone (**2**) in quantitative yield (Table 1). The

Table 1. Products and isolated yields for the reactions of **1** and CF_3SO_3H at 80 °C.



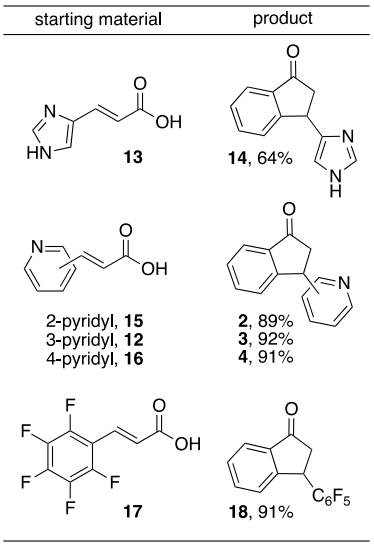
same substrate does not cyclize in excess H_2SO_4 or weaker acids at 80 °C. Likewise, the pyridyl isomers **1b,c** give the respective products **3** and **4** in good yields. Halogenated derivatives **5-6** and alkylated derivatives **7-8** are prepared in fair to good yields. Cyclization involving a 1-napthyl ring provides product **9** in 92% yield, with cyclization occurring preferentially at the 2-position. Other *N*-heterocyclic groups promote the cyclization, including the pyrazine and benzothiazole derivatives to give **10-11**, respectively. Heterocycle-substituted 1-indanones have been useful as pharmaceutical intermediates and the above chemistry provides improved access to these structures. For example, the synthesis of compound **4** was described recently in a patent and an optimized procedure required no less than five synthetic steps (yields not given).[11] Our methodology provides this compound in just two synthetic steps.

Some time ago, we reported the condensation reactions of acrylic acid derivatives with benzene in superacid.[12] It was observed that electron-deficient substrates, including those with *N*-heterocyclic derivatives, provide 1-phenylprop-2-en-1-ones. For example, 3-(pyridin-3-yl)acrylic acid (**12**) provides the aza-chalcone (**1b**) in 85% yield from a reaction with CF_3SO_3H and C_6H_6 at 25°C (eq 1).[12] We reasoned that the cyclization reaction



conditions (80°C) should provide substituted-indanones directly from the electron deficient acrylic acid derivatives. Thus, reaction of the imidazole derivative **13** provides the cyclization product **14** in a single synthetic step in 64% yield (Table 2). Likewise, the pyridine derivatives (**12**, **15-16**) give good yields of the respective

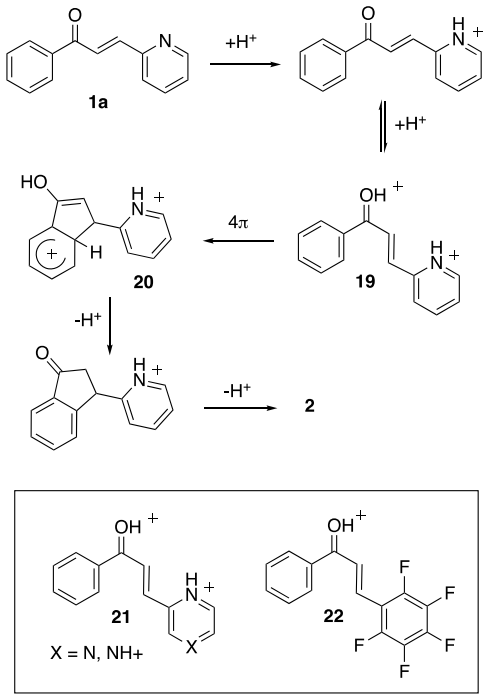
Table 2. Products and yields from the reactions of acrylic acid derivatives with CF_3SO_3H and C_6H_6 at 80 °C.



indanones (**2**, **3**, and **4**). The previous study from our group also showed that pentafluorocinnamic acid (**17**) reacts with benzene in triflic acid to provide the fluorinated chalcone.[12] Similar to the heterocyclic derivatives, pentafluorocinnamic acid (**17**) provides the cyclization product (**18**) in high yield.

In the conversions to indanones, the cyclizations of the 1-arylprop-2-en-1-one (**1**) derivatives likely involve diprotonated species or electron-deficient carboxonium ions. For example, compound **1a** is first protonated at the *N*-heterocycle and then at the carbonyl group to provide the dication **19** (Scheme 2). It is suggested that this superelectrophilic species triggers the 4π electrocyclization - which leads to intermediate **20**. Deprotonation steps then provide the final product, indanone **2**. Previous work by Ohwada and coworkers has suggested that charge delocalization is

