

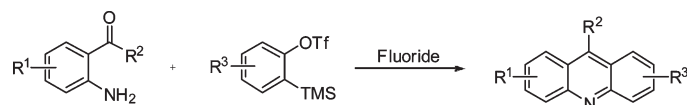
Synthesis of Acridines by the [4 + 2] Annulation of Arynes and 2-Aminoaryl Ketones

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Received January 21, 2010



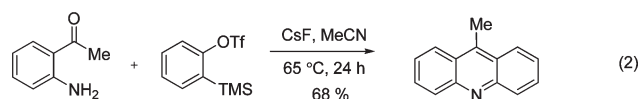
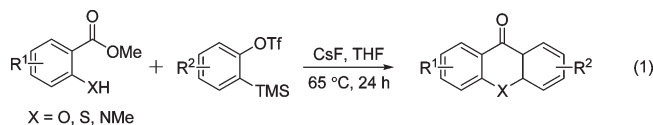
The reaction of 2-aminoaryl ketones and arynes generated by the treatment of various *o*-(trimethylsilyl)aryl triflates with CsF results in [4 + 2] annulation to afford substituted acridines in good yields.

Introduction

The use of arynes as building blocks in the construction of heteroaromatic structures has become increasingly popular in recent years.¹ The electrophilic coupling of arynes, in particular, as opposed to transition-metal-catalyzed or pericyclic reactions, has produced a number of very useful syntheses of biologically active heteroaromatics, including indoles,² benzofurans,³ quinoxalines,⁴ thiazines,³ oxazines,³ benzotriazoles,⁵ benzoxazines,⁶ clavilactones,⁷ indoloquinones,⁸ carbazoles,⁹ dibenzofurans,⁹ dibenzothiophenes,⁹ and phenanthridines.¹⁰

Recently, our group reported the reaction of arynes and *ortho*-heteroatom-substituted benzoates, which affords medicinally relevant acridones, xanthenes, and thioxanthenes in good overall yields under very mild reaction conditions (eq 1).¹¹ The success of this novel methodology led us to examine the corresponding *ortho*-substituted

ketones and aldehydes. Using similar mild conditions, it was initially found that 2-aminoacetophenone and *o*-(trimethylsilyl)phenyl triflate react to produce 9-methylacridine in a 68% yield (eq 2).



Acridines have demonstrated important biological activity,¹² including activity against cancer¹³ due to their ability to intercalate into DNA and disrupt unwanted cellular processes.¹⁴ This unique property of acridines has been exploited in many areas of medicine. As a result, significant biological activity toward viruses,¹⁵ bacteria,¹⁶ parasites,¹⁷ fungus,¹⁸ Alzheimer's disease,¹⁹ and HIV/AIDS²⁰ has also been reported.

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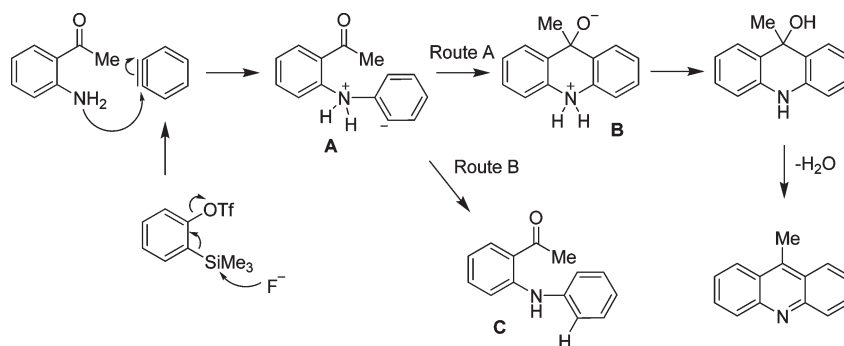
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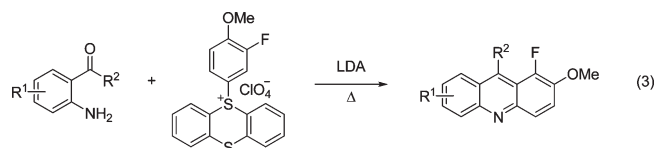
SCHEME 1. Proposed Mechanism



