Tetrabutylammonium Bromide Catalyzed Tandem Addition/Cyclization of *o*-Aralkynylaryl Aldehydes with Trimethyl(trifluoromethyl)silane: Synthesis of Trifluoromethyl Group Containing Phthalans

Bo-Lun Hu, Chun-Lin Li, Zhi-Yong Liao, Xing-Guo Zhang*

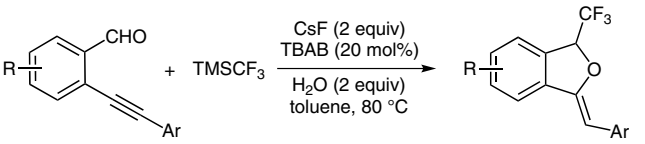
College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, P. R. of China
Fax +86(577)86689615; E-mail: zxg@wzu.edu.cn

Received: 06.08.2013; Accepted after revision: 01.10.2013

Abstract: A tetrabutylammonium bromide catalyzed trifluoromethylation/cyclization reaction of *o*-aralkynylaryl aldehydes with trimethyl(trifluoromethyl)silane and cesium fluoride has been developed. A variety of 1-alkylidene-3-(trifluoromethyl)phthalans were prepared in moderate to excellent yields by tandem nucleophilic addition and cyclization.

Key words: heterocycles, polycycles, cyclizations, alkylations, aldehydes, alkynes

The phthalan (1,3-dihydro-2-benzofuran) group is an important heterocyclic moiety that occurs widely in various biologically active compounds.[1] Moreover, the phthalan group is a key structural unit in many natural products, such as pestacin[2] and membranolide.[3] Consequently, the development of efficient strategies for the construction of the phthalan scaffold has attracted considerable attention,[4] and many reliable and versatile methods have been developed that involve transition-metal-catalyzed or base-promoted annulations of *o*-alkynylbenzyl alcohols.[5] Most of these protocols suffer from the need to use metal catalysts or stoichiometric amounts of base. For example, Wobser and Marks reported a thorium-catalyzed hydroalkoxylation/cyclization of alkynyl alcohols to give methylene-1,3-dihydro-2-benzofurans.[6] Abbiati and coworkers developed a base-promoted synthesis of dihydro-2-benzo-furans by domino addition/annulation reactions of *o*-alkynylbenzaldehydes with alcohols.[7] However, to the best of our knowledge, the synthesis of trifluoromethylated phthalans has not been explored, although the incorporation of a trifluoromethyl groups into aromatic compounds often enhances their biological activity, and this has become a powerful and widely employed tactic in the process of drug design.[8] As a part of our ongoing studies on syntheses of trifluoromethylated aromatic compounds,[9] we wished to prepare trifluoromethyl group containing phthalans from cheap and commercially available trifluoromethylated reagents. Here, we report a simple and efficient protocol for the synthesis of 3-trifluoromethylated phthalans by tetrabutylammonium bromide catalyzed tandem nucleophilic addition and cyclization of *o*-aralkynylaryl aldehydes with Ruppert's reagent, trimethyl(trifluoromethyl)silane (Scheme 1).[10]



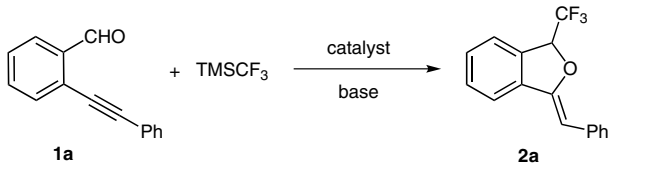
Scheme 1 Tetrabutylammonium bromide catalyzed tandem trifluoromethylation/cyclization reactions of *o*-aralkynylaryl aldehydes with trimethyl(trifluoromethyl)silane

We chose the reaction of 2-(phenylethynyl)benzaldehyde (**1a**) with trimethyl(trifluoromethyl)silane and cesium fluoride to screen for the optimal conditions for the reaction (Table 1). Initially, we investigated various metal catalysts including palladium(II) acetate, copper(II) acetate, copper(II) triflate, and zinc(II) acetate, and we obtained the desired product **2a** in low yields (entries 1–4). Better results were obtained when phase-transfer catalysts were used in the tandem reaction (entries 5–8). For example, treatment of substrate **1a** with tetrabutylammonium bromide (10 mol%), trimethyl(trifluoromethyl)silane (3 equiv), and cesium fluoride (2 equiv) in toluene gave the desired product **2a** in 62% yield (entry 6). We were pleased to find that the yield of **2a** increased to 88% when 20 mol% of tetrabutylammonium bromide was used (entry 8). In the absence of catalyst, no cyclization product was obtained, and the nucleophilic addition product was obtained instead (entry 9). Subsequently, other sources of fluoride ion were tested for the generation of trifluoromethyl anion. A 73% yield was obtained by using potassium fluoride as the base (entry 10), but tetrabutylammonium fluoride gave no product (entry 11). Finally, several solvents (tetrahydrofuran, acetonitrile, and *N*,*N*-dimethylformamide) were examined, but all were less effective than toluene. It is noteworthy that two equivalents of water played a key role in the tandem reactions and that the required product could not be obtained in the absence of water.[11] Presumably water enhances the nucleophilicity of the alkoxide ion and provides the protons required to form the cyclization product.[7]