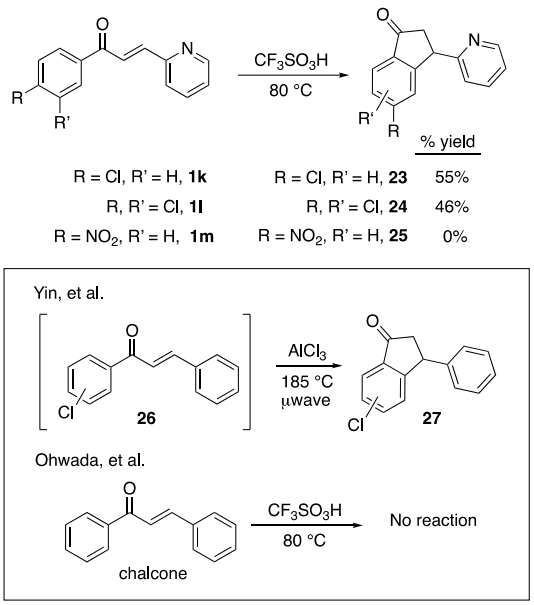
Scheme 2.



an important driving force in the Nazarov cyclization with dicationic or superelectrophilic species.[13] The cyclization of dication **19** effective separates the two cationic charges, wherein dication **20** has two monocation π-systems that are no longer in conjugation. In the case of the pyrazine substrate, protonation will likely give an equilibrium containing both the di- and triprotonated species (**21**). In the conversions involving pentafluorocinnamic acid (**17**), Friedel-Crafts chemistry gives the corresponding chalcone and the protonated derivative **22** is assumed to be the reactive intermediate leading to the Nazarov cyclization product. No other reasonably good base-site exists, so diprotonation is not likely with the pentafluorochalcone. With intermediate **22**, charge-charge repulsive effects are not a likely a driving force for the cyclization. Rather, cyclization is driven by the strongly electrophilic β-carbon of this species. A similar inductive effect may also be an important contributing factor in the cyclizations of the aza-chalcones.

One of the hallmarks of superelectrophiles is their ability to react with weak nucleophiles and deactivated aromatic rings.[2] In order to examine this aspect of the chemistry, aza-chalcones (**1k-m**) were prepared with increasingly deactivated aryl groups (Scheme 3). Upon reaction in superacid, reasonable yields were obtained from both the chlorophenyl and 3,4-dichlorophenyl derivatives. Thus, substrate **1k** gives a 55% yield of the 5-chloro-1-indanone (**23**). While the dichlorophenyl derivative (**1l**) does undergo cyclization in fair yield, the two regioisomers (**24**) are formed. The 4-nitrophenyl derivative (**1m**) did not undergo cyclization, even with elevated temperatures and prolonged reaction times. Substrate **1m** could be isolated quantitatively following the unsuccessful efforts. These results suggest a modest or slight increase in reactivity for the aza-chalcones over the chalcones. For example, Yin and coworkers studied the $AlCl_3$-promoted reactions of substituted benzenes with cinnamoyl chloride using microwave irradiation.[7a] In the case of chlorobenzene, the chloro-substituted chalcone (**26**) is formed as a

Scheme 3.



mixture of regioisomers and the corresponding isomeric 1-indanones (**27**) are obtained in a crude yield of 88%. Purification of 5-chloro-3-phenyl-1-indanone (the phenyl analog of **23**) provides a 45% isolated yield of this indanone product. Considering the microwave induced transformation of **26** is done at 185 °C, while the aza-chalcone chemistry is done at a lower temperature (80 °C), this is consistent with a somewhat higher level of reactivity for the aza-chalcone (**1k**). A reasonably good yield of the dichloroindanone product (**24**) is also obtained, despite the deactivating effects of the 3,4-dichlorophenyl group in the aza-chalcone **1l**. Nevertheless, attempts to obtain the cyclization product were unsuccessful with the 4-nitrophenyl derivative **1m**. In excess superacid, this system is likely protonated at the three good base sites – the pyridyl, carbonyl, and nitro groups. As such, the protonated 4-nitrophenyl group is expected to be highly deactivated, consequently even forcing conditions do not trigger the Nazarov cyclization. It has also been previously reported that chalcone does not undergo the Nazarov cyclization in excess CF_3SO_3H at 80°C,[13] the same conditions used to provide good yields from the aza-chalcones (Table 1). This observation suggests an increase in reactivities for the aza-chalcone and a strong activating effect from the protonated *N*-heterocyclic groups.

3. Conclusion

In summary, we have found that aza-chalcones undergo efficient Nazarov cyclizations in the presence of superacidic CF_3SO_3H. The chemistry represents a simple method of preparing 1-indanones having *N*-heterocyclic substituents. A mechanism is proposed involving dicationic intermediates. Empirical evidence suggests that the protonated *N*-heterocyclic substituents activate the system towards cyclization - leading to good yields of products at modest temperatures.

