Synthesis of Isoquinoline-3-Carboxylates and Benzocyclobutanes via Reaction of 2-Amidoacrylate Esters with Arynes

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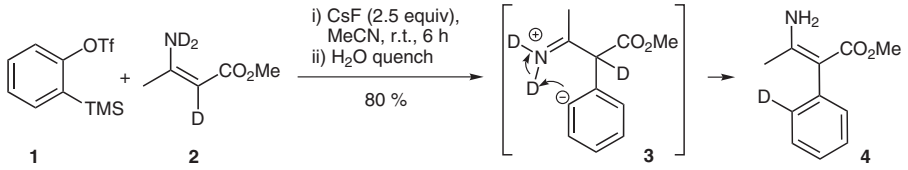
Abstract: A mild and general method for the synthesis of a variety of 2-substituted isoquinoline 3-carboxylates and benzocyclobutanes from the reaction of 2-amidoacrylate esters with arynes has been developed.

Key words: arynes, isoquinoline heterocycles, benzocyclobutanes, annulations, 2-amidoacrylate esters

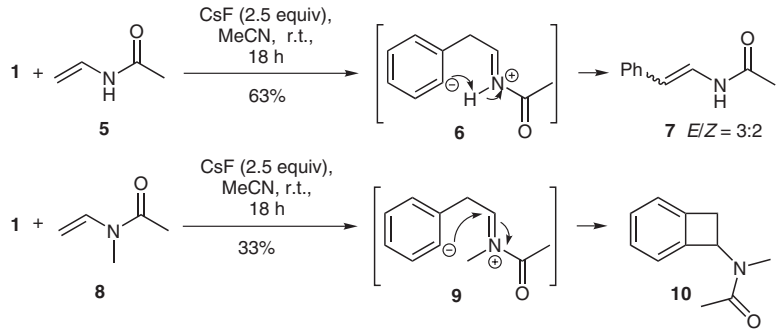
In recent years, the use of arynes to generate 1,2-functionalized arenes has seen a growing interest in the field of organic synthesis.[1,2] This emergence of aryne chemistry is largely due to the development of a mild and general method for generating arynes from *ortho*-silyl aryltriflates and fluoride anion.[3] Due to its electrophilicity, a wide variety of anionic and uncharged nucleophiles readily add to arynes to generate substituted arenes. Typical examples include addition of amines, sulfonamides, carbamates, phenols, carboxylic acids,[4] β-ketoesters,[5] malonate esters,[6] and α-cyanocarbonyl compounds.[7] We recently reported an efficient method for the C-arylation of β-enamino esters and ketones[8] with benzyne precursor **1** (Scheme 1). Using deuterium labeling experiments we showed that the reaction with trideuterated β-enamino ester **2** proceeded via an intramolecular deuterium transfer of the zwitterionic species **3** to generate the *ortho*-deuterated aryl product **4**.

While investigating the substrate scope of this reaction, we observed that simple *N*-vinyl amides react with the benzyne precursor **1**, presumably via the zwitterionic intermediate **6** to produce a mixture of *E*- and *Z*-arylated product **7** (3:2 ratio) in 63% yield (Scheme 2). Interestingly, when the N–H proton is replaced by a methyl **8**, the anion **9** adds to the iminium carbon to generate the benzocyclobutane product **10** in a low yield of 33% together with unreacted starting material **8**.

We envisioned that if the N–H proton of **5** is made sufficiently acidic so that it is deprotonated by cesium fluoride, then instead of protonation, the intermediate anion could react with the amide carbonyl to generate annulated aromatic ring systems. To this end, 2-phenylacetamidoacrylate ester **11a** (Scheme 3) was reacted with benzyne precursor **1** at 80 °C and we were pleased to see that iso-



