ORGANIC LETTERS

2010
Vol. 12, No. 1
168−171

Insertion of Benzene Rings into the Amide Bond: One-Step Synthesis of Acridines and Acridones from Aryl Amides

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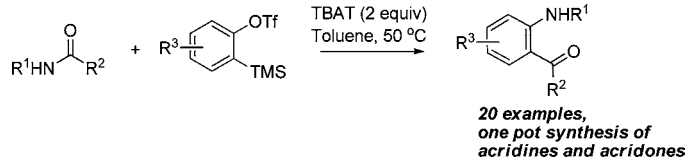
Received November 5, 2009

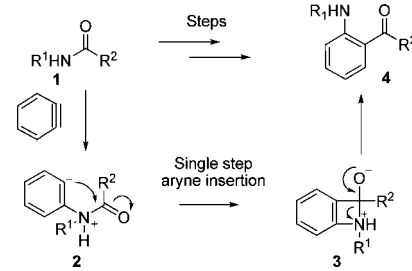
ABSTRACT



Insertion of benzene rings into the amide bond using the reactive intermediate benzyne is described. Aromatic amides undergo smooth insertion when treated with *O*-triflatophenyl silane benzyne precursors, producing versatile aminobenzophenone products in good to excellent yield. The process is entirely metal-free and has been exemplified on the synthesis of biologically active acridones and acridines.

The insertion of a benzene ring into amide bonds represents a powerful synthetic and topological transformation. The amide bond is split to form one new aryl C−N and one aryl C−C bond, forming aminobenzophenone products of fundamental importance in the synthesis of biologically active heterocycles such as benzodiazepines, quinolines, and acridones. While a number of multistep processes for the transformation can be envisaged,[1] a one-step, general method has yet to be developed. A possible solution to the problem is to employ the reactive intermediate benzyne in a σ-insertion reaction.[2,3] The weakly nucleophilic amide nitrogen can attack the reactive aryne molecule, forming a zwitterion intermediate **2**, which can rearrange through the intermediacy of a transient azetidinium ion **3** to produce the desired aminobenzophenone **4** (Scheme 1).

Scheme 1. Aryne Insertion into the Amide Bond



The amide insertion reaction has been demonstrated by Larock for one specific substrate class, activated trifluoroacetanilides ($R^2 = CF_3$).[4] This valuable precedent, taken with

(1) (a) MacNeil, S. L.; Wilson, B. J.; Snieckus, V. *Org. Lett.* **2006**, *8*, 1133–1136. (b) Ding, F.; Zhang, Y.; Qu, B.; Li, G.; Farina, V.; Lu, Z. B.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1067–1070.

(2) Review Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579–3581.

(3) Recent examples of aryne σ-insertion reactions: (a) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745–13754. (b) Yoshida, H.; Kishida, T.; Watanabe, M.; Ohshita, J. *Chem. Commun.* **2008**, *45*, 5963–5965. (c) Yoshida, H.; Morishita, T.; Ohshita, J. *Org. Lett.* **2008**, *10*, 3845–3847. (d) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699–5713. (e) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A. *J. Org. Chem.* **2008**, *73*, 5452–5457. (f) Beltran-Rodil, S.; Peña, D.; Guitián, E. *Synlett* **2007**, *8*, 1308–1310.

(4) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113. See also: Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247–3249.

10.1021/ol902568x
Published on Web 12/02/2009

our own interest in new aryne-based methods,[5] encouraged us to develop an amide insertion reaction having broad utility.

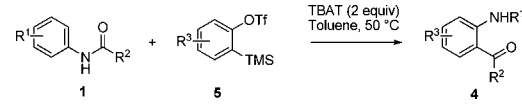
Using the versatile *O*-triflato silane **5a** (R^3 = H) as the aryne precursor,[6] a survey of reaction solvents and fluoride sources established the viability of the reaction for *N*-pivaloylaniline **1a** (Table 1, entry 1). Stirring in toluene in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT) triggered a clean insertion at 50 °C, affording the *tert*-butylketone **4a** in 64% yield. Exploration of substrate scope[7] showed the reaction to be general for a variety of aniline derivatives, enabling the preparation of diverse electron-poor and electron-rich aminobenzophenones in very good yield (entries 1−10). In each case the *N*-pivaloyl and *N*-phenyl derivatives were similarly efficient substrates. The aryne insertion reaction offers a new entry point to *tert*-butylarylketones that is operationally simple and does not require any metal reagents. Literature routes to this compound class are somewhat restricted and invariably use stoichiometric organometallics.[8]

