RSC Advances

RSC Publishing

PAPER

View Article Online
View Journal

Utilization of carbon disulfide as a powerful building block for the synthesis of 2-aminobenzoxazoles†

Cite this: DOI: 10.1039/c3ra41189c

Tirumaleswararao Guntreddi, Bharat Kumar Allam and Krishna Nand Singh*

Received 11th March 2013,
Accepted 10th April 2013

DOI: 10.1039/c3ra41189c

www.rsc.org/advances

This protocol describes a novel, mild and convenient route to afford 2-aminobenzoxazoles in high yields, and represents a significant advance towards an environmentally friendly strategy. Aliphatic amines are made to react with carbon disulfide to provide intermediate dithiocarbamates (DTC), which in the presence of 2-aminophenol, subsequently undergo successive intermolecular nucleophilic attack and desulfurization to produce 2-aminobenzoxazoles within 3 h.

1. Introduction

Eco-friendly straightforward processes and innovative products, which have lower the environmental impact, are now a top priority. Integrating green chemistry principles into the development of new processes and re-evaluation of existing processes are the key elements of sustainable development. In order to replace processes which have negative environmental impacts, new developments must use nontoxic materials, save energy, and generate less waste.[1]

Nitrogen-rich heterocyclic compounds have a profound effect on human health because these chemical motifs are present in a number of drugs used to combat a broad range of diseases and pathophysiological conditions.[2] Functionalized azoles are especially important structural designs present in a variety of natural products.[3] Amongst them, 2-aminobenzoxazoles exhibit potential therapeutic activities.[4] Therefore, the development of efficient and eco-safe protocols for the construction of these heterocycles is highly desirable.

2-Aminobenzoxazoles have been prepared by the nucleophilic displacement of 2-substituted benzoxazoles with an amine,[5a–c] cyclodesulfurization of 2-hydroxyarylthioureas,[5d,5e] and also *via* direct amination of benzoxazoles.[5f,5g] More importantly, 2-aminobenzoxazoles can be expediently synthesized from 2-aminophenol by three versatile routes (Fig. 1) *viz.* a) preparation of polymer-bound 2-mercaptobenzoxazole resins by the reaction of Merrifield resin with 2-aminophenols and CS_2 in the presence of *N*,*N*′-diisopropylcarbodiimide (DIC) in CH_3CN, followed by further oxidation of the resulting resin and subsequent treatment with amines,[6] b) a reaction involving tetramethyl orthocarbonate, an amine and 2-aminophenol,[7] and c) by the reaction of aryl isothiocyanates with 2-aminophenols.[8,9] While these protocols have advantages, they also possess limitations such as availability and toxicity of reagents. Furthermore, these protocols demonstrate poor step efficiency, which makes them unattractive from a sustainability point of view. Solvent-free reactions have drawn considerable attention because of their environmentally benign character.[10] Carbon disulfide, the sulfur analogue of carbon dioxide, is a valuable C_1 building block and solvent used in the chemical industries for the production of materials such as rayon and cellophane and for the synthesis of a wide range of organosulfur compounds including dithiocarbamates, xanthates and thioureas. Notably, CS_2 is more reactive towards nucleophiles due to the weaker π-donor ability of the sulfido centres, which renders the carbon more electrophilic.[11]

In view of the above and as a part of our ongoing explorations,[12] we have envisioned and undertaken a straightforward connective route for the preparation of 2-aminobenzoxazoles using a one-pot reaction of 2-aminophenol, carbon disulfide, and amines without a catalyst and a solvent.

2. Results and discussion

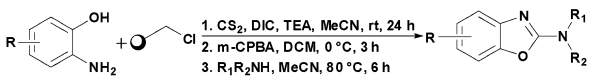
Our initial studies were aimed at optimizing the reaction conditions by using a model reaction involving piperidine (**1a**), carbon disulfide (**2**), and 2-aminophenol (**3a**). The findings are given in Table 1. To our delight the reaction proceeded smoothly in the absence of catalyst and solvent to selectively afford the target 2-piperidobenzoxazole (**4a**) in 71% yield at 100 °C after five hours (Table 1, entry 1). A modest increase in the reaction temperature (110 °C), however, brought about a considerable enhancement in the product yield (90%) in three hours (Table 1, entry 2). Increasing the temperature further did not increase the yield of the reaction (Table 1, entry 3). To study the effect of base on the yield of the reaction, a series of bases, *viz.* K_2CO_3, Na_2CO_3 and Cs_2CO_3 were screened and it was found that they did not improve the yield of the reaction

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, India. E-mail: knsingh@bhu.ac.in

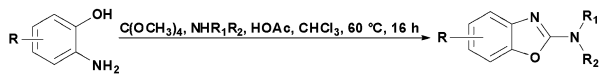
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra41189c

Progress to date:

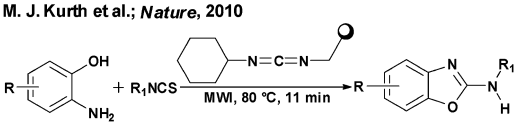
Y.-D. Gong et al.; *J. Comb. Chem.*, 2006



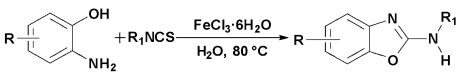
C. L. Cioffi et al.; *J. Org. Chem.*, 2010



M. J. Kurth et al.; *Nature*, 2010



X. Zhang et al.; *Green Chem.*, 2011



This work:

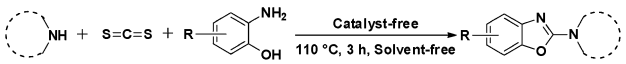
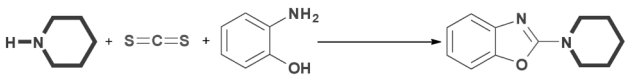


Fig. 1 Approaches for the synthesis of 2-aminobenzoxazoles.

(Table 1, entries 4–6). In order to observe the effect of solvent on the reaction, various polar and non-polar solvents such as DMF, CH_3CN, THF, 1,4-dioxane, DCE, DMSO, H_2O, NMP and toluene (Table 1, entries 7–15) were tried but none of them could match the end result of the solvent free conditions.

Table 1 Optimization of reaction conditions[a]



