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Trifluoroacetic acid-mediated facile construction of 6-substituted phenanthridines

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ABSTRACT

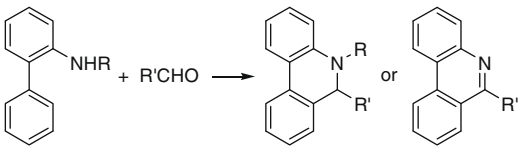
The trifluoroacetic acid-mediated reaction of 2-arylanilines with arylaldehydes has been developed to give a variety of 6-substituted phenanthridines. This is a very simple and convenient one-pot process for library construction.

Phenanthridines have attracted considerable attention in medicinal chemistry and in material science due to their biological activity and their presence in a variety of significant natural products and synthetic dye-stuffs.[1] Consequently, a number of synthetic strategies have been reported for the construction of phenanthridines. However, multistep reactions,[2d–g] the limited substrate scope, and frequent requirement of harsh reaction conditions (e.g., P_4O_{10}, $POCl_3$, or PCl_5 at elevated temperature),[2a–c] extremely high temperature (200–300 °C),[2l] anhydrous conditions,[2e,f] air-sensitive organometallic reagents,[2e,f] or metal catalysis[2g–k] limit the usefulness and generality of these methods.[2] Therefore, there is great demand to develop simple, convenient protocol for the expeditious synthesis of phenanthridine derivatives.

In parallel with our efforts to develop new synthetic methods of heterocycles,[3] we were interested in developing a more versatile and simpler one-pot synthesis of phenanthridines from 2-arylanilines and aldehydes via sequential C–N and C–C bond formations with high efficiency (Scheme 1). Herein we report the trifluoroacetic acid (TFA)-mediated coupling reaction of 2-arylanilines with arylaldehydes for the direct synthesis of phenanthridines in a one-pot process.[2o]

2-Phenylanilines such as *N*-Ts-2-phenylaniline[4a] and *N*-Ac-2-phenylaniline[4b] are known to undergo C–H bond activation and C–C or C–N bond formations in the presence of Pd(II) catalysts. Therefore, we envisioned that Pd(II)-catalyzed C–H bond functionalization of 2-phenylaniline derivatives with aldehydes could afford dihydrophenanthridines. First, we examined the reaction of *N*-Ts-2-phenylaniline (**1a**) and benzaldehyde in TFA in the presence of $Pd(OAc)_2$ (5 mol %) and oxidants (benzoquinone (BQ) or $Cu(OAc)_2$). When reaction mixture was heated at 120 °C for 35 h, 6-phenylphenanthridine (**2a**) was obtained in good yields, instead of the corresponding 5,6-dihydrophenanthridine derivative, via sequential deprotection/aromatization (Table 1, entries 1 and 2). Then, the same reaction was performed in TFA in the absence of $Pd(OAc)_2$ and oxidant. Almost the same result was obtained, which suggests that $Pd(OAc)_2$ is not essential in this reaction (Table 1, entry 3 vs entries 1 and 2). HCl, H_2SO_4, and mixture of TFA and H_2O were ineffective, while AcOH, propionic acid, and mixture of TFA and organic solvents such as CH_2Cl_2 and toluene gave lower conversion than only TFA (Table 1, entries 4–13). These results suggest that TFA plays a dual role of catalyst and solvent in this coupling process.[5] Both lowering reaction temperature and short reaction time decreased the yield of **2a** dramatically (Table 1, entries 14–17).