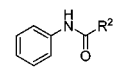
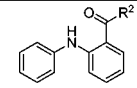
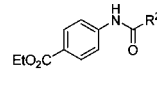
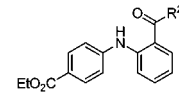
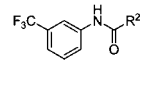
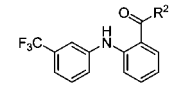
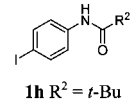
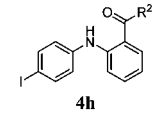
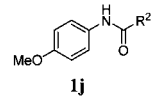
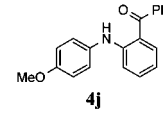
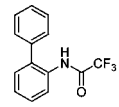
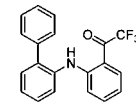
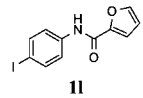
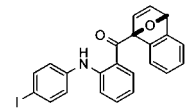
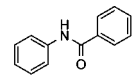
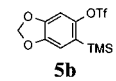
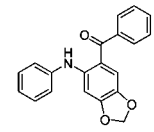
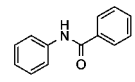
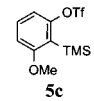
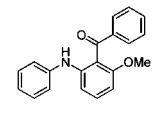
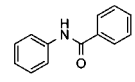
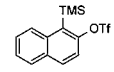
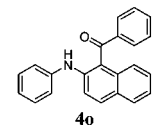
Trifluoroacetanilides, previously investigated by Larock, were excellent substrates for the reaction, with the sterically hindered trifluoromethyl amide **1k** undergoing insertion in very high yield (entry 11). The reaction was also effective for *N*-heteroaroyl substrates, with the furoyl derivative **1l** undergoing tandem furan Diels−Alder reaction and insertion in high yield when treated with an excess of benzyne (entry 12). The structure of the highly functionalized product **4l** was secured by X-ray crystallography.

We next examined substituted arynes in the reaction with *N*-phenylbenzamide (entries 13−15). The electron-rich methylenedioxy aryne **5b** underwent smooth insertion to produce the oxygenated benzophenone **4m** (entry 13). The unsymmetrical aryne precursors **5c** and **5d** produced insertion adducts as single regioisomers (entries 14 and 15), assigned as drawn on the basis of well-known selectivities in nucleophilic additions to unsymmetrical arynes.[9] Finally, we examined the two imide derivatives **1m** and **1n** in the reaction, an important substrate class as it permits the preparation of protected amino ketones as versatile building blocks for heterocycle synthesis (Scheme 2). Insertion was selective for the amide over the carbamate linkage in both cases, providing the Boc and CBz-protected amines **4p** and **4q** in 70% and 75% yield, respectively.

We exemplified the power of the reaction as a rapid entry point to nitrogenated heteroaromatics by developing a divergent synthesis of acridones and acridines. These tricyclic aza-arenes are important targets in medicinal and materials chemistry having multifaceted biological (e.g., antimalarial,

Table 1. Amide Insertion



entry	amide	aryne	product	yield (%)[a]
		**5a**		
1	**1a** R^2 = *t*-Bu		**4a**	64
2	**1b** R^2 = Ph		**4b**	81
3	**1c** R^2 = *m*-Tol		**4c**	88
		**5a**		
4	**1d** R^2 = *t*-Bu		**4d**	71
5	**1e** R^2 = Ph		**4e**	85
		**5a**		
6	**1f** R^2 = *t*-Bu		**4f**	61
7	**1g** R^2 = Ph		**4g**	76
		**5a**		
8	**1h** R^2 = *t*-Bu		**4h**	69
9	**1i** R^2 = Ph		**4i**	81
10	 **1j**	**5a**	 **4j**	65
11	 **1k**	**5a**	 **4k**	90
12[b]	 **1l**	**5a**	 **4l**	82
13	 **1b**	 **5b**	 **4m**	76
14	 **1b**	 **5c**	 **4n**	65
15	 **1b**	 **5d**	 **4o**	78

[a] Isolated yields. Reaction conditions: amide (0.25 mmol), TBAT (0.50 mmol), and **5** (0.375 mmol) in toluene (3 mL); 50 °C for 16 h. [b] 2.8 equiv of **5a** added.