Having identified the optimal reaction conditions,[12] we explored the substrate scope with respect to the *o*-alkynylaryl aldehyde (Scheme 2).

SYNLETT 2013, 24, 2748–2750
Advanced online publication: 08.11.2013
DOI: 10.1055/s-0033-1340076; Art ID: ST-2013-W0758-L

Table 1 Optimization of the Reaction Conditions



1a **2a**

Entry[a]	Base	Catalyst (mol%)	Solvent	Yield[b] (%)
1	CsF	$Pd(OAc)_2$ (10)	toluene	18
2	CsF	$Cu(OAc)_2$ (10)	toluene	31
3	CsF	$Cu(OTf)_2$ (10)	toluene	38
4	CsF	$Zn(OAc)_2$ (10)	toluene	26
5	CsF	TBAF (10)	toluene	54
6	CsF	TBAB (10)	toluene	62
7	CsF	Bu_4NOAc (10)	toluene	46
8	CsF	TBAB (20)	toluene	88
9	CsF	–	toluene	0
10	KF	TBAB (20)	toluene	73
11	TBAF	TBAB (20)	toluene	0
12	CsF	TBAB (20)	THF	5
13	CsF	TBAB (20)	MeCN	20
14	CsF	TBAB (20)	DMF	10
15[c]	CsF	TBAB (20)	toluene	0

[a] Reaction conditions: **1a** (0.3 mmol), $TMSCF_3$ (3 equiv), base (2 equiv), catalyst, 0 °C, 1 h, then H_2O (2 equiv), stirring, 80 °C, 6 h.
[b] Isolated yield.
[c] In the absence of H_2O.

Initially, we examined the effects of substituents on the aryl group of the aralkyne moiety. Both electron-rich and electron-deficient aryl groups were tolerated and the corresponding products were obtained in moderate to good yields (**2b**–**h**). Aldehydes containing *p*-, *m*-, and *o*-tolyl groups gave the corresponding products **2b**–**d** in yields of 71, 82, and 77%, respectively. The 4-methoxylphenyl

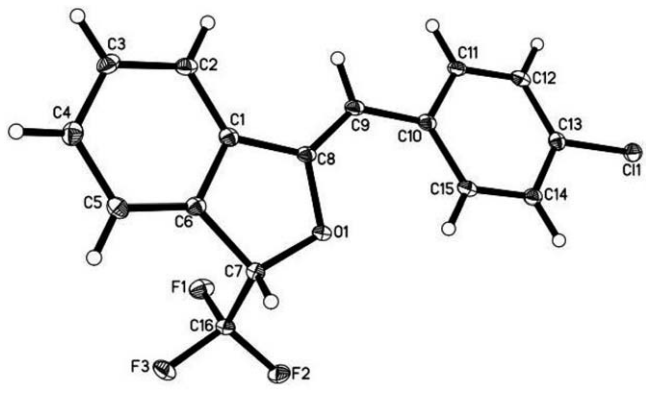
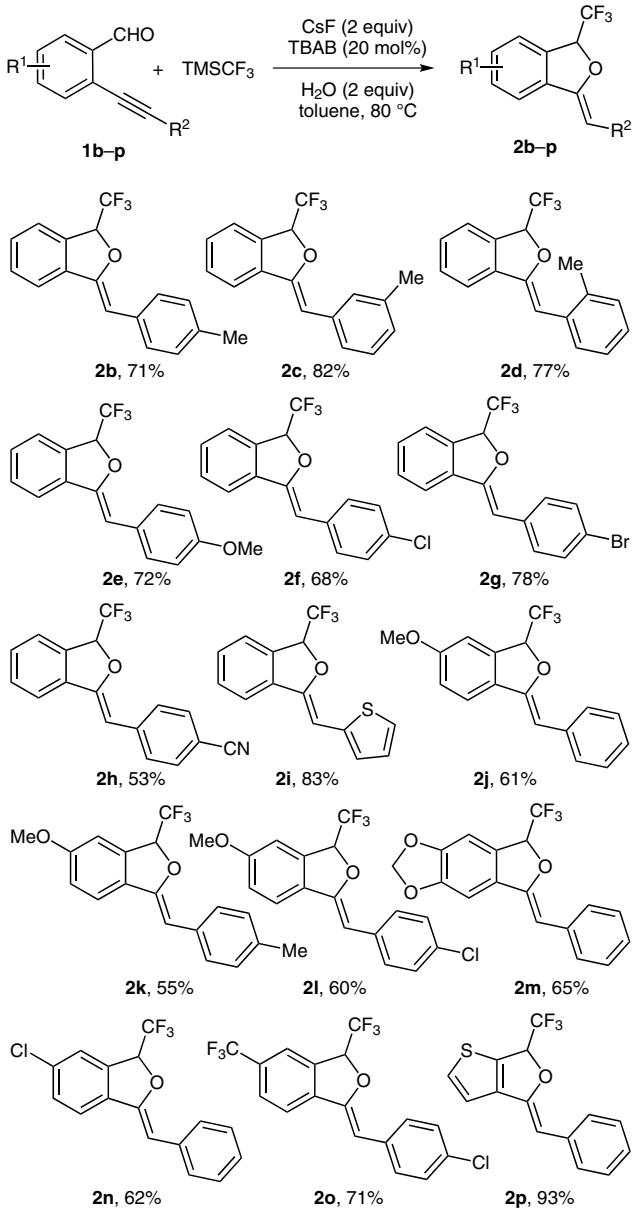