9-Methylacridines have also been used recently in the construction of new fluorescent probes that emit light at longer wavelengths in order to inhibit unwanted absorption, autofluorescence, and scattering by neighboring biological tissue.²¹ Acridines complexed with iridium have also been used as triplet state, light emitting materials for applications in OLEDs.²²

Most of the current methods to synthesize acridines require rather harsh conditions. For example, intramolecular versions of the original acridine synthesis, the Bernthsen reaction,²³ continue to employ high temperatures and strongly acidic media.²⁴ Another commonly used method for preparing acridines involves the reduction of acridones.²⁵ However, until our recent report (eq 1), the syntheses of acridones have also required high temperatures and strongly acidic conditions to affect intramolecular electrophilic aromatic substitution of *N*-phenylanthranilic acids.^{25a,26} Also published recently were the annulations of 2-oxoaryl azides and 2-azidobenzenecarbonitrile by benzene, giving rise to a variety of acridines, including 9-aminoacridine.²⁷

In 2005, Kim et al.²⁸ reported the synthesis of acridines using 5-arylthianthrenium perchlorates as benzyne precursors to affect [4 + 2] annulations with *ortho*-aminoaryl ketones, esters, and aldehydes (eq 3). Although the scope of this methodology appears fairly broad, and the yields are generally good, some drawbacks to this methodology are evident. Not only is there no commercial source for Kim's benzyne precursor, but its synthesis requires the use of a highly explosive salt, thianthrene cation radical perchlorate.²⁹ In addition, a strongly activated aryl substrate, such as anisole, is needed in order for the requisite electrophilic aromatic substitution to take place efficiently. Depending on the acridine's ultimate use, one may or may not want the fluorine and methoxy groups present in the final products. Lastly, in order to generate benzyne from a 5-arylthianthrenium perchlorate, a very strong base, such as LDA, is needed. These harsh conditions severely limit the types of functional groups, which can be accommodated. Our approach to acridines, however, utilizes Kobayashi's³⁰ very mild reaction conditions for generating benzyne in situ through fluorine-induced elimination of *o*-(trimethylsilyl)aryl triflates to affect annulation with commercially available *ortho*-aminoaryl ketones and aldehydes.



The reaction of *ortho*-aminoaryl carbonyl compounds and alkynes containing electron-withdrawing groups is a process analogous to our aryne methodology.³¹ First reported in the 1960s, this chemistry affords good yields of the corresponding 2,3,4-trisubstituted quinolines in one step (eq 4). As with our acridine synthesis, the initially formed secondary alcohol rapidly dehydrates and forms the more stable aromatic system. Because the acridine core is important in so many areas of chemistry and there are currently very few mild, functionally tolerant methodologies available for the efficient synthesis of acridines, it was our goal to investigate the scope of the process described in eq 2, first through optimization of the

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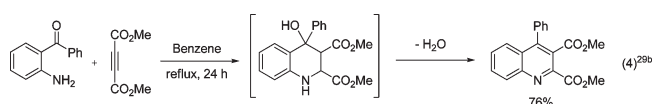
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TABLE 1. Optimization Studies^a

entry	aryne precursor (equiv)	fluoride (equiv) ^b	solvent (mL)	temp (°C)	% yield ^c
1	1.2	CsF (3)	MeCN (10)	65	70
2	1.4	CsF (3)	MeCN (10)	65	66
3	1.6	CsF (3)	MeCN (10)	65	52
4	1.2	CsF (2)	MeCN (10)	65	65
5	1.2	CsF (4)	MeCN (10)	65	62
7	1.2	CsF (3)	THF (10)	65	15
8	1.2	TBAT (3)	THF (10)	rt	52
9	1.4	TBAT (3)	THF (10)	rt	67
10	1.4	TBAT (2)	THF (10)	rt	63
11	1.4	TBAT (4)	THF (10)	rt	69
12	1.4	TBAT (3)	THF (10)	rt	64
13	1.4	TBAT (3)	DME (10)	rt	70
14	1.2	TBAT (3)	DME (5)	rt	64

^aTo a sealed 6 dram vial containing 2-aminoacetophenone, the benzyne precursor, a stir bar, and half the total volume of solvent was added CsF, followed by the remainder of the solvent. The reaction was sealed and allowed to stir for a given time before brine (10 mL) was added. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate ($2 \times 15\text{--}25$ mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo before anisole (~ 50 mg) was added for quantitative ^1H NMR spectroscopic analysis. ^bEquivalent of CsF per 1 equiv of aryne precursor. ^c ^1H NMR spectroscopic yield.

reaction conditions and second by examining its scope and limitations.