With the establishment of a one-pot transformation of Ts-biaryl amide (**1a**) to 6-phenylphenanthridine (**2a**), we turned our attention to substrates containing other amine protecting groups. 2-Aminobiphenyl protected as other amides such as acetamide (**1b**), methanesulfonamide (**1c**), benzamide (**1d**), and *tert*-butylcarboxycarbonylamide (Boc-amide, **1e**) provided much lower yields of the desired products (Table 1, entries 18–21). In contrast, 2-phenylaniline itself (**1f**) did result in the production of **2a** as efficiently as the corresponding Ts-amide (**1a**) (Table 1, entry 22). Recently, the modified Pictet-Spengler reaction involving 2-(2-aminopyrimidin-4-yl)aniline derivatives has been reported in which the presence of amino substituent on pyrimidine moiety may serve as an electron–donating group to facilitate π–cyclization in the presence of strong Brønsted acid such as triflic acid.[6] Since



Scheme 1. One-pot synthesis of phenanthridines from 2-arylanilines and aldehydes via sequential C–C/C–N bond formations.

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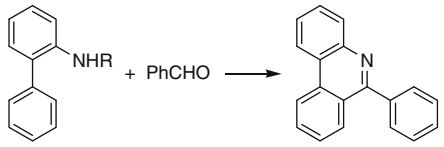
Table 1
Optimization studies for the synthesis of 6-phenylphenanthridine[a]



1 **2a**

Entry	R	Solvent	Yield[b] (%)
1[c]	Ts (**1a**)	TFA	60
2[d]	Ts (**1a**)	TFA	88
3	Ts (**1a**)	TFA	80
4	Ts (**1a**)	AcOH	15
5	Ts (**1a**)	$CH_3CH_2CO_2H$	45
6	Ts (**1a**)	TFA/CH_2Cl_2 (2/1)	70
7	Ts (**1a**)	TFA/CH_2Cl_2 (1/1)	50
8	Ts (**1a**)	TFA/CH_2Cl_2 (1/2)	60
9	Ts (**1a**)	TFA/CH_2Cl_2 (1/4)	15
10	Ts (**1a**)	TFA/H_2O (2/1)	—
11	Ts (**1a**)	TFA/toluene (2/1)	50
12	Ts (**1a**)	H_2SO_4[e]	—
13	Ts (**1a**)	HCl[f]	—
14[g]	Ts (**1a**)	TFA	40
15[h]	Ts (**1a**)	TFA	10
16[i]	Ts (**1a**)	TFA	30
17[j]	Ts (**1a**)	TFA	20
18	Ac (**1b**)	TFA	50
19	Ms (**1c**)	TFA	40
20	Bz (**1d**)	TFA	50
21	Boc (**1e**)	TFA	50
22	H (**1f**)	TFA	85

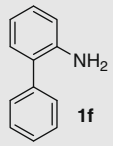
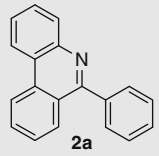
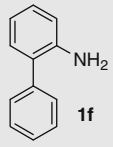
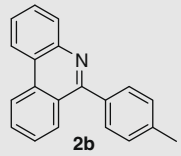
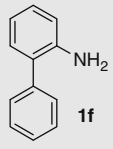
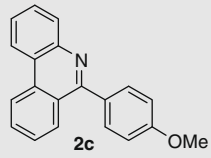
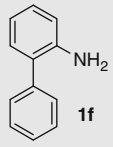
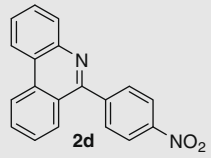
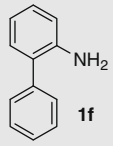
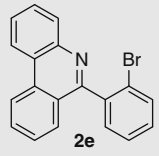
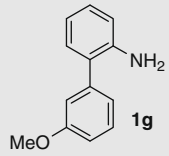
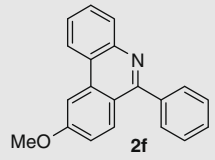
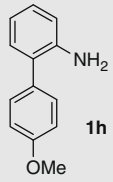
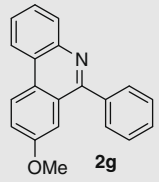
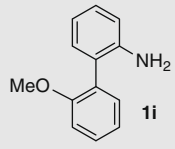
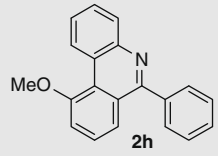
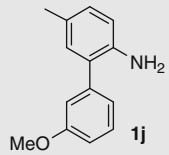
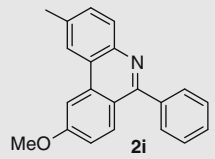
[a] Reaction conditions: **1** (1 equiv), PhCHO (2 equiv), solvent (0.1 M), 120 °C, 35 h, unless otherwise noted.
[b] Determined by ^{1}H NMR using trichloroethylene as an internal standard.
[c] Performed in the presence of 5 mol % of $Pd(OAc)_2$ and 2 equiv of BQ.
[d] Performed in the presence of 5 mol % of $Pd(OAc)_2$ and 2 equiv of $Cu(OAc)_2$.
[e] Concd H_2SO_4 (98%).
[f] Aq HCl (37%).
[g] Performed at 100 °C.
[h] Performed at 80 °C.
[i] Performed for 24 h.
[j] Performed for 12 h.