Figure 1 Structure of product **2f**



Scheme 2 Trifluoromethylation/cyclization of *o*-aralkynylaryl aldehydes with trimethyl(trifluoromethyl)silane. *Reagents and conditions*: **1b**–**p** (0.3 mmol), $TMSCF_3$ (0.9 mmol), CsF (0.6 mmol), TBAB (0.06 mmol), toluene, 0 °C, 1 h, then H_2O (2 equiv), stirring, 80 °C, 6 h.

product **2e** was obtained in 72% yield. Similar results were obtained for the 4-chlorophenyl and 4-bromophenyl products **2f** and **2g**, respectively. The configuration of product **2f** was unambiguously confirmed by single-crystal X-ray diffraction analysis (Figure 1).[13]

The electron-deficient 4-cyanophenyl-substituted aldehyde gave the corresponding product **2h** in 53% yield. Interestingly, the 2-thienyl group was also compatible with the reaction, and the corresponding product **2i** was obtained in 83% yield. However, with alkanols, the cyclization reaction failed although the nucleophilic addition proceeded smoothly.

We also investigated the effects of ring substituents on the aryl aldehyde moiety. Methoxy-substituted *o*-aralkynylbenzaldehydes gave the corresponding product **2j**–**m** in 55–65% yield. 5-Chloro-2-(phenylethynyl)benzaldehyde gave the corresponding product **2n** in 62% yield. Electron-deficient 5-(trifluoromethyl)-2-(phenylethynyl)benzaldehyde gave product **2o** in 71% yield. To our surprise, the reaction of 2-(phenylethynyl)thiophene-3-carbaldehyde also proceeded successfully to give the thienofuran product **2p** in 93% yield.

In summary, we have developed a tetrabutylammonium bromide catalyzed tandem trifluoromethylation/cyclization reaction. In the presence of tetrabutylammonium bromide and cesium fluoride, a variety of *o*-aralkynylaryl aldehydes underwent tandem nucleophilic addition and 5-*exo*-dig heterocyclization with trimethyl(trifluoromethyl)silane to give the corresponding (*Z*)-1-alkylidene-3-(trifluoromethyl)phthalans in moderate to excellent yields. This regio- and stereospecific reaction shows good functional-group tolerance. The one-pot procedure and the use of an inexpensive catalyst and trifluoromethyl source are significant advantages of this reaction. The process might facilitate the synthetic applications of trifluoromethyl-containing building blocks and provides a new option for constructing the 1,3-dihydro-2-benzofuran ring system.

Acknowledgments

We thank the National Natural Science Foundation of China (No. 21002070, 21272177 and 21276200) for financial support.

References

(1) (a) Moore, N.; Verdoux, H.; Bruno, F. *Int. Clin. Psychopharmacol.* **2005**, *20*, 131. (b) Brown, D. S.; Elliot, M. C.; Moody, C. J.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1137. (c) Martin, C.; Mailliet, P.; Maddaluno, J. *J. Org. Chem.* **2001**, *66*, 3797. (d) Lipka, E.; Vaccher, M. P.; Vaccher, C.; Len, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 501.