Results and Discussion

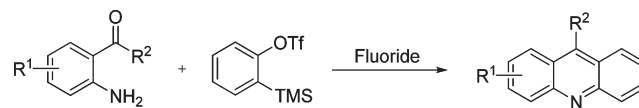
Initial studies on optimization of the reaction between 2-aminoacetophenone and *o*-(trimethylsilyl)phenyl triflate focused on determining the appropriate solvent. The major byproduct in this annulation reaction, which can also be isolated by column chromatography, is the *N*-arylated product **C** (Scheme 1). The byproduct is formed when the aryl carbanion of intermediate **A** is protonated, therefore preventing it from attacking the neighboring carbonyl group (Route B).

Formation of the desired annulated product over the arylated byproduct can sometimes be sensitive to solvents containing acidic protons, such as acetonitrile (MeCN).¹¹ In our reaction, however, MeCN proved to be a superior solvent over tetrahydrofuran (THF) (another commonly used solvent in benzyne chemistry) when CsF is used as the benzyne initiator (Table 1, entries 1–5). It is worth mentioning that even though 1 equiv of water [a proton source that can promote Route B (Scheme 1)] is formed for every equiv of acridine produced, the addition of drying agents, such as molecular sieves, MgSO_4 , CaO, or MgO, failed to improve the overall yield. However, this observation is not entirely surprising since at least four other sources of protons are expected to be present in the reaction mixture at any given time: the ammonium cation and the methyl ketone (both sources can provide protons intra- or intermolecularly), untreated amine, and the solvent (MeCN). DME is the best solvent when employing 3 equiv of tetrabutylammonium triphenyldifluorosilicate (TBAT) as the fluoride source (Table 1, entry 13). The remaining key reaction parameters, time, temperature, etc., have been examined, and it has been found that 1.2 equiv of the benzyne precursor and 3.6 equiv of CsF in MeCN (10 mL) at 65 °C afford the highest yield of acridine (entry 1 = conditions A). As an alternative set of

reaction conditions, 1.4 equiv of benzyne precursor and 4.2 equiv of TBAT in THF (10 mL) at ambient temperature can be used (entry 13 = conditions B).

With two sets of optimized reaction conditions in hand, a series of *ortho*-aminoaryl carbonyl compounds have been examined in this process, including *ortho*-aminoacetophenones, *ortho*-aminobenzophenones, and *ortho*-aminoanthraquinones (Table 2). The parent system gave a respectable 70% yield under both sets of reaction conditions. When inductively electron-withdrawing groups, such as 4,5-dimethoxy (**2a**) and 4,5-methylenedioxy (**3a**) groups, were introduced onto the aromatic ring, conditions A gave increased yields, while conditions B gave the opposite results (entries 3–6). A similar result was obtained with 2-amino-3,5-dibromoacetophenone (entries 7 and 8). It is hypothesized that the favorable performance of this substrate may be attributed to the steric bulkiness of the 3-bromo substituent, in that its large size can push the nitrogen lone pair out of conjugation, thus increasing the nucleophilicity of the nitrogen. In general, it is observed that substrates containing both electron-donating groups and halogens are tolerated well under our optimized reaction conditions. In addition, conditions A proved to be more effective for all acetophenones examined. This trend is not observed for the benzophenones (entries 9–18). In fact, conditions B proved to give better results overall with these substrates, although the reason is not yet completely understood. Consistent with the acetophenones is the fact that benzophenones containing electron-donating groups or halogens are well-tolerated and give good yields of the corresponding acridines when reacted with benzyne (entries 11–18). As demonstrated in entries 13–16, a chlorine substituent can be placed on either ring of the benzophenone system and the overall yield is not affected. In general, all of the benzyne reactions with the benzophenones afford clean thin layer chromatograms, except the reaction of 2-amino-5-nitrobenzophenone, which gave a complicated, inseparable mixture. We were pleased to see that 2-aminoanthraquinone (**11a**) reacted with benzyne efficiently using conditions A to produce the corresponding fused six-membered ring system **11b** (entries 20 and 21). Although only moderate yields were obtained, 2-amino-fluorenone (**13a**) reacted with benzyne to form another fused five-membered ring system (entries 23 and 24). The