(5) (a) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199–5202. (b) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589–5592. (c) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426–7427.

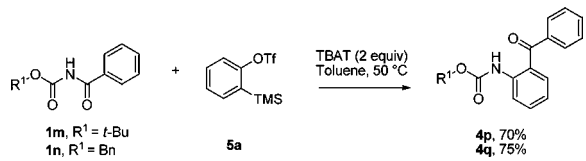
(6) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.

(7) See Supporting Information.

(8) (a) Díaz-Valenzuela, M. B.; Phillips, S. D.; France, M. B.; Gunn, M. E.; Clarke, M. L. *Chem.−Eur. J.* **2009**, *15*, 1227–1232. (b) Koreeda, T.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 7238–7239.

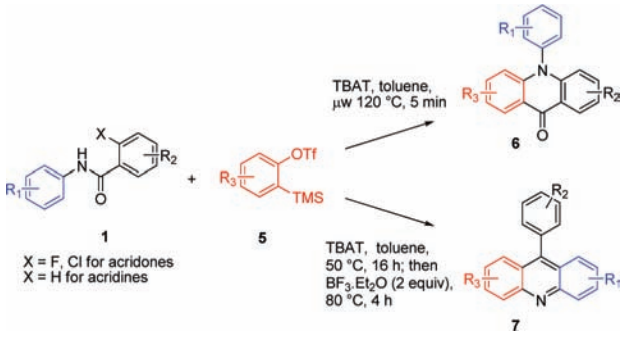
(9) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215–291.

Scheme 2. Imide Insertion



anticancer), optical, and redox properties.[10] Acridones were accessed from readily available *o*-halobenzamides through initial aryne σ-insertion, followed by an in situ S_NAr reaction (Scheme 3).

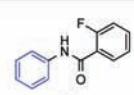
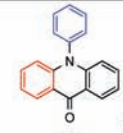
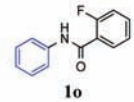
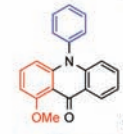
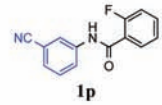
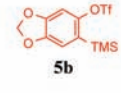
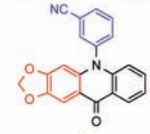
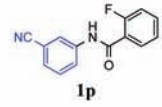
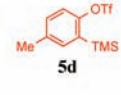
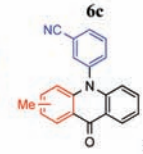
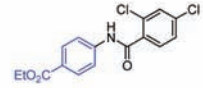
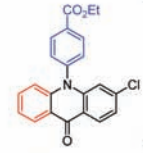
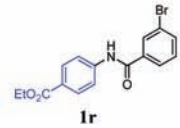
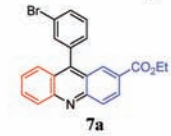
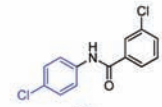
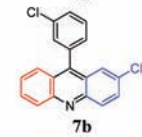
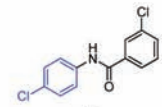
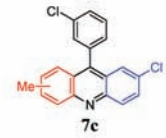
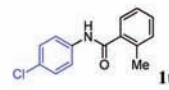
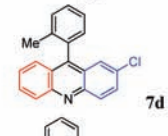
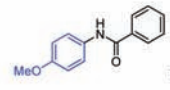
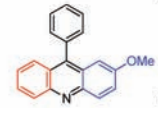
Scheme 3. Divergent Synthesis of Acridones and Acridines



We developed a single-step method using just 5 min of microwave irradiation at 120 °C in the presence of TBAT (Table 2, entries 1−5). The compatibility of precursors **5** with microwave heating has recently been remarked upon and is testament to their superb versatility in aryne chemistry.[11] Yields of acridones were generally excellent; in the case of the 3-methyl aryne precursor **5d**, a 1:1 mixture of regioisomeric acridones was isolated, underlining the intermediacy of the reactive aryne intermediate in the reaction (entry 4).[12]

We could divert the insertion product to the acridine structure **7** through Lewis acid mediated intramolecular Friedel−Crafts acylation and dehydration. Again, the versatility of the aryne precursors enabled the development of a one-pot procedure: adding $BF_3{\cdot}OEt_2$ to the reaction mixture following insertion and increasing the reaction temperature to 80 °C produced good yields of diverse acridine products (Table 2, entries 6−10). Each synthesis incorporates the aryne moiety into the heterocycle framework and can be directed toward the display of either *N*-aryl (acridones) or *C*-aryl (acridines) groups according to the cyclization conditions.