(2) (a) Strobel, G.; Ford, E.; Worapang, J.; Harper, J. K.; Arif, A. M.; Grant, D. M.; Fung, P. C.; Chau, R. M. W. *Phytochemistry* **2002**, *60*, 179. (b) Strobel, G. *Can. J. Plant Pathol.* **2002**, *24*, 14.

(3) Ankisetty, S.; Amsler, C. D.; Clintock, J. B.; Baker, B. J. *J. Nat. Prod.* **2004**, *67*, 1172.

(4) (a) Fieser, L. F.; Haddadin, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 2081. (b) Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599. (c) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (d) Haddadin, M. J. *Heterocycles* **1978**, *9*, 865. (e) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135. (f) Wiersum, U. E. *Aldrichimica Acta* **1981**, *14*, 53. (g) Wiersum, U. E.; Mijs, W. J. *J. Chem. Soc., Chem. Commun.* **1972**, 347. (h) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354. (i) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849. (j) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287. (k) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689. (l) Yasuo, H.; Mikako, W.; Tooru, F.; Takeshi, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.

(5) (a) Praveen, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 4767. (b) Hiroya, K.; Jouke, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697. (c) Varela-Fernández, A.; González-Rodríguez, C.; Varela, J. A.; Castedo, L.; Sáa, C. *Org. Lett.* **2009**, *11*, 5350. (d) Zanardi, A.; Mata, J. A.; Peris, E. *Organometallics* **2009**, *28*, 4335. (e) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (f) Padwa, A.; Krumpe, K. E.; Weingarten, M. D. *J. Org. Chem.* **1995**, *60*, 5595. (g) Khan, M. W.; Kundu, N. G. *Synlett* **1999**, 456.

(6) Wobser, S.; Marks, T. *Organometallics* **2013**, *32*, 2517.

(7) Dell'Acqua, M.; Facoetti, D.; Abbiati, G.; Rossi, E. *Synthesis* **2010**, 2367.

(8) (a) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(9) (a) Chen, M.-W.; Zhang, X.-G.; Zhong, P.; Hu, M.-L. *Synthesis* **2009**, 1431. (b) Dong, S.-X.; Zhang, X.-G.; Liu, Q.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Synthesis* **2010**, 1521. (c) Li, C.-L.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 7037. (d) Sun, L.-L.; Liao, Z.-Y.; Tang, R.-Y.; Deng, C.-L.; Zhang, X.-G. *J. Org. Chem.* **2012**, *77*, 2850. (e) Shi, S.; Sun, L.-L.; Liao, Z.-Y.; Zhang, X.-G. *Synthesis* **2012**, 966. (f) Wang, W.-Y.; Feng, X.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. *J. Org. Chem.* **2013**, *78*, 6025.

(10) (a) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195. (b) Iwanami, K.; Oriyama, T. *Synlett* **2006**, *1*, 112. (c) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (d) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613.

(11) Yao, X.-Q.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953.

(12) **1-Alkylidine-3-(trifluoromethyl)-1,3-dihydro-2-benzofurans 2; General Procedure**
A flame-dried Schlenk tube equipped with a magnetic stirring bar was charged with *o*-aralkynylaryl aldehyde **1** (0.3 mmol), $TMSCF_3$ (0.9 mmol), CsF (0.6 mmol), TBAB (0.06 mmol), and anhyd toluene (2 mL), and the mixture was stirred at 0 °C for 1 h. H_2O (2 equiv) was added and the mixture was stirred at 80 °C for 6 h. The mixture was then poured into EtOAc and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash column chromatography (hexane–EtOAc).
(1*Z*)-1-Benzylidene-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran (2a)
White solid; yield: 73.1 mg (88%); mp 47.5–48.5 °C. IR (KBr): 2991, 1742, 1242, 1047, 848, 797 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.9 Hz, 2 H), 7.58 (d, *J* = 8.1 Hz, 1 H), 7.48 – 7.45 (m, 2 H), 7.41 – 7.34 (m, 3 H), 7.22 – 7.18 (m, 1 H), 6.03 (s, 1 H), 5.83 (q, *J* = 6.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.8, 135.6, 135.0, 132.8, 130.1, 129.2, 128.5, 128.4, 126.3, 123.0 (q, J_{C-F} = 279.6 Hz), 122.8, 120.1, 99.0, 81.5 (q, J_{C-F} = 34.3 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –77.95. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}F_3O^+$: 277.0835; found: 277.0819.

(13) Crystallographic data for compound **2f** have been deposited with the accession number CCDC 968707 and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