there is no need for prefunctionalization (e.g., protection of amine or imine synthesis) for practical purposes, we focused on the reaction of free amine substrates with aldehydes in TFA.

We set out to explore the scope of this process. As shown in Table 2, a variety of 2-arylanilines and arylaldehydes underwent coupling reaction in TFA to form the corresponding phenanthridines.[7] Both electron-rich and electron-deficient arylaldehydes as well as sterically hindered arylaldehyde were all successful in this reaction (Table 2, entries 1–5). However, heteroarylaldehydes, α,β-unsaturated aldehydes, and alkylaldehydes led to a complicated mixture and only a small amount of the desired products (<30%).

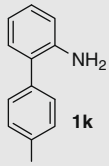
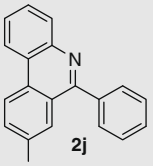
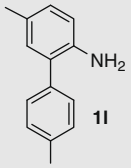
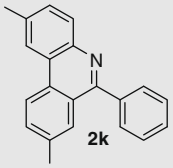
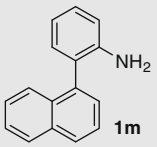
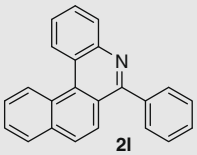
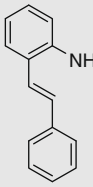
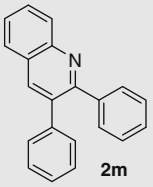
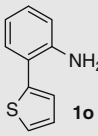
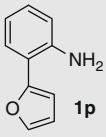
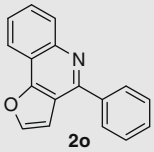
We proceeded to examine the effects of substituents at the 2-arylaniline moiety. A variety of substituted 2-arylanilines were prepared by the Suzuki–Miyaura coupling reaction of 2-bromoaniline and appropriate arylboronic acids (Scheme 2). Both electronic and steric effects of substituents in the 2-phenyl ring (bottom ring) seem to influence the efficiency of the coupling reaction. *Ortho* substitution to the biaryl axis hampered the reactions (Table 2, entry 8). Compared to the substrate with methoxy substituent at *para* position to the biaryl axis, *meta*-substituted one showed enhanced reactivity (Table 2, entries 6 and 7). Furthermore, both 2-(3-nitrophenyl)aniline and 2-(4-chlorophenyl)aniline did not undergo conversion to the corresponding phenanthridines. Taking these results into consideration, it is likely that this reaction proceeds through an electrophilic pathway involving imine activation by acid, iminium ion (Fig. 1).[2o,6,8] It should be noted that the cyclization reaction

Table 2
Synthesis of 6-substituted phenanthridines by TFA-mediated reaction of 2-arylanilines with arylaldehydes[a]

