ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 13056

Received 13th August 2014,
Accepted 2nd September 2014

DOI: 10.1039/c4cc06369d

www.rsc.org/chemcomm

Synthesis of *N*-aryl-1-aminoindoles *via* intermolecular redox amination†

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A redox amination strategy was developed for the synthesis of *N*-aryl-1-aminoindoles by N–N bond formation. Reaction of nitrosobenzenes with readily available indolines using Brønsted acid catalysis allows N–N bond formation under mild conditions. This method exploits the inherent reducing power of indoline to synthesize biologically relevant molecular architectures *via* redox amination. A one-pot synthesis of 1-aminoindoles starting from simple aniline and indolines is likewise described.

The indole core is considered a privileged scaffold on the basis of the many applications of indoles in medicinal chemistry.[1] A particularly interesting class of indoles are the 1-amino indoles. While less developed than *N*-alkyl indoles, *N*-substituted-1-aminoindoles are known to possess a wide range of biological effects,[2] including activities against the symptoms of Alzheimer's disease,[2a,b] Chagas disease,[2c] and depression (Fig. 1).[2d,e] Despite their promising biological activities, there are few reports detailing the synthesis of *N*-substituted-1-aminoindoles.[3] Due to the relative paucity of methods for formation of N–N bonds,[4] known synthetic methods focus on synthesis of 1-amino indoles from precursors such as hydrazines and diazenes that already contain the requisite N–N bond.

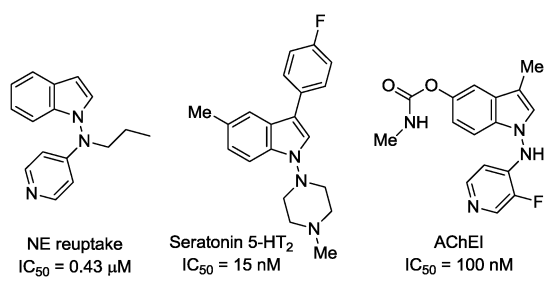

Fig. 1 Biologically active 1-amino indoles.

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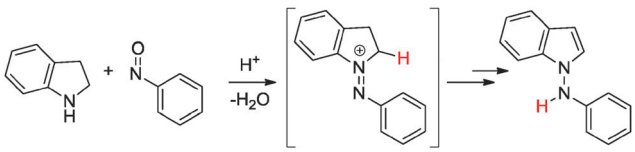
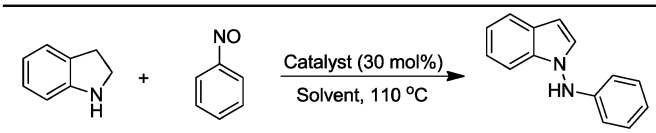
† Electronic supplementary information (ESI) available: Full characterization and spectra of all new compounds. See DOI: 10.1039/c4cc06369d



Scheme 1 Intermolecular redox amination.

Recently redox amination has emerged as a powerful synthetic tool for the formation of C–N bonds.[5–7] For example, our group reported a redox amination reaction between pyrroline and carbonyl compounds for the synthesis of *N*-alkyl pyrrole derivatives.[6] *N*-alkyl indoles are likewise available by redox amination of aldehydes with indolines or 2-carboxy indolines.[7] On the basis of this precedent, we hypothesized that the N–N bond in 1-amino indoles could be formed *via* redox amination of nitroso compounds with indolines.[8,9] Herein we report the synthesis of *N*-aryl-1-aminoindoles by a new N–N bond forming redox amination using mild Brønsted acid catalysis (Scheme 1).