TABLE 2. Reactions of Benzyne with Amine-Containing Acetophenones, Benzophenones, and Anthraquinones



entry	substrate	product	conditions ^a	% yield
1	1a	1b	A	70
2	1a	1b	B	70
3	2a	2b	A	78
4	2a	2b	B	55
5	3a	3b	A	78
6	3a	3b	B	68
7	4a	4b	A	77
8	4a	4b	B	71
9	5a	5b	A	68
10	5a	5b	B	72
11	6a	6b	A	71
12	6a	6b	B	72
13	7a	7b	A	71
14	7a	7b	B	80
15	8a	8b	A	72
16	8a	8b	B	77
17	9a	9b	A	51
18	9a	9b	B	72
19	10a	Complicated mixture	A	-
20	11a	11b	A	70
21	11a	11b	B	<10
22	12a	12b	A	40
23			A	53
24	13a	13b	B	<10
25	14a	14b	A	38 ^b , 30
26	14a	14b	B	38 ^b
27	15a	15b	A	30

^aExperimental details for conditions A and conditions B can be found in the Experimental Section. ^bReaction was performed at 0 °C.

TABLE 3. Reactions of *ortho*-Aminoaryl Ketones with Various Aryne Precursors^a

entry	substrate	aryne	product	% yield ^b
1				51
2				36
3				82
4				52
5				96
6				70
7				95
8				88
9				82
10				55

^aAll reactions were carried out using reaction conditions A (see the Experimental Section). ^bIsolated yields.

central five-membered ring of the fluorenone substrate increases the intramolecular distance between the nucleophile and the electrophile, and this may explain the decrease in yield when compared with the corresponding benzophenone and anthraquinone systems (entries 9, 10 and 20, 21).

Lastly, a couple of 2-aminobenzaldehydes were examined. However, yields were drastically reduced (entries 25–27). For example, the parent aldehyde substrate, 2-aminobenzaldehyde (**14a**), gave only a 38% yield of the desired product, even though the crude mixture produced a thin layer chromatogram indicating only one spot and the starting material was entirely gone (entry 25). Concern that the substrate might self-polymerize, as warned by the manufacturer, forced us to run the reaction at 0 °C. Our hesitation in heating the reaction mixture was supported by the results reported in entry 25 where an even lower yield was obtained. Aminobenzaldehyde **15a** gave a low yield similar to **14a** when reacted with benzyne.

After a number of carbonyl substrates were examined, we turned our focus to other aryne (Table 3). Initially, symmetrical benzynes were investigated, thus regioisomeric product mixtures were avoided. The parent substrate **1a** and benzyne precursor **16b** reacted to afford acridine **16c** (entry 1) in a lower yield compared to that of entry 1 of Table 1. This trend was also observed when substrate **2a** was allowed to react with the same benzyne precursor (entry 2). On the other hand, substrate **4a** gave an improved yield when compared with entry 7 of Table 1. Substrate **4a** performed well in all cases. For example, nearly quantitative yields of the desired acridines were obtained in the reactions reported in entries 5 and 7. Again, this may best be explained by the steric bulkiness of the 3-bromo substituent next to the amino group, as it can push the nitrogen lone pair out of conjugation, thus making it more nucleophilic toward the aryne. To our delight, the anthraquinone **11a** afforded a good yield, even when reacted with the more electron-rich benzyne precursor **17b** (entry 6).

We next explored some unsymmetrical benzyne precursors in order to establish the regioselectivity of our methodology. First, benzyne precursor **18b** was examined, and as expected, on the basis of previous related literature,³² the reaction with substrate **4a** led to only one regioisomer in an excellent yield (entry 7). The structure of this compound was confirmed by 2D NOE experiments (see the Supporting Information). Substrate **6a** efficiently reacted with **18b** to produce a single regioisomer, as well (entry 8). In addition, the naphthalene precursor **19b** demonstrated impressive regioselectivity, where the amino group attacks the least hindered carbon of the aryne. Thus, the reactions of **19b** with substrates **6a** and **9a** produced the single regioisomers **24c** and **25c**, respectively. The structure of **24c** was established through X-ray crystallography (see the Supporting Information).