Entry	Substrate	Aldehyde	Product	Yield[b] (%)
1	 **1f**	PhCHO	 **2a**	91
2	 **1f**	4-MeC_6H_4CHO	 **2b**	90
3	 **1f**	4-$MeOC_6H_4CHO$	 **2c**	75
4	 **1f**	4-$NO_2C_6H_4CHO$	 **2d**	68
5	 **1f**	2-BrC_6H_4CHO	 **2e**	74
6	 **1g**	PhCHO	 **2f**	70
7	 **1h**	PhCHO	 **2g**	59
8	 **1i**	PhCHO	 **2h**	23
9	 **1j**	PhCHO	 **2i**	79

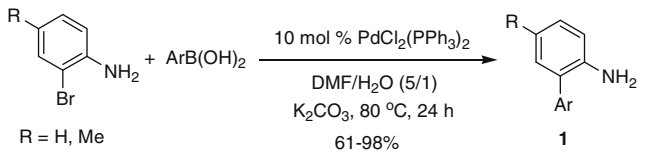
(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Aldehyde	Product	Yield[b] (%)
10	 **1k**	PhCHO	 **2j**	86
11	 **1l**	PhCHO	 **2k**	64
12	 **1m**	PhCHO	 **2l**	83
13	 **1n**	PhCHO	 **2m**	59
14	 **1o**	PhCHO	 **2n**	45
15	 **1p**	PhCHO	 **2o**	20

[a] Reaction conditions: **1** (1 equiv), aldehyde (2 equiv), TFA (0.1 M), 120–140 °C, 1.5–7 days.
[b] Isolated yields.

occurred with excellent regioselectivity for unsymmetrically substituted substrates, 2-(3-methoxyphenyl)aniline (**1g**), and 2-(3-methoxyphenyl)-4-methylaniline (**1j**) (Table 2, entries 6 and 9). Coupling at the more hindered carbon was not observed. 2-(1-Naphthyl)aniline also underwent the coupling reaction in good yields (Table 2, entry 12). In addition, 2-heteroarylanilines (Table 2, entries 14 and 15) and 2-cinnamylaniline (Table 2, entry 13) proved to be suitable substrates, affording the corresponding quinoline derivatives.



Scheme 2. Synthesis of various 2-arylanilines by the Suzuki–Miyaura coupling reaction.

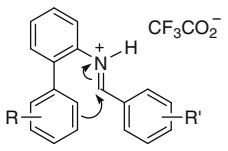


Figure 1. Possible mechanism.

In summary, we have developed a simple and convenient one-pot procedure, TFA-mediated reaction of 2-arylanilines with arylaldehydes to afford 6-substituted phenanthridines. The fact that this process can tolerate various functional groups such as methoxy, bromo, nitro, furyl, and thienyl groups is noteworthy. All 6-aryl-substituted phenanthridines prepared from this facile reaction were highly fluorescent and will have important applications in material science and as DNA-intercalating agents. While limitation of this process includes the requirement of harsh reaction conditions (in TFA at 120–140 °C for 1.5–7 days) and a specific substrate class (such as arylaldehydes), the operational simplicity and use of simple reactants without requirement of synthesis of complicated precursors, strictly anhydrous conditions, air-sensitive organometallic reagents, or expensive metal catalysts make it particularly attractive for library construction of fluorescent molecules, which could be directly utilized for DNA-sequencing.

Acknowledgments

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Supplementary data

Supplementary data (full experimental details, characterization data of substrates and products, and copies of ^{1}H, ^{13}C NMR spectra of all products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.071.