Table 1 Optimization of acid catalyzed redox amination[a]

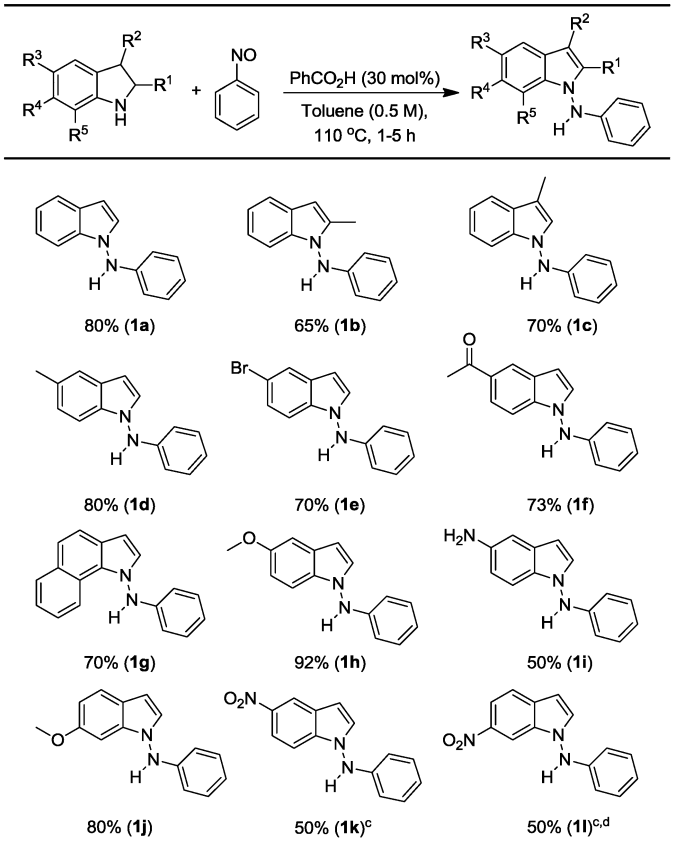


Entry	Catalyst	Solvent	Indoline (equiv.)	Time (min)	Yield[b] (%)
1	$PhCO_2H$	Toluene	1.0	90	60
2[c]	$PhCO_2H$	Toluene	2.0	120	70
3[d]	**$PhCO_2H$**	Toluene	**1.0**	**60**	**80**
4	—	Toluene	1.0	60	—
5[d]	$Bi(OTf)_3$	Toluene	1.0	60	—
6[d]	TfOH	Toluene	1.0	60	—
7[d]	TFA	Toluene	1.0	60	25
8[d]	CH_3CO_2H	Toluene	1.0	60	63
9[d]	$PhCO_2H$	DMSO	1.0	60	19
10[d]	$PhCO_2H$	THF	1.0	60	59
11[d]	$PhCO_2H$	DCM	1.0	60	63

[a] Reactions were carried out at 0.5 mmol indoline in the presence of 30 mol% catalyst. [b] Isolated yield. [c] Room temperature. [d] Dropwise addition of nitrosobenzene over 1 hour.

We initiated our studies using conditions similar to those used for redox amination of aldehydes with pyrrolines (Table 1, entry 1). Gratifyingly, heating a solution of indoline and nitrosobenzene at 110 °C in toluene led to a 60% yield of the desired 1-aminoindole. Importantly, analysis of the crude reaction mixture revealed that the moderate yield resulted from competing reductive dimerization of nitrosobenzene.[10] Indeed, increasing the equivalents of indoline led to an increased yield of 1-aminoindole (entry 2). Ultimately, to avoid dimerization of nitrosobenzene, while utilizing a single equivalent of indoline, a solution of nitrosobenzene was added dropwise to a solution of benzoic acid catalyst and indoline (entry 3). Under these conditions, an 80% yield of 1-amino indole was isolated. The reaction did not proceed without catalyst or when using highly acidic $Bi(OTf)_3$ or TfOH catalysts (entries 4–6). Weaker Brønsted acids are superior catalysts, with TFA giving just 25% yield while acetic acid provides the product in 63% yield (entries 7, 8). We propose that the dependence of the reaction yield on acid strength can be explained by the need for the conjugate base of the catalyst to facilitate prototropic rearrangement of the putative azonium intermediate (Scheme 1). Finally, the redox amination is solvent dependent, with the polar solvent DMSO giving a poor yield (19%, entry 9) and the non-polar solvent toluene giving the highest yield (80%, entry 3).

