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

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Abstract

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).

(1)

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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>.

(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 towards viruses,¹⁵ bacteria,¹⁶ parasites,¹⁷ fungus,¹⁸ Alzheimer's disease,¹⁹ and HIV/AIDS²⁰ have also been reported. 9-Methylacridines have also been used recently in the construction of new fluorescent probes that emit light at longer wave lengths 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 OLED's.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-oxo aryl azides and 2-azidobenzenecarbonitrile by benzene, giving rise to a variety of acridines, including 9-aminoacridine.²⁷

In 2005, Kim²⁸ *et. al.* 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, like LDA, is needed. These harsh conditions severely limit the types of functional groups, which can be accommodated. Our approach to acridines, however, utilizes Kobayahi'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.

(3)

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

1960's, 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 equation 2, first through optimization of the reaction conditions and second by examining its scope and limitations.

(4)^{29b}

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 by-product in this annulation reaction, which can also be isolated by column chromatography, is the *N*-arylated product **C** (Scheme 1). The by-product 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 by-product 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's worth mentioning that even though one 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, MgSO₄, CaO, or MgO, failed to improve the overall yield. However, this observation is not entirely surprising, since at least 4 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), unreacted 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 affords 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 has 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 6-membered ring system **11b** (entries 20–21). Although, only moderate yields were obtained, 2-aminofluorenone (**13a**) reacted with benzyne to form another fused 5-membered ring system (entry 23–24). The central 5-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 arynes (Table 3). Initially, symmetrical benzyne 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 towards 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, based on 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 by-product 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, since 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's 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 work-up and purification procedures for conditions A were then employed to yield a 72% yield of compound **6b** (see **Conditions A** for characterization data).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Chen, Y.; Larock, RC. *Modern Arylation Methods*. Ackerman, J., editor. Wiley/VCH; New York: 2009. p. 401
2. Beller MA, Breindl C, Riermeier TH, Tillack A. *J Org Chem* 2001;66:1403. [PubMed: 11312973]
3. Huang XC, Liu YL, Liang Y, Pi SF, Wang F, Li JH. *Org Lett* 2008;10:1525. [PubMed: 18338899]
4. Dixon S, Wang X, Lam KS, Kurth MJ. *Tetrahedron Lett* 2005;46:7443.
5. Shi F, Waldo JP, Chen Y, Larock RC. *Org Lett* 2008;10:2409. [PubMed: 18476707]
6. Yoshida H, Fukushima H, Oshita J, Kunai A. *J Am Chem Soc* 2006;128:11040. [PubMed: 16925418]
7. Larrosa I, Da Silva MI, Gomez PM, Hannen P, Ko E, Lenger SR, Linke SR, White AJP, Wilton D, Barret AGM. *J Am Chem Soc* 2006;128:14042. [PubMed: 17061883]
8. Mal D, Senapati BK, Pahari P. *Synlett* 2005:994.
9. Sanz R, Fernández Y, Castroviejo MP, Pérez A, Fañanás FJ. *J Org Chem* 2006;71:6291. [PubMed: 16872224]
10. Pawlas J, Begtrup M. *Org Lett* 2002;4:2687. [PubMed: 12153210]
11. (a) Zhao J, Larock RC. *J Org Chem* 2007;72:583. [PubMed: 17221977] (b) Zhao J, Larock RC. *Org Lett* 2005;7:4273. [PubMed: 16146405]
12. Denny WA. *Med Chem Rev Online* 2004;1:257.
13. (a) Opegard LM, Ougolkov AV, Luchini DN, Schoon RA, Goodell JR, Kaur H, Billadeau DD, Ferguson DM, Hiasa H. *Eur J Pharm* 2009;602:223. (b) Goodell JR, Ougolkov AV, Hiasa H, Kaur H, Rimmel R, Billadeau DD, Ferguson DM. *J Med Chem* 2008;51:179. [PubMed: 18163538] (c) Kapuriya N, Kapuriya K, Zhang X, Chou TC, Kakadiya R, Wu YT, Tsai TH, Chen YT, Lee TC, Shah A, Naliapara Y, Su TL. *Bioorg Med Chem* 2008;16:5413. [PubMed: 18450456] (d) Martins C, Gunaratnam M, Stuart J, Makwana V, Greciano O, Reszka AP, Kelland LR, Neidle S. *Bioorg Med Chem* 2007;17:2293. (e) Nelson EM, Tewey KM, Liu LF. *Proc Natl Acad Sci U S A* 1984;81:1361. [PubMed: 6324188]
14. Belmont P, Dorange I. *Expert Opin Ther Pat* 2008;18:1211.
15. Taraporewala IB. *Tetrahedron Lett* 1991;32:39.
16. (a) Wainwright M. *J Antimicrob Chemother* 2001;47:1. [PubMed: 11152426] (b) Kavitha HP. *Asian J Chem* 2004;16:1191. (c) Patel CL, Parekh H. *Ind Chem Soc* 1988;65:282.
17. (a) Fattorusso C, Campiani G, Kukreja G, Persico M, Butini S, Romano MP, Altarelli M, Ros S, Brindisi M, Savini L, Novellino E, Nacci V, Fattorusso E, Parapini S, Basilico N, Taramelli D, Yardley V, Croft S, Borriello M, Gemma S. *J Med Chem* 2008;51:1333. [PubMed: 18278859] (b) Giorgio CD, Shimi K, Boyer G, Delmas F, Galy JP. *Eur J Med Chem* 2007;42:1277. [PubMed: 17418916] (c) Stocks PA, Bray PG, Barton VE, Helal MA, Jones M, Araujo NC, Gibbons P, Ward SA, Hughes RH, Biagini GA, Davies J, Amewu R, Mercer AE, Ellis G, O'Neill PM. *Angew Chem, Int Ed* 2007;46:6278. (d) Chauhan PMS, Srivastava SK. *Curr Med Chem* 2001;8:1535. [PubMed: 11562283]
18. Patel NA, Sruthi SC, Patel RD, Patel MP. *Phosphorus, Sulfur, Silicon Relat Elem* 2008;183:2191.
19. Dolphin GT, Chierici S, Ouberaï M, Dumy P, Garcia J. *Chembiochem* 2008;9:952. [PubMed: 18330854]
20. Lee Y, Hyun S, Kim HJ, Yu J. *Angew Chem, Int Ed* 2007;47:134.