References and notes

1. (a) Keene, B. R. T.; Tissington, P. *Adv. Heterocycl. Chem.* **1971**, *13*, 315; (b) Troll, T.. In *Houben-Weyl-Methods of Organic Chemistry*; Georg Thieme: Stuttgart, 1992; Vol. E7b, p 157; (c) Atwell, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1988**, *31*, 774; (d) Eisch, J.; Gilman, H. *Chem. Rev.* **1957**, *57*, 525; (e) Zimmermann, H. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 115; (f) Firth, W. J., III; Watkins, C. L.; Graves, D. E.; Yielding, L. W. *J. Heterocycl. Chem.* **1983**, *20*, 759.
2. (a) Mamalis, P.; Petrow, V. *J. Chem. Soc.* **1950**, 703; (b) Buuï-Ho, N. P.; Jaquignon, P.; Long, C. T. *J. Chem. Soc.* **1957**, 505; (c) Bartram, C. A.; Harrison, D.; Short, W. F. *J. Chem. Soc.* **1958**, 1158; (d) Patra, P. K.; Suresh, J. R.; Ila, H.; Junjappa, H. *Tetrahedron* **1998**, *54*, 10167. and references cited therein; (e) Lysén, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2002**, *4*, 257; (f) Pawlas, J.; Begtrup, M. *Org. Lett.* **2002**, *4*, 2687; (g) Bowman, W. R.; Lyon, J. E.; Pritchard, G. J. *Synlett* **2008**, 2169; (h) Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 11723; (i) Hilt, G.; Hess, W.; Schmidt, F. *Eur. J. Org. Chem.* **2005**, 2526; (j) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463; (k) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720; (l) Mehta, B. K.; Yanagisawa, K.; Shiro, M.; Kotsuki, H. *Org. Lett.* **2003**, *5*, 1605; (m) Leardini, R.; Tundo, A.; Zanardi, G. *Synthesis* **1985**, 107; (n) Shou, W.-G.; Yang, Y.-Y.; Wang, Y.-G. *J. Org. Chem.* **2006**, *71*, 9241; (o) Very recently, a similar result for the synthesis of phenanthridines was published. And it was described that the strategy is based on the modified Pictet-Spengler reaction. For the modified Pictet-Spengler strategy, see also references therein. Mandadapu, A. K.; Saifuddin, M.; Agarwal, P. K.; Kundu, B. *Org. Biomol. Chem.* DOI: 10.1039/b905696c.
3. (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055; (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859; (c) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581; (d) Youn, S. W.; Eom, J. I. *Org. Lett.* **2005**, *7*, 3355; (e) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521; (f) Youn, S. W. *Org. Prep. Proced. Int.* **2006**, *38*, 505; (g) Youn, S. W.; Eom, J. I. *J. Org. Chem.* **2006**, *71*, 6705; (h) Youn, S. W. *Synlett* **2007**, 3050; (i) Youn, S. W.; Song, J.-H.; Jung, D.-I. *J. Org. Chem.* **2008**, *73*, 5658.
4. (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211; (b) Tsang, W. C. P.; Zhang, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560.

5. For selected examples of TFA-mediated coupling reactions, see: (a) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881; (b) Wu, Y.-C.; Liu, L.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2007**, *72*, 9383; (c) Cincinelli, R.; Dallavalle, S.; Merlini, L. *Synlett* **2008**, 1309; (d) Augustine, J. K.; Naik, Y. A.; Mandal, A. B.; Alagarsamy, P.; Akabote, V. *Synlett* **2008**, 2429; (e) Che, X.; Zheng, L.; Dang, Q.; Bai, X. *J. Org. Chem.* **2008**, *73*, 1147.
6. Agarwal, P. K.; Sharma, S. K.; Sawant, D.; Kundu, B. *Tetrahedron* **2009**, *65*, 1153.
7. General procedure for the synthesis of 6-substituted phenanthridines by TFA-mediated reaction of 2-arylanilines and arylaldehydes: To a solution of 2-arylaniline **1** in TFA (0.1 M) in a pressure tube was added arylaldehyde (2 equiv). The pressure tube was tightly capped and the resulting mixture was heated with stirring at the reported temperature (120–140 °C) for the reported time. After the reaction was completed, the solvent was blown off with Ar and the residue was diluted with CH_2Cl_2, basified with satd $NaHCO_3$, extracted with CH_2Cl_2 (three times), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane = 1:8–1:30) to give the corresponding product **2**.
8. One referee suggested that 1,6-electrocyclization of azatriene systems should be used as the key word to explain the plausible mechanism and we agree that this cannot be excluded.