Table 2 Redox amination of indolines with nitrosobenzene[a,b]



[a] Reactions were carried out in a mixture of indoline (0.5 mmol) and $PhCO_2H$ (0.15 mmol) in 0.2 mL toluene with dropwise addition of nitrosobenzene (0.5 mmol, 0.625 M). [b] Isolated yields. [c] 1.0 mmol indoline. [d] 19 h reaction time.

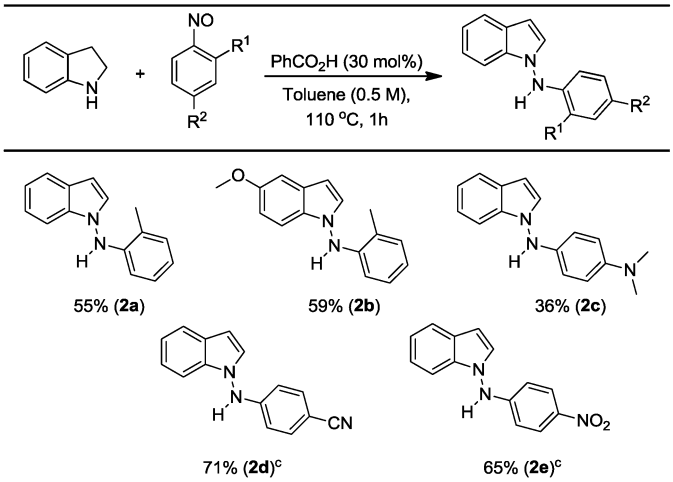
With the optimized reaction conditions for the redox amination of indoline with nitrosobenzene in hand, we decided to investigate the substrate scope of redox amination reaction with respect to functionalized indolines (Table 2). Thus, a series of indolines containing different functional groups were treated with nitrosobenzene and 30 mol% of benzoic acid catalyst at 110 °C in toluene to furnish *N*-aryl-1-aminoindoles. Aminoindole products were formed in good to excellent yields as shown in Table 2. 2-Me, 3-Me and 5-Me substituted indolines gave good yields of the redox aminated products (**1a–c**). The reaction is compatible with indolines that bear electron withdrawing or donating substituents, however an electron-rich indoline (**1h**) gave the highest yield.

Importantly, an acetyl substituted indoline gave the expected redox aminated product **1f** with no evidence of competing redox amination of the ketone.[6] Lastly, an indoline with an unprotected aniline was compatible with our redox amination, although the product **1i** was formed in moderate yield. In addition, a benzo-fused indoline gave product **1g** in good yield; benzoindoles are a basic skeleton found in several biologically active compounds.[11]

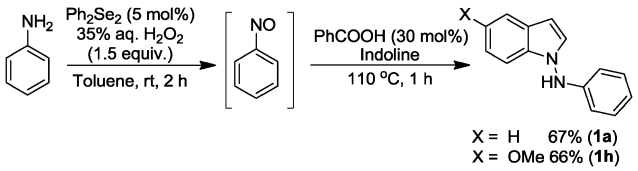
After successful demonstration of the different indoline substrates in the redox amination we further studied the scope of the reaction with several different nitrosobenzenes (Table 3). While the sterically demanding and electron rich, *ortho*-nitrosotoluene gave moderate yields of product (**2a,b**), nitrosoarenes with electron withdrawing substituents gave better yields of the redox aminated products **2d–e**. While some yields are modest, the ability to access 1-aminoindoles in such a rapid and simple manner is noteworthy.

Lastly, since nitrosoarenes are not commercially available, the development of a one-pot synthesis of *N*-aryl-1-aminoindoles starting from simple anilines is attractive. With this in mind, aniline was utilized in a selenium-catalyzed oxidation with hydrogen peroxide followed by treatment with 1 equiv. of indoline and catalytic benzoic acid.[12] This one-pot process furnished the expected *N*-aryl-1-aminoindoles (**1a,h**) in good yields (Scheme 2).