Scheme 1



Scheme 2

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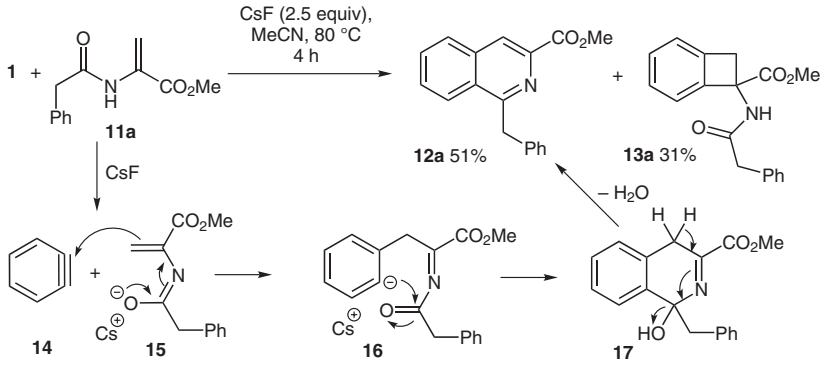
DOI: 10.1055/s-2008-1072723; Art ID: S00208ST

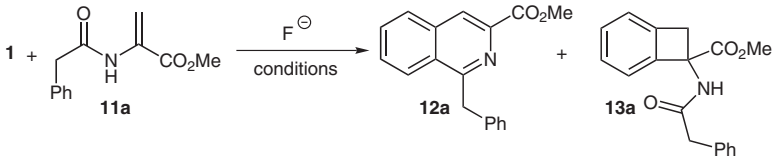


Scheme 3

quinoline-3-carboxylate[9] **12a** and benzocyclobutane **13a** were isolated in 51% and 31% yield, respectively. We hypothesize that the reaction proceeds via an initial nucleophilic addition of acrylate anion **15** onto benzyne **14** to generate intermediate **16**. Subsequent electrophilic cyclization on the carbonyl generates hemi-aminal intermediate **17**, which after dehydration would afford isoquinoline **12a**. Alternatively, the anion **16** could also react at the imine carbon thereby generating the benzocyclobutane **13a**. The possibility of benzocyclobutane **13a** being an intermediate in the reaction could be ruled out because treatment of **13a** under the reaction conditions in the presence of cesium fluoride, base (cesium carbonate) or acid (trifluoroacetic acid) did not produce any isoquinoline **12a**. Although simple unsubstituted isoquinolines are known to react with benzyne at the nitrogen position followed by a subsequent reaction with acetonitrile,[10] it should be noted that no such reaction was observed in our case, presumably due to the 1,3-substituents which make the nitrogen atom more hindered and less reactive.

The isoquinoline **12a** and benzocyclobutane **13a** can be separated by flash column chromatography over silica gel using a gradient elution of ethyl acetate and hexanes. Interestingly, after isolation of product **12a** and **13a**, we observed that an additional 10% of the isoquinoline **12a** (Table 1, entry 1) was isolated when the silica gel column was flushed with a more polar solvent system, such as 100% ethyl acetate. The amount of this additional product **12a** gradually increases from 10% to 23% with decreasing temperature (80 °C to r.t., entries 1–4). We speculate that this additional product might be derived from a polar intermediate such as the hemi-aminal derivative **17**, which

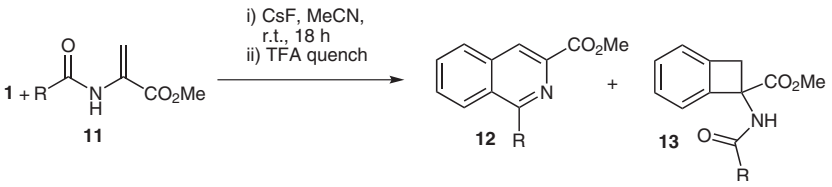
Table 1 Optimization of Reaction Conditions[a]

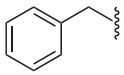
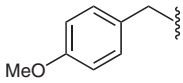
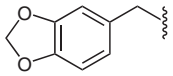
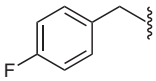
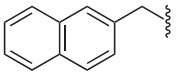
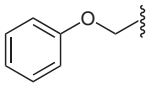
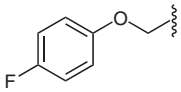
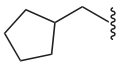