21. Yan P, Xie A, Wei M, Loew LM. *J Org Chem* 2008;73:657.
22. Li C, Sun P, Yan L, Pan Yi, Cheng CH. *Thin Solid Films* 2008;516:6186.
23. (a) Bernthsen A. *Ann* 1878;192:1. (b) Bernthsen A. *Ann* 1884;224:1.
24. (a) Popp FD. *J Org Chem* 1962;27:2658. For recent synthetic routes to 9-methylacridine, see: (b) Crawford LA, McNab H, Mount AR, Wharton SI. *J Org Chem* 2008;73:6642. [PubMed: 18693770] (c) Joseph J, Kuruvilla E, Achuthan AT, Ramaiah D, Schuster GB. *Bioconjugate Chem* 2004;15:1230.
25. (a) Sourdon V, Mazoyer S, Pique V, Galy JP. *Molecules* 2001;6:673. (b) Lartia R, Bertrand H, Teulade-Fichou MP. *Synlett* 2006:610. (c) Ferencz L, Farcasan V, Silberg IA. *Rev Roum Chim* 2003;48:801. (d) Kamal A, Srinivas O, Ramulu P, Ramesh G, Kumar PP. *Bioorg Med Chem Lett* 2004;14:4107. [PubMed: 15225736] (e) Antonini I, Polucci P, Magnano A, Gatto B, Palumbo M, Menta E, Pescalli N, Martelli S. *J Med Chem* 2003;46:3109. [PubMed: 12825949]
26. (a) Wu M, Wu W, Gao X, Lin X, Xie Z. *Talanta* 2008;75:995. [PubMed: 18585174] (b) Gopinath VS, Thimmaiah P, Thimmaiah KN. *Bioorg Med Chem* 2008;16:474. [PubMed: 17933543] (c) Scarpellini-Charras K, Boyer G, Filloux N, Galy JP. *J Heterocycl Chem* 2008;45:67.
27. Fraleoni-Morgera A, Zanirato P. *Arkivoc* 2006;(xii):111.
28. Yoon K, Ha SM, Kim K. *J Org Chem* 2005;70:5741. [PubMed: 15989364]
29. Silber J, Shine H. *J Org Chem* 1971;36:2923.
30. Himeshima Y, Sonoda T, Kobayashi H. *Chem Lett* 1983:1211.
31. (a) Hendrickson JB, Rees R. *J Am Chem Soc* 1961;83:1250. (b) Taylor EC, Heindel ND. *J Org Chem* 1967;32:1666. (c) Sinsky MS, Bass RG. *J Heterocycl Chem* 1984;21:759.
32. (a) Liu Z, Shi F, Martinez PDG, Raminelli C, Larock RC. *J Org Chem* 2008;73:219. [PubMed: 18067316] (b) Blackburn T, Romtohl YK. *Synlett* 2008:1159. (c) Jayanth TT, Cheng CH. *Angew Chem, Int Ed* 2007;46:5921.

Scheme 1.
Proposed Mechanism

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 × 15–25 mL). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo* before anisole (~50 mg) was added for quantitative ¹H NMR spectroscopic analysis.

^bEquiv of CsF per one equiv of aryne precursor.

^c¹H NMR spectroscopic yield.

conditions ^a	% yield
<p>R =</p>	1b	A 70 B 70

product	conditions ^a	% yield		
2b	A B	78 55	4,5-(OMe) ₂	
3b	A B	78 68	4,5-(OCH ₂) ₂	
4b	A B	77 71	3,5-Br ₂	
5b	A B	68 72	H	
6b	A B	71 72	4-Me	
7b	A B	71 80	5-Cl	
8b	A B	72 77	4'-Cl	
9b	A B	51 72	5-Cl,2'-F	
Complicated mixture	A	-	5-NO ₂

product	conditions ^a	% yield
R =	11b H
	A B	70 <10

		product		conditions ^a	% yield
		6-Cl	12b	A	40
				A B	53 <10
		R=			
		H	14b	A B	38 ^b , 30 38 ^b
		5-Cl	15b	A	30

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

entry	substrate
1	1a

entry

substrate

2

3

entry	substrate
4	2a
5	4a

entry

substrate

6

11a

entry	substrate
7	<chem>CC(=O)c1cc(Br)cc(N)c1Br</chem> 4a

entry

substrate

8

entry

substrate

9

6a

6a

entry

substrate

10

9a

^a All reactions were carried out using reaction conditions A (see the Experimental Section).

^b Isolated yields.