Table 3 Redox amination of indolines with different nitrosobenzenes[a,b]



[a] Reactions were carried out in a mixture of indoline (0.5 mmol) and $PhCO_2H$ (0.15 mmol) in 0.2 mL toluene with dropwise addition of nitrosobenzene (0.5 mmol, 0.625 M) in 0.8 mL toluene for 1 hour. [b] Isolated yields. [c] Nitrosobenzene added in one portion.



Scheme 2 Redox amination in one-pot from aniline.

In conclusion, redox amination is a straightforward method for the formation of N–N bonds from indolines and nitrosoarenes. This process is driven by the inherent reducing power of indolines and is facilitated by a mild Brønsted acid catalyst. Ultimately the redox amination described herein provides rapid access to biologically relevant *N*-aryl-1-aminoindoles. Moreover, the one-pot synthesis of *N*-aryl-1-aminoindoles was demonstrated starting from simple anilines and indolines.

Notes and references

1 (*a*) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970; (*b*) R. J. Sundberg, Pyrroles and Their Benzoderivatives: Synthesis and Applications, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 4, pp. 313–376; (*c*) R. J. Sundberg, *in Best Synthetic Methods, Indoles*, Academic Press, New York, 1996, pp. 7–11; (*d*) E. Breitmaier, *Alkaloide*, Teubner Studienbücher Chemie, Stuttgart, 1997, pp. 116–129.

2 (*a*) J. T. Klein, L. Davis, G. E. Olsen, G. S. Wong, F. P. Huger, C. P. Smith, W. W. Petko, M. Cornfeldt, J. C. Wilker, R. D. Blitzer, E. Landau, V. Haroutunian, L. L. Martin and R. C. Effland, *J. Med. Chem.*, 1996, **39**, 570–581; (*b*) C. P. Smith, G. M. Bores, W. Petko, M. Li, D. E. Selk, D. K. Rush, F. Camacho, J. T. Winslow, R. Fishkin, D. M. Cunningham, K. M. Brooks, J. Roehr, H. B. Hartman, L. Davis and H. M. Vargas, *J. Pharmacol. Exp. Ther.*, 1997, **280**, 710–720; (*c*) B. Mester, R. M. Claramunt, J. Elguero, J. Atienza, A. G. Barrio and J. A. Escario, *Chem. Pharm. Bull.*, 1991, **29**, 1990–1993; (*d*) L. Anderson, J. Perregaard, J. Arnt, J. Bay Nielsen and M. Begtrup, *J. Med. Chem.*, 1992, **35**, 4823–4831; (*e*) D. Morin, A. Zlnl, S. Urien and J. P. Tillement, *J. Pharmacol. Exp. Ther.*, 1989, **249**, 288–296.

3 (*a*) B. A. Frontana-Uribe, C. Moinet and L. Toupet, *Eur. J. Org. Chem.*, 1999, 419–430; (*b*) K. Kirschke, A. Misller, E. Schmitz, R. J. Kuban and B. Schulz, *Tetrahedron Lett.*, 1986, **27**, 4281–4284; (*c*) U. R. Aulwurm, J. U. Melchinger and H. Kisch, *Organometallics*, 1995, **14**, 3385–3395; (*d*) S. Messaoudi, J. D. Brion and M. Alami, *Tetrahedron Lett.*, 2011, **52**, 2687–2691; (*e*) N. Halland, M. Nazaré, J. Alonso, O. R'kyek and A. Lindenschmidt, *Chem. Commun.*, 2011, 1042–1044; (*f*) F. J. Weiberth, R. G. Hanna, G. L. Lee, Y. Polverine and J. T. Klein, *Org. Process Res. Dev.*, 2011, **15**, 704–709; (*g*) M. Somei and M. Natsume, *Tetrahedron Lett.*, 1974, **15**, 461–462; (*h*) N. Ghavtadze, R. Narayan, B. Wibbeling and E.-U. Würtheim, *J. Org. Chem.*, 2011, **76**, 5185–5197.

4 For a recent example of oxidative N–N bond formation see: B. R. Rosen, E. W. Werner, A. G. O'Brien and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5571–5574.