Entry	Solvent	F^- Source	Temp (°C)	Time (h)	Reaction quench	Yield of **12a** (%)[b]	Yield of **13a** (%)[b]
1	MeCN	CsF	80	4	H_2O	51 + 10[c]	31
2	MeCN	CsF	60	4	H_2O	48 + 12[c]	27
3	MeCN	CsF	40	6	H_2O	46 + 15[c]	23
4	MeCN	CsF	r.t.	18	H_2O	42 + 23[c]	21
5	MeCN	CsF	6	18	H_2O	41 + 17[c]	18
6	MeCN	CsF	r.t.	18	HCl (1 N)	60 + 3[c]	23
7	MeCN	CsF	r.t.	18	TFA[d]	64	24
8	THF	CsF	r.t.	18	TFA[d]	12	2
9	THF	TBAF	r.t.	4	TFA[d]	25	13
10	THF	KF/18-C-6	r.t.	18	TFA[d]	45	16

[a] Reaction conditions: *o*-silyl aryltriflate **1** (0.5 mmol), acrylate **11a** (0.4 mmol), and fluoride source (1 mmol) in 0.2 M solvent in a sealed vial.
[b] Isolated yield.
[c] Additional product **12a** isolated after flushing SiO_2 column with 100% EtOAc.
[d] Five equivalents of TFA were used.

Table 2 Reaction of Substituted 2-Amidoacrylate Esters with Benzyne[a,15]

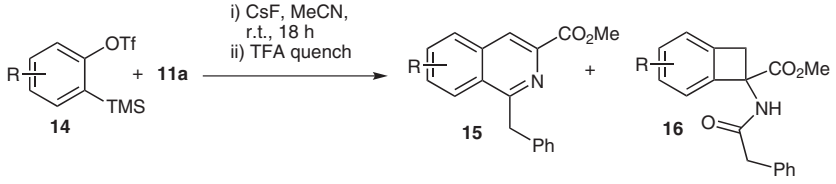


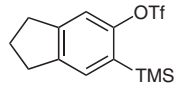
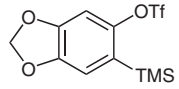
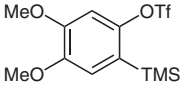
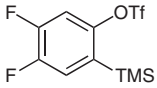
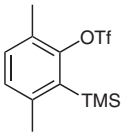
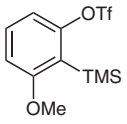
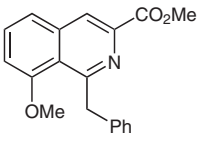
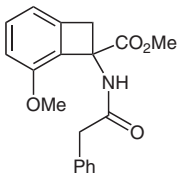
Entry	R of **11**	Yield of **12** (%)[b]	Yield of **13** (%)[b]
1	 **11a**	64	24
2	 **11b**	59	21
3	 **11c**	64	22
4	 **11d**	62	18
5	 **11e**	51	21
6	 **11f**	66	25
7	 **11g**	69	24
8	 **11h**	56	22
9	 **11i**	42	12
10	 **11j**	66	22
11	 **11k**	42	11

[a] Reaction conditions: *o*-silyl aryltriflate **1** (0.5 mmol), acrylate **11** (0.4 mmol), and CsF (1 mmol) in 0.2 M MeCN in a sealed vial stirred at r.t. for 18 h then quench with TFA (2 mmol).
[b] Isolated yield.

slowly dehydrates over the slightly acidic silica gel. So, by quenching the reaction mixture with acid (1 N HCl or TFA, entries 6 and 7) we were able to convert almost all the suspected polar intermediate **17** into isoquinoline **12a**. In addition, a slight decrease in the amount of benzocyclobutane **13a** was observed (from 31% to 23%) as the temperature is lowered from 80 °C to room temperature (entries 1–4). Further temperature lowering had no additional improvement on the yield or selectivity of the reaction. However, using THF as the solvent with CsF and other reported sources of fluoride for generating aryne

Table 3 Reaction of 2-Phenylacetamidoacrylate Ester **11a** with Substituted Benzyne[a]