Table 2. Acridone and Acridine Synthesis

entry	amide	aryne	product	yield (%)[a]
1	 1o	 5a	 6a	92
2	 1o	 5c	 6b	62
3	 1p	 5b	 6c	89
4	 1p	 5d	 6d	85[b]
5	 1q	5a	 6e	88
6	 1r	5a	 7a	72
7	 1s	5a	 7b	78
8	 1s	5d	 7c	67[b]
9	 1t	5a	 7d	74
10	 1j	5a	 7e	62

[a] Isolated yields. Reaction conditions: for acridones, amide (0.25 mmol), TBAT (0.75 mmol), and **5** (0.75 mmol) in toluene (3 mL); 120 °C, 5 min; for acridines, amide (0.25 mmol), TBAT (0.50 mmol), and **5** (0.425 mmol) in toluene (3 mL); 50 °C, 16 h, then $BF_3{\cdot}Et_2O$ (0.50 mmol), 80 °C, 4 h. [b] 1:1 mixture of regioisomers.

Insertion substrates containing hydrogens adjacent to the amide bond generally underwent preferable *N*-phenylation under the reaction conditions. Given that the first step of the σ-insertion reaction is proceeding, the failure to rearrange may be due to an intramolecular proton abstraction in the zwitterion **2** quenching the reaction (Scheme 1).[13] To gain

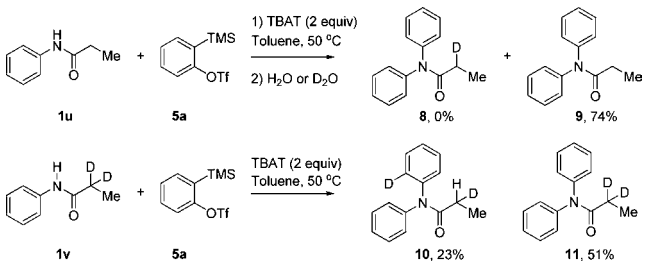
(10) Kelly, J. X.; Smilkstein, M. J.; Brun, R.; Wittlin, S.; Cooper, R. A.; Lane, K. D.; Janowsky, A.; Johnson, R. A.; Dodean, R. A.; Winter, R.; Hinrichs, D. J.; Riscoe, M. K. *Nature* **2009**, *459*, 270–273.

(11) (a) Ankati, H.; Biehl, E. *Tetrahedron Lett.* **2009**, *50*, 4677–4682. (b) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587–1590.

(12) For an alternative acridone synthesis involving aryne addition to aminobenzophenones, see: Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583–588.

insight into the mechanism, we carried out deuterium labeling studies using *N*-phenylpropionamide **1u** (Scheme 4). Stirring

Scheme 4. Deuterium Labelling Studies



under the standard conditions of TBAT for 16 h, followed by aqueous workup, produced the *N*,*N*-diphenyl compound **9** in high yield. Repeating the reaction with a D_2O quench produced the same result, as did running the reaction in d_6-benzene as reaction solvent. Repeating the reaction using the doubly deuterated derivative **1v** produced an identical yield of the *N*,*N*-diphenyl compound, as a ca. 1: 2 mixture of **10** and **11**.

(13) A similar intramolecular quenching mechanism has been identified in the aza-Fries rearrangement of iodoarylamides when treated with butyl lithium; see ref 1b.

The incorporation of deuterium in the aryl ring of **10** implicates 1,5-hydrogen abstraction as a minority quenching mechanism for alkyl-substituted amide substrates. The major quenching pathway is likely from transfer of the amide proton to the phenyl anion, confirmed by reacting the N-D derivative of **1u** with benzyne and observing deuterium incorporation into the aryl ring of the product.[7]

In conclusion, we have developed an aryne σ-insertion reaction for the ubiquitous aryl amide and imide functional groups. The process is high-yielding and operationally simple and uses no metal reagents. The process has been applied to the one-pot synthesis of acridones and acridines; further applications to biologically relevant targets are underway in our group.

Acknowledgment. We thank the University of Edinburgh for the award of a studentship to D.G.P. and the EPSRC mass spectrometry service at Swansea. Dr. Fraser White is thanked for X-ray crystallography.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902568X