This acridine synthesis is thought to proceed through the mechanism proposed in Scheme 1. After the benzyne is generated through fluorine-induced 1,2-elimination of TMS-OTf, the nucleophilic amino group of the *ortho*-

aminoaryl carbonyl compound attacks one end of the benzyne unsaturation, generating aryl carbanion **A**, which can follow one of two paths, Route A or Route B. Route A produces the desired product through attack on the carbonyl group by intermediate **A** to form a zwitterion **B**, which then undergoes a proton transfer, followed by subsequent dehydration. As previously mentioned, the major byproduct observed in these reactions is arylation of the nitrogen, which presumably proceeds via Route B. It is believed that the proton transfer occurs intramolecularly from the ammonium intermediate, rather than the water produced in the reaction, because the addition of drying agents did not beneficially affect the overall yield.

Conclusions

Acridines have proven to be important in many areas of chemistry, including medicine and materials. So far, however, only methodologies requiring harsh, functionality-intolerant conditions have been reported. As a result, there exists a need for a methodology that is mild enough to tolerate a diverse array of functionality, while remaining practical in terms of the length of the synthesis. We have developed a convenient and mild methodology for the construction of acridines in one step starting from commercially available *ortho*-aminoacetophenones, *ortho*-aminobenzophenones, and *ortho*-aminoanthraquinones and appropriate aryne precursors. *ortho*-Aminobenzaldehydes, on the other hand, give poor yields when subjected to our optimized reaction conditions. Although it is hypothesized that these aldehydes may be self-polymerizing, this has not been proven, and currently, we are exploring alternative conditions. Some unsymmetrical aryne precursors, when reacted with our amino carbonyl substrates, led to single regioisomers in good yields.

Experimental Section

Representative Procedure for the Annulation of Arynes and 2-Aminoaryl Carbonyl Compounds. Conditions A: To a dry 5 dram vial containing a solution of amino substrate (0.5 mmol) and the aryne precursor (0.6 mmol) in MeCN (10 mL, anhydrous) was added CsF (1.8 mmol). The vial was sealed and placed in an oil bath, where it was allowed to stir for 24 h at 65 °C. The reaction mixture was then poured into brine (5 mL), and the organic layer was separated. The water layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined, dried (Na₂SO₄), and concentrated in vacuo. The crude product was then subjected to flash chromatography using gradient solvent combinations of ethyl acetate and hexane or dichloromethane and hexanes to yield a 71% yield of **6b** as a yellow solid: mp = 149–151 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 8.0 Hz, 1 H), 8.05 (s, 1 H), 7.75 (ddd, *J* = 1.2, 6.4, 8.8 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.55–7.62 (m, 4 H), 7.37–7.44 (m, 3 H), 7.25 (dd, *J* = 1.6, 9.2 Hz, 1 H), 2.60 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 149.3, 149.0, 147.0, 140.5, 136.2, 130.6, 129.9, 129.6, 128.59, 128.55, 128.0, 127.0, 126.6, 125.3, 125.0, 123.7, 115.5, 22.3; HRMS (EI) calcd for C₂₀H₁₅N 269.1205, found 269.1209. **Conditions B:** To a dry 5 dram vial containing a solution of the amino substrate (0.5 mmol) and aryne precursor (0.7 mmol) in DME (10 mL, anhydrous) was added TBAT (2.1 equiv). The vial was sealed, and the mixture was allowed to stir at room temperature for 24 h. The workup and purification procedures for conditions A were then employed to yield a 72%

(32) (a) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219. (b) Blackburn, T.; Romtohl, Y. K. *Synlett* **2008**, 1159. (c) Jayanth, T. T.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5921.

yield of compound **6b** (see conditions A for characterization data).

Acknowledgment. We thank the National Institute of General Medical Sciences (GM070620 and GM079593) and the National Institutes of Health Kansas University Center of Excellence in Chemical Methodology and Library Development (P50 GM069663) for their generous financial support, as well as Dr. Feng Shi for his help in the

preparation of some of the aryne precursors. We also thank Dr. Arkady Ellern and the Molecular Structure Laboratory of Iowa State University for their help with the X-ray crystallography.

Supporting Information Available: Experimental procedures and characterization of previously unreported products. This material is available free of charge via the Internet at <http://pubs.acs.org>.