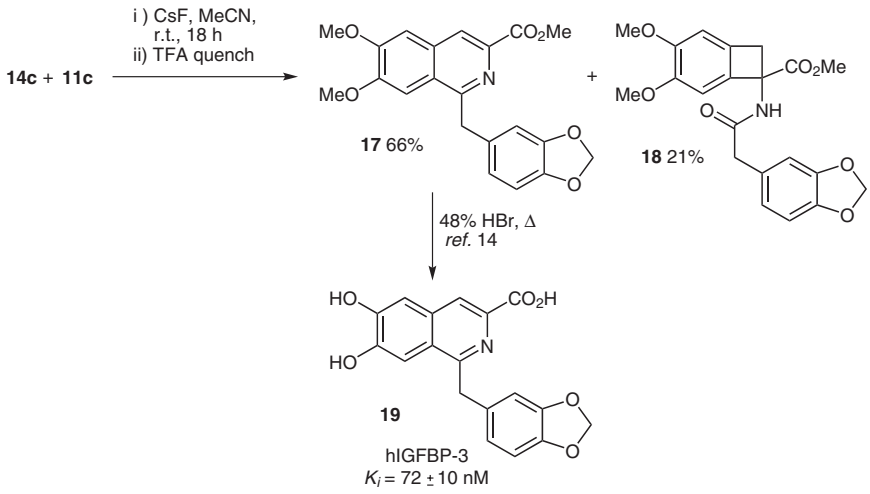
Entry	R of **14**	Yield of **15** (%)[b]	Yield **16** (%)[b]
1	 **14a**	40	11
2	 **14b**	52	20
3	 **14c**	66	22
4	 **14d**	28	9
5	 **14e**	11	14
6[c]	 **14f**	 **15f**, 52%	 **16f**, 16%

[a] Reaction conditions: *o*-silyl aryltriflate **14** (0.5 mmol), acrylate **11a** (0.4 mmol), and CsF (1 mmol) in 0.2 M MeCN in a sealed vial stirred at r.t. for 18 h then quench with TFA (2 mmol).
[b] Isolated yield.
[c] Structure of products was determined by NOE.

such as TBAF[3] or KF/18-crown-6[11] had a deleterious effect on the yield (entries 8–10).

With the optimal condition set at room temperature (Table 1, entry 7), we began investigating the substrate scope with a variety of substituted 2-amidoacrylate esters **11a–k** (Table 2) which can readily be accessed over two steps starting from serine methyl ester.[12] A variety of aromatic substrates substituted with electron-donating and electron-withdrawing groups worked well, affording good yield of the isoquinoline products (entries 2–4). Even bulky substituent such as naphthalene (entry 5) is tolerated giving a reasonable yield of the corresponding isoquinoline. Substrates substituted with a phenoxy group also afforded good yield of the isoquinoline products (entries 6 and 7). Aliphatic substitutions on the substrates can also be accommodated (entries 9–11). However, one limitation is the stability of some of the acrylates such as **11e** and **11k** which tend to polymerize on standing and they had to be used right away after synthesis. This might explain the slightly lower yield of the corresponding isoquinoline product (entries 5 and 11).

We next examined the annulation of substituted arynes with 2-phenylacetamidoacrylate ester (**11a**). As shown in Table 3, reaction with arynes bearing an electron-donating group works well giving good yield of the corresponding isoquinolines (entries 2 and 3). However, arynes with electron-withdrawing group (entry 4) gave a low yield the isoquinoline product, presumably due to the high electrophilicity and reactivity of the aryne which makes the reaction nonselective. When 3,6-dimethyl-substituted aryne



Scheme 4

precursor **14e** was used, a poor yield of the desired isoquinoline product was isolated (entry 5) which might be due to steric hindrance of the two methyl substituents. Finally, reaction with unsymmetrical benzyne precursor **14f** proceeded with high regioselectivity affording the corresponding isoquinoline **15f** and benzocyclobutane **16f**. This regioselectivity which is presumably due to steric and electronic effect of the methoxy group has been reported previously[13] and it further substantiates a benzyne mechanism rather than a [4+2]- or [2+2]-cycloaddition mechanism leading to isoquinoline **15f** and benzocyclobutane **16f**, respectively.