5 (*a*) M. Haibach, I. Deb, C. K. De and D. Seidel, *J. Am. Chem. Soc.*, 2011, **133**, 2100–2103; (*b*) S. Murarka, I. Deb, C. Zhang and D. Seidel, *J. Am. Chem. Soc.*, 2009, **131**, 13226–13227; (*c*) S. Murarka, C. Zhang, M. D. Konieczynska and D. Seidel, *Org. Lett.*, 2009, **11**, 129–132; (*d*) C. Zhang, S. Murarka and D. Seidel, *J. Org. Chem.*, 2009, **74**, 419–422; (*e*) C. Zhang, C. K. De, R. Mal and D. Seidel, *J. Am. Chem. Soc.*, 2008, **130**, 416–417; (*f*) I. Deb, D. J. Coiro and D. Seidel, *Chem. Commun.*, 2011, 6473–6475; (*g*) M. F. Aly, H. Ardill, R. Grigg, S. L. Ling, S. Rajviroongit and S. Surendrakumar, *Tetrahedron Lett.*, 1987, **28**, 6077–6080; (*h*) H. Mao, S. Wang, P. Yu, H. Lu, R. Xu and Y. Pan, *J. Org. Chem.*, 2011, **76**, 1167–1169; (*i*) M. K. Vecchione, A. X. Sun and D. Seidel, *Chem. Sci.*, 2011, **2**, 2178–2181; (*j*) L. Li and D. Seidel, *Org. Lett.*, 2010, **12**, 5064–5067.

6 N. K. Pahadi, M. Paley, R. Jana, S. R. Waetzig and J. A. Tunge, *J. Am. Chem. Soc.*, 2009, **131**, 16626–16627.

7 (*a*) M. F. Aly, H. Ardill, R. Grigg, S. Leong-Ling, S. Rajviroongit and S. Surendrakumar, *Tetrahedron Lett.*, 1987, **28**, 6077–6080; (*b*) C. Zhang and D. Seidel, *J. Am. Chem. Soc.*, 2010, **132**, 1798–1799; (*c*) I. Deb, D. Das and D. Seidel, *Org. Lett.*, 2011, **13**, 812–815; (*d*) C. Zhang, D. Das and D. Seidel, *Chem. Sci.*, 2011, **2**, 233–236; (*e*) H. Mao, R. Xu, J. Wan, Z. Jiang, C. Sun and Y. Pan, *Chem. – Eur. J.*, 2010, **16**, 13352–13355.

8 For reductive amination (dimerization) of nitroso and nitroarenes see: (*a*) M. D. Rausch, W. E. McEwen and J. Kleinber, *Chem. Rev.*, 1957, **57**, 417–437; (*b*) J. M. Khurana and S. Singh, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1893–1895.

9 M. C. R. Ruiz and A. Vasella, *Helv. Chim. Acta*, 2011, **94**, 785–800.

10 (*a*) N. Sakai, K. Fujii, S. Nabeshima, R. Ikeda and T. Konakahara, *Chem. Commun.*, 2010, **46**, 3173–3175; (*b*) D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2005, **7**, 1577–1580.

11 (*a*) E.-M. Karg, S. Luderer, C. Pergola, U. Bühring, A. Rossi, H. Northoff, L. Sautebin, R. Troschütz and O. Werz, *J. Med. Chem.*, 2009, **52**, 3474–3483; (*b*) A. Koeberle, E.-M. Haberl, A. Rossi, C. Pergola, F. Dehma, H. Northoff, R. Troschuetz, L. Sautebin and O. Werz, *Bioorg. Med. Chem.*, 2009, **17**, 7924–7932.

12 For the synthesis of nitroso compounds see: (*a*) B. Priewish and K. Ruck Braun, *J. Org. Chem.*, 2005, **70**, 2350–2352; (*b*) S. Tollari, M. Cuscela and F. Porta, *J. Chem. Soc., Chem. Commun.*, 1993, 1510–1511; (*c*) D. Zhao, M. Johansson and J. E. Bäckvall, *Eur. J. Org. Chem.*, 2007, 4431–4436.