4. Experimental

All reactions were performed using oven – dried glassware under an argon atmosphere. Trifluoromethanesulfonic acid (triflic acid) was freshly distilled prior to use. A previous report describes

a procedure for the quantitative recycling of trifluoromethanesulfonic acid.[14] All commercially available compounds and solvents were used as received. ^{1}H and ^{13}C NMR were done using either 300 MHz or 500 MHz spectrometer. Reaction done with benzene at 80°C were done in a high-pressure, glass reaction tube having a Teflon screw cap (obtained from a commercial glassware supplier). Low resolution mass spectra were obtained from a gas chromatography instrument equipped with a mass-selective detector. Ionization was accomplished with electron impact ionization. High resolution mass spectroscopy was done by a commercial laboratory (electron impact ionization or electrospray; sector instrument analyzer type). Aza-chalcones **1a**,[15] **1b**,[16] **1c**,[16] **1f**,[17] **1h**,[18] **1k**,[19] **1l**,[20] and **1m**,[19] are known compounds. Indanone **23** is a known compound.[7a] Compounds **12**, **13**, **15-17**, were purchased from a commercial supplier.

Procedure A: Synthesis of aza-chalcones, 1. A solution is prepared from 10 mL H_2O, 5 mL ethanol, pyridine (0.16 mL, 0.154 g, 2 mmol), and NaOH (0.2 g, 5 mmol). To this solution is added the aryl ketone (1 mmol) and heterocyclic aldehyde (1 mmol) and the solution is stirred at 25 °C for 12 hr. A precipitate generally forms and this is filtered off, rinsed with water, and dried. The crude aza-chalcone is then further purified by silica gel column chromatography.[14]

Procedure B: Synthesis of 1-indanones. In a vessel flushed with inert gas, the aza-chalcone (1 mmol) is added to 2 mL of CF_3SO_3H (22 mmol). The vessel is sealed, heated to 80°C, and the solution stirred for 18 hrs. Following the reaction period, the solution is cooled and then poured over ice. Chloroform (15 mL) is added to the mixture and the aqueous solution is made basic by the addition of saturated sodium bicarbonate. The organic extract is washed with water, then brine, and dried with anhydrous sodium sulfate. Filtration and removal of the solvent gives the crude indanone product - which is further purified by column chromatography (hexanes:ethyl acetate).

Procedure C: Synthesis of 1-indanones. NOTE: this procedure is done near the boiling point of benzene, so adequate precautions should be made to handle the potential buildup of pressure in a closed reaction vessel. In a vessel flushed with inert gas, benzene (0.5 mL) and CF_3SO_3H (2 mL, 22 mmol) are combined, into which is added the acrylic acid derivative (1 mmol). The vessel is sealed, heated to 80°C, and the solution stirred for 18 hrs. Following the reaction period, the solution is cooled and then poured over ice. Chloroform (15 mL) is added to the mixture and the aqueous solution is made basic by the addition of saturated sodium bicarbonate. The organic extract is washed with water, then brine, and dried with anhydrous sodium sulfate. Filtration and removal of the solvent gives the crude indanone product - which is further purified by column chromatography (hexanes:ethyl acetate).

4.1. (E)-3-(6-Bromopyridin-2-yl)-1-phenylprop-2-en-1-one ***(1d)***

Using General Procedure A, acetophenone (120 mg, 1 mmol) and 6-bromopicolinaldehyde (186 mg, 1 mmol) provides aza-chalcone **1d** (259 mg, 0.90 mmol, 90%) as yellow solid, R_f = 0.6 (hexane: ethyl acetate, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.09 (1H, s), 8.05 (2H, t, J = 7 Hz), 7.65 (1H, s), 7.62-7.55 (2H, m), 7.49 (2H, t, J = 7.5 Hz), 7.44 (1H, d, J = 7.5 Hz), 7.39 (1H, d, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 190.0, 154.4, 142.6, 140.8, 139.1, 137.6, 133.2, 128.8, 128.75, 128.72, 126.9, 124.0. Mass spectrum (low resolution, EI): 287 [M+], 260, 210, 180, 105, 77, 51. HRMS calculated for $C_{14}H_{11}BrNO$, 288.0024 (MH^+). Found 288.0012.

4.2. (E)-1-(4-Bromophenyl)-3-(pyridin-2-yl)prop-2-en-1-one ***(1e)***

Using General Procedure A, 4-bromoacetophenone (199 mg, 1 mmol) and 2-pyridinecarboxyaldehyde (107 mg, 1 mmol) provides aza-chacone (**1e**) (259 mg, 0.90 mmol, 90%) as yellow solid, R_f = 0.7 (hexane: ethyl acetate, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.62 (1H, d, J = 3 Hz), 8.01 (1H, d, J = 15 Hz), 7.89 (2H, d, J = 8 Hz), 7.73-7.65 (2H, m), 7.56 (2H, d, 8 Hz), 7.40 (1H, d, J = 7.5 Hz), 7.23 (1H, t, J = 5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 189.1, 152.9, 150.2, 143.2, 136.9, 136.5, 131.9, 130.2, 128.2, 125.5, 124.8, 124.5. HRMS calculated for $C_{14}H_{11}BrNO$, 288.0024 (MH^+). Found 288.0014.

4.3. (E)-2-Methyl-1-phenyl-3-(pyridin-2-yl) prop-2-en-1-one ***(1g)***

Propiophenone (134.2 mg,1 mmol) is dissolved in 10 mL of ethyl ether and sodium hydride (36 mg, 1.5 mmol) is added to the mixture at 0°C. After stirring for 30 min, 2-pyridinecarboxyaldehyde (109 mg, 1 mmol) is added to the mixture. The solution is allowed to warm to room temperature, stirred for another 12 hrs and then 5mL of 1M HCl is added to the mixture. The solution is stirred for 5 hr and then poured over 10 g of ice, neutralized by saturated $NaHCO_3$, and the organic product is extracted into diethyl ether. The organic extract is washed with water and then (2x) with brine solution, followed by drying with sodium sulfate, filtration, and concentrating under vacuum. The crude product mixture is purified by flask chromatography (hexane: ethyl acetate) to provide aza-chalcone (**1g**). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.70 (1H, s), 7.79 (2H, t, J = 5 Hz), 7.70 (1H, dd, J = 1.5, J = 7.5 Hz), 7.53 (1H, dd, J = 2, J = 6 Hz), 7.46 (2H, d, J = 4.5 Hz), 7.36 (1H, d, J = 5.5 Hz), 7.21 (1H, t, J = 1 Hz), 7.12 (1H, d, J = 0.5 Hz), 2.45 (3H, d, J = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 199.6, 155.1, 149.7, 140.3, 139.4, 137.9, 136.3, 131.9, 129.5, 128.3, 125.5, 122.6. 14.7. HRMS calculated for $C_{15}H_{14}NO$, 224.1075 (MH^+). Found 224.1069.

4.4. (E)-1-(Naphthalen-1-yl)-3-(pyridin-2-yl)prop-2-en-1-one ***(1h)***

Known compound, but unreported characterization data.[21] Using General Procedure A, compound **1h** was isolated. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.68 (1H, d, J = 4 Hz), 8.47 (1H, d, J = 8.5 Hz), 8.01 (1H, d, J = 8 Hz), 7.93-7.85 (3H, m), 7.73-7.70 (1H, m), 7.66-7.53 (4H, m), 7.47 (1H, d, J = 8 Hz), 7.29-7.27 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.2, 153.2, 150.2, 143.9, 136.8, 136.5, 133.9, 132.1, 130.6, 130.3, 128.5, 127.9, 127.6, 126.5, 125.7, 124.9, 124.5, 124.4. Mass spectrum (low resolution, EI): 258 [M^+], 230, 181, 127, 104, 78, 51. HRMS calculated for $C_{18}H_{14}NO$, 260.1075 (MH^+). Found 260.1062.

4.5. (E)-1-Phenyl-3-(pyrazin-2-yl)prop-2-en-1-one ***(1i)***

1-Phenylprop-2-yn-1-ol (159 mg, 1.2 mmol), 2-iodopyrazine (205 mg, 1 mmol), triethyl amine (0.2 mL), 1.5 mL THF are added in a 5mL microwave vial. The mixture is then degassed by an argon gas stream. To this solution, CuI (19 mg, 0.1 mmol) and palladium bis triphenylphosphine dichloride (70 mg, 0.1 mmol) is added, the vial is sealed, and placed in microwave reactor. The reaction is run for 15 min at 150 °C, after which the product mixture iss diluted with 10 mL of diethyl ether and washed with brine (10 mL). The aqueous phase is back extracted with diethyl ether (2 × 5 mL), the organic lextracts are combined, and dried over anhydrous $MgSO_4$. Removal of the solvent is followed by purification of the product with flash column chromatography (ethyl acetate:hexanes, 1:1) to provide aza-chalcone **1i** (99 mg, 0.47 mmol, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.68 (1H, d, J = 1.2 Hz), 8.59 (1H, t, J = 2.1 Hz), 8.52 (1H, d, J = 2.4 Hz), 8.15 (1H, d, J = 15.3 Hz), 8.03 (2H, t, J = 6.9 Hz), 7.75 (1H, d, J =15.3 Hz), 7.59-7.53 (1H, m), 7.49-7.44 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 189.6, 148.8, 145.8, 145.2, 144.8, 138.7, 137.4, 133.3,

128.72, 128.70, 127.5. HRMS calculated for $C_{13}H_{11}N_2O$, 211.0871 (MH^+). Found 211.0870.

*4.6. (E)-3-(Benzo[d]thiazol-2-yl)-1-phenylprop-2-en-1-one **(1j)***

Using General Procedure A, acetophenone (120 mg, 1 mmol) and 2-pyridinecarboxyaldehyde (163 mg, 1 mmol) in 25 mL of water provide aza-chalcone **1j** (164.5 mg, 0.62 mmol, 62%) as yellow solid; R_f = 0.56 (hexane: ethyl acetate, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.07 (1H, d, *J* = 8 Hz), 8.03 (2H, d, *J* = 8 Hz), 7.89 (2H, d, *J* = 7.5 Hz), 7.86 (1H, d, *J* = 8.5 Hz), 7.58 (1H, t, *J* = 7.5 Hz), 7.48 (3H, t, *J* = 7.5 Hz), 7.40 (1H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 189.1, 163.8, 154.0, 137.2, 135.9, 135.4, 133.4, 128.8, 128.7, 128.6, 126.9, 126.5, 124.0, 121.8. Mass spectrum (low resolution, EI): 265 [M^+], 236, 160, 116, 105, 77, 51. HRMS calculated for $C_{16}H_{11}NOS$, 266.0640 (MH^+). Found 266.0636.

*4.7. 3-(2-Pyridyl)-1-indanone **(2)***

Using General Method B, aza-chalcone **1a** (209.1 mg, 1 mmol) provides indanone **2** (198.6 mg, 0.95 mmol, 95%). Alternatively, General Method C also provides indanone **2**. Thus, aryclic acid **15** (149.1 mg, 1 mmol) provides indanone **2** (186.1 mg, 0.89 mmol, 89%) as yellow solid, R_f = 0.5 (hexane: ethyl acetate, 1: 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.53 (1H, dd, *J* = 1.8, *J* = 5.7 Hz), 7.80 (1H, d, *J* = 7.5 Hz), 7.64 (1H, td, *J* = 1.8, *J* = 9.3 Hz), 7.55 (1H, td, *J* = 1.2, *J* = 7.5 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 7.28 (1H, dd, *J* = 0.9, *J* = 7.8 Hz), 7.18-7.14 (2H, m), 4.77-4.73 (1H, m), 3.23-3.14 (1H, m), 3.03-2.95 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.7, 162.1, 156.6, 149.9, 136.9, 136.7, 134.9, 128.0, 126.5, 123.7, 122.1, 122.0, 46.5, 44.5. Mass spectrum (low resolution, EI): 209 [M^+], 180, 152, 131, 77, 51. HRMS calculated for $C_{14}H_{12}NO$, 210.0919 (MH^+). Found 210.0910.

*4.8. 3-(3-Pyridinyl)-1-indanone **(3)***

Using General Method B, aza-chalcone **1b** (209.1 mg, 1 mmol) provides indanone **3** (194.3 mg, 0.93 mmol, 93%). Alternatively, General Method C also provides indanone **3**, Thus, aryclic acid **12** (149.1 mg, 1 mmol) provides indanone **3** (192.3mg, 0.92 mmol, 92%) as a yellow oil. R_f = 0.3 (hexane: ethyl acetate, 1: 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.51 (2H, s), 7.79 (1H, d, *J* = 7.5 Hz), 7.57 (1H, td, *J* = 0.9, *J* = 7.5 Hz), 7.43 (1H, t, *J* = 7.5 Hz), 7.32 (1H, t, *J* = 5.7 Hz), 7.27-7.19 (3H, m), 4.62-4.59 (1H, m), 3.29-3.22 (1H, m), 2.67-2.59 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.8, 156.6, 149.3, 148.6, 139.2, 136.8, 135.3, 134.7, 128.3, 126.7, 129.6, 46.4, 41.8. Mass spectrum (low resolution, EI): 209 [M^+], 180, 152, 131, 103, 77, 51. HRMS calculated for $C_{14}H_{12}NO$, 210.0919 (MH^+). Found 210.0908.

*4.9. 3-(4-Pyridyl)-1-indanone **(4)***

Using General Method B, aza-chalcone **1a** (209.1 mg, 1 mmol) provides indanone **4** (194.3 mg, 0.93 mmol, 93%). Alternatively, General Method C also provides indanone **4**. Thus, aryclic acid **16** (149.1 mg, 1 mmol) provides indanone **4** (192.3 mg, 0.92 mmol, 92%) as yellow oil. R_f = 0.6 (hexane: ethyl acetate, 1: 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.53 (2H, d, *J* = 5.7 Hz), 7.82 (1H, d, *J* = 7.5 Hz), 7.59 (1H, td, *J* = 0.9, *J* = 7.5 Hz), 7.45 (1H, t, *J* = 6 Hz), 7.26 (2H, d, *J* = 8.1 Hz), 7.05 (2H, d, *J* = 6 Hz), 4.58-4.53 (1H, m), 3.27-3.18 (1H, m), 2.68-2.60 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.5, 155.9, 152.4, 150.3, 136.8, 135.3, 128.4, 126.7, 123.7, 122.8, 45.9, 43.7. Mass spectrum (low resolution, EI): 209 [M^+], 180, 131, 103, 77, 51. HRMS calculated for $C_{14}H_{12}NO$, 210.0919 (MH^+). Found 210.0918.

*4.10. 3-(6-Bromo-2-pyridyl)-1-indanone **(5)***

Using General Method B, aza-chalcone **1d** (289.0 mg, 1 mmol) provides indanone **5** (257.2 mg, 0.89 mmol, 89%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.79 (1H, d, *J* = 7.5 Hz), 7.57 (1H, t, *J* = 7.2 Hz), 7.51-7.39 (2H, m), 7.34 (2H, t, *J* = 8.4 Hz), 7.03 (1H, *J* = 7.5 Hz), 4.77-4.73 (1H, m), 3.23-3.14 (1H, m), 2.98-2.90 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 205.0, 163.8, 155.6, 142.0, 139.2, 136.7, 135.0, 128.3, 126.5, 123.8, 120.6, 46.1, 44.3. Mass spectrum (low resolution, EI): 287 [M+], 260, 210, 180, 105, 77, 51. HRMS calculated for $C_{14}H_{11}BrNO$, 288.0024 (MH^+). Found 288.0021.

*4.11. 5-Bromo-3-(2-pyridyl)-1-indanone **(6)***

Using General Method B, aza-chalcone **1e** (289.1 mg, 1 mmol) provides indanone (**6**) (130 mg, 0.45 mmol, 45%) as a light yellow solid, MP =119-121 °C, R_f = 0.45 (hexane: ethyl acetate, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 8.58 (1H, s), 7.72 (1H, s), 7.69 (1H, d, *J* = 8.5 Hz), 7.57 (1H, d, *J* = 8.5 Hz), 7.47 (1H, s), 7.28-7.21 (2H, m), 4.75 (1H, t, *J* = 3.5 Hz), 3.21-3.17 (1H, m), 3.07-3.03 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ =204.2, 161.2, 158.1, 150.1, 137.1, 135.6, 131.7, 130.2, 129.8, 124.9, 122.3, 122.3, 46.2, 44.4. Mass spectrum (low resolution, EI): 289 [M+], 258, 155, 132, 104, 78, 51. HRMS calculated for $C_{14}H_{11}BrNO$, 288.0024 (MH^+). Found 288.0011.

*4.12. 5-Methyl-3-(2-pyridyl)-1-indanone **(7)***

Using General Method B, aza-chalcone **1f** (223 mg, 1mmol) provides indanone **7** as dark orange solid (180 mg, 0.81 mmol, 81%), MP: 102-104 °C, R_f = 0.38 (hexane: ethyl acetate, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.55 (1H, d, *J* = 4.5 Hz), 7.70 (1H, d, *J* = 8 Hz), 7.67-7.63 (1H, m), 7.21 (1H, d, *J* = 7.5 Hz), 7.18-7.14 (2H, m), 7.08 (1H, s), 4.72-4.69 (1H, m), 3.19-3.13 (1H, m), 3.00-2.95 (1H, m), 2.37 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 205.2, 162.3, 157.1, 149.9, 146.1, 136.9, 134.5, 129.3, 126.7, 123.5, 122.1, 122.0, 46.4, 44.7, 22.1. Mass spectrum (low resolution, EI): 223 [M+], 194, 115, 89, 78, 51. HRMS calculated for $C_{15}H_{14}NO$, 224.1075 (MH^+). Found 224.1065.

*4.13. trans-2-Methyl-3-(2-pyridyl)-1-indanone **(8)***

Using General Method B, aza-chalcone **1g** (224 mg, 1 mmol) provided indanone **8** (170.2 mg, 0.76 mmol, 76%) as an oil. R_f = 0.36 (hexane: ethyl acetate/ 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.59 (1H, dd, *J* = 2, *J* = 5.5 Hz), 7.82 (1H, d, *J* = 8 Hz), 7.72-7.68 (1H, m), 7.57 (1H, td, *J* = 1, *J* = 8.5 Hz), 7.42 (1H, t, *J* = 7.5 Hz), 7.23-7.21 (3H, m), 4.26 (1H, d, *J* = 5 Hz), 3.03-2.97 (1H, m), 1.41 (3H, d, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 207.7, 161.5, 154.9, 149.7, 136.9, 136.2, 134.9, 128.1, 126.2, 123.8, 122.8, 122.2, 55.6, 51.3, 14.3. Mass spectrum (low resolution, EI): 223 [M+], 208, 194, 180, 167, 115, 78, 51. HRMS calculated for $C_{15}H_{14}NO$, 224.1075 (MH^+). Found 224.1067.

*4.14. 3-(Pyridin-2-yl)-2,3-dihydro-1H-cyclopenta[a]naphtha-len-1-one **(9)***

Using General Method B, aza-chalcone **1h** (259 mg, 1mmol) provides ketone **9** (238 mg, 0.92mmol, 92%) as yellow solid, MP: 115-117 °C, R_f = 0.48 (hexane: ethyl acetate/ 1:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.21 (1H, d, *J* = 8.5 Hz), 8.52 (1H, d, *J* = 4.5 Hz), 7.94 (1H, d, *J* = 8.5 Hz), 7.82 (1H, d, *J* = 8 Hz), 7.65 (1H, t, *J* = 7 Hz), 7.61-7.59 (1H, m), 7.53 (1H, t, *J* = 8 Hz), 7.27 (1H, d, *J* = 8.5 Hz), 7.13 (2H, t, *J* = 5 Hz), 4.77-4.75 (1H, m), 3.28-3.23 (1H, m), 3.08-3.03 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 206.2, 161.9, 159.3, 149.9, 136.9, 136.0, 132.8, 130.8, 129.2, 129.0, 128.1, 126.9, 124.3, 123.5, 122.3, 122.1, 46.5, 45.2. Mass spectrum (low resolution, EI): 259 [M+], 230, 152, 126, 78, 51. HRMS calculated for $C_{18}H_{14}NO$, 260.1075 (MH^+). Found 260.1072.

*4.15. 3-(2-Pyrazinyl)-1-indanone **(10)***

Using General Method B, aza-chalcone **1i** (210 mg, 1mmol) provides indanone **10** (182.8 mg, 0.87 mmol, 87%) as brown oil. R_f = 0.16 (hexane: ethyl acetate/ 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.63 (1H, s), 8.54 (2H, s), 7.86 (1H, d, *J* = 8 Hz), 7.61 (1H, td, *J* = 1.5, *J* = 7.5 Hz), 7.47 (1H, t, *J* = 7.5 Hz), 7.30 (1H, dd, *J* = 1, *J* = 8 Hz), 4.83 (1H, dd, *J* = 4, *J* = 8 Hz), 3.22 (1H, dd, *J* = 8, *J* = 10.5 Hz), 3.05 (1H, dd, *J* = 4, *J* = 15 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 204.8, 155.3, 144.8, 143.8, 143.4, 136.7, 135.1, 128.4, 126.3, 123.9, 43.9, 43.8. Mass spectrum (low resolution, EI): 210 [M+], 181, 127, 102, 77, 51. HRMS calculated for $C_{13}H_{11}N_2O$, 211.0871 (MH^+). Found 211.0869.

*4.16. 3-(2-Benzthiazolyl)-1-indanone **(11)***

Using General Method B, aza-chalcone **1j** (264 mg, 1 mmol) provided indanone **11** as yellow solid (250 mg, 0.95 mmol, 95%), MP: 139-143 °C R_f = 0.47 (hexane: ethyl acetate, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (1H, d, *J* = 8.4 Hz), 7.85 (2H, t, *J* = 6.6 Hz), 7.65-7.61 (2H, m), 7.53-7.47 (2H, m), 7.41-7.36 (1H, m), 5.18-5.16 (1H, m), 3.41-3.32 (1H, m), 3.22-3.14 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 203.6, 172.4, 153.9, 153.1, 136.4, 135.2, 135.0, 128.9, 126.9, 126.3, 125.3, 123.9, 123.0, 121.7, 44.3, 43.2. Mass spectrum (low resolution, EI): 265 [M+], 236, 103, 77, 63, 51. HRMS calculated for $C_{16}H_{11}NOS$, 266.0640 (MH^+). Found 266.0633.

*4.17. 3-(1H-Imidazol-4-yl)-1-indanone **(14)***

Using General Method C, acrylic acid derivative **13** (138 mg, 1 mmol) provides indanone **14** (126.7 mg, 0.64 mmol, 64%) as yellow oil, R_f = 0.4 (ethyl acetate: methanol, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ =7.75 (1H, d, *J* = 7.5 Hz), 7.62 (1H, t, *J* = 8 Hz), 7.53 (1H, s), 7.49 (1H, d, *J* = 8 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 6.79 (1H, s), 4.69-4.66 (1H, m), 3.19-3.14 (1H, m), 2.88-2.83 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 205.9, 156.6, 136.6, 135.4, 134.9, 128.5, 128.4, 127.9, 126.6, 123.5, 44.7, 37.3. HRMS calculated for $C_{12}H_{11}N_2O$, 199.0871 (MH^+). Found 199.0864.

*4.18. 3-(Pentafluorophenyl)-1-indanone **(18)***

Using General Method C, pentafluorocinnamic acid **17** (238.2 mg, 1 mmol) provides indanone **18** (271.3 mg, 0.91 mmol, 91%) as white solid, MP = 101-103, R_f= 075 (hexane: ethyl acetate, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.84 (1H, d, *J* = 7.5 Hz), 7.64-7.60 (1H, m), 7.47 (1H, t, *J* = 7.5 Hz), 7.27 (1H, d, *J* = 7.5 Hz), 5.01-4.99 (1H, m), 3.24-3.19 (1H, m), 2.86-2.82 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 203.4, 154.1, 136.3, 135.3, 128.5, 125.5, 123.9, 43.0, 33.0, and 146-116 (pentafluorophenyl multiplets). Mass spectrum (low resolution, EI): 298 [M+], 250, 219, 201, 131, 76, 50. HRMS calculated for $C_{15}H_{18}F_5O$, 299.0495 (MH^+). Found 299.0501.

*4.19. Dichloro-3-(pyridin-2-yl)-2,3-dihydro-1H-inden-1-one **(24a,b)***

Using General Procedure B, aza-chalcone **1l** (0.28 g, 1 mmol) provides indanone **24** as an inseparable mixture of regioisomers (**24a,b**, 128 mg, 0.46 mmol, 46%). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ 8.48 (dd, J= 5.38 Hz, J= 1.52 Hz, 1H), 8.43 (dq, J= 3.98 hz, J= 0.78 Hz, 1H), 7.79 (s, 1H), 7.65-7.54 (m, 3H), 7.49 (d, J= 8.07 Hz, 1H), 7.32 (d, J= 0.85 Hz, 1H), 7.19 (s, 1H), 7.16-7.12 (m, 2H), 7.08 (qd, J= 2.72 Hz, J= 1.06 Hz, 2H), 4.76 (dd, J= 8.25 Hz, J= 2.63 Hz, 1H), 4.63 (dd, J= 7.89 hz, J= 4.06 Hz, 1H), 3.20-3.08 (m, 2H), 2.98 (dd, J= 18.90 Hz, J= 4.20 Hz, 1H), 2.77 (dd, J= 18.90 hz, J= 2.80 Hz, 1H). ; ^{13}C NMR (300 MHz, $CDCl_3$, 25 ºC): δ 203.43, 202.99, 160.71, 155.34, 154.76, 150.17, 149.93, 139.74, 139.36, 137.61, 137.18, 136.73, 136.29, 133.29, 131.56, 130.96, 128.47, 125.17, 122.98, 122.48, 122.36, 122.26, 122.05, 46.11, 45.77, 45.72, 44.61. High-Resolution MS (EI) (M+H), calcd for $C_{14}H_{10}NOCl_2$, 278.0139, found, 278.0137.

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5. Experimental

The paper must include the following: (1) Introduction, (2) Results/Discussion, (3) Conclusion, (4) Experimental Section and (5) References. Supplementary data and other sections are optional. You will usually want to divide your article into (numbered) sections and subsections (perhaps even subsubsections). Code section headings using the options in the 'Styles' menu. Headings should reflect the relative importance of the sections. Note that text runs on after a 4th order heading. Use the heading style for the whole paragraph, but remove the italic coding except for the actual heading.

Ensure that all tables, figures and schemes are cited in the text in numerical order. Trade names should have an initial capital letter, and trademark protection should be acknowledged in the standard fashion, using the superscripted characters for trademarks and registered trademarks respectively. All measurements and data should be given in SI units where possible, or other internationally accepted units. Abbreviations should be used consistently throughout the text, and all nonstandard abbreviations should be defined on first usage. Authors are requested to draw attention to hazardous materials or procedures by adding the word CAUTION followed by a brief descriptive phrase and literature references if appropriate. The experimental information should be as concise as possible, while containing all the information necessary to guarantee reproducibility.

Acknowledgments

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10. Aza-chalcones in this study: **1a**, R_1=H, R_2=H, R_3= 2-pyridyl; **1b**, R_1=H, R_2=H, R_3= 3-pyridyl; **1c**, R_1=H, R_2=H, R_3= 4-pyridyl; **1d**, R_1=H, R_2=H, R_3= 2-(6-bromopyridyl); **1e**, R_1=4-bromophenyl, R_2=H, R_3= 2-pyridyl; **1f**, R_1=4-tolyl, R_2=H, R_3= 2-pyridyl; **1g**, R_1=H, R_2=methyl, R_3= 2-pyridyl; **1h**, R_1=1-naphyl, R_2=H, R_3= 2-pyridyl; **1i**, R_1=H, R_2=H, R_3= 2-pyrazinyl; **1j**, R_1=H, R_2=H, R_3= 2-benzothiazolyl; **1k**, R_1=4-chlorophenyl, R_2=H, R_3= 2-pyridyl; **1l**, R_1=3,4-dichlorophenyl, R_2=H, R_3= 2-pyridyl; **1m**, R_1=4-nitrophenyl, R_2=H, R_3= 2-pyridyl.
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Supplementary Material

^{1}H and ^{13}C NMR spectra for new compounds.

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