To demonstrate the usefulness of this methodology for rapid analogue synthesis of biologically active compounds, we have used this reaction in the formal synthesis of a potent insulin-like growth-factor (IGF) inhibitor **19** (K_i = 72 ± 10 nM)[14] that inhibits the binding of IGF to human-IGF binding protein-3 (hIGFBP-3). As shown in Scheme 4, reaction of acrylate **11c** with benzyne precursor **14c** proceeded smoothly to afford isoquinoline **17** together with benzocyclobutane **18** in 66% and 21% yield, respectively. The isoquinoline **17** could be demethylated with 48% HBr to produce inhibitor **19** as reported previously.[14]

In summary, we have developed a mild and general method for the synthesis of 2-substituted isoquinoline 3-carboxylates and benzocyclobutanes from the reaction of 2-amidoacrylate esters with arynes. The reaction presumably proceeds via a nucleophilic addition of the acrylate to the aryne followed by an electrophilic cyclization and a final dehydration to generate the isoquinoline. This methodology provides a facile and direct access to a variety of biologically interesting substituted isoquinoline 3-carboxylates. Further studies to expand the substrate scope are in progress.

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(15) **Representative Experimental Procedure**
To a mixture of methyl 2-acetamidoacrylate (**11j**, 57.3 mg, 0.4 mmol, 1 equiv) and CsF (152 mg, 1 mmol, 2.5 equiv) in dry MeCN (2 mL, 0.2 M) was added *o*-silyl aryltriflate (**1**) (121 μL, 0.5 mmol, 1.25 equiv) in an oven-dried 4 mL glass vial. The vial was capped under nitrogen and the mixture was stirred at r.t. overnight (ca. 18 h). The reaction mixture was quenched with HCl (1 N) or TFA (154 μL, 2 mmol, 5 equiv) and the solvent was evaporated. The residue was diluted with $NaHCO_3$ (2 mL, 5%) and extracted with EtOAc (3 × 1 mL). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by CombiFlash chromatography (ISCO) on silica gel column using a gradient elution of 30–80% EtOAc–hexanes to afford methyl 1-methylisoquinoline-3-carboxylate (**12j**) and methyl 7-(acetylamino)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate (**13j**).
Methyl 1-methylisoquinoline-3-carboxylate (**12j**): solid (53 mg, 66%). ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.38 (s, 1 H), 8.23 (d, *J* = 8.23 Hz, 1 H), 8.07 (d, *J* = 8.03 Hz, 1 H), 7.84–7.74 (m, 2 H), 3.93 (s, 3 H), 2.94 (s, 3 H). ^{13}C NMR (126 MHz, acetone-d_6): δ = 22.4, 52.4, 123.0, 126.5, 129.4, 129.5, 130.2, 131.5, 136.3, 141.6, 159.6, 166.7. HRMS (ESI, MH^+): *m/z* calcd for $C_{12}H_{12}NO_2$: 202.0862; found: 202.0863.
Methyl 7-(acetylamino)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate (**13j**): solid (19 mg, 22%). ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.38 (s, 1 H), 7.33–7.28 (m, 1 H), 7.25–7.14 (m, 3 H), 3.91 (d, *J* = 14.18 Hz, 1 H), 3.62 (s, 3 H), 3.24 (d, *J* = 14.18 Hz, 1 H), 1.92 (s, 3 H). ^{13}C NMR (126 MHz, acetone-d_6): δ = 22.2, 43.2, 52.5, 64.1, 123.3, 124.2, 128.2, 130.4, 144.1, 144.9, 170.9, 171.9. ^{1}H–^{1}H COSY (500 MHz, acetone-d_6): correlation of the cyclobutane methylene protons at δ = 3.62 and 3.24. ^{1}H–^{13}C HMQC (500 MHz, acetone-d_6): correlation of the cyclobutane methylene protons at δ = 3.62 and 3.24 with the methylene carbon at δ = 43.2. HRMS (ESI, MH^+): *m/z* calcd for $C_{12}H_{14}NO_3$: 220.0968; found: 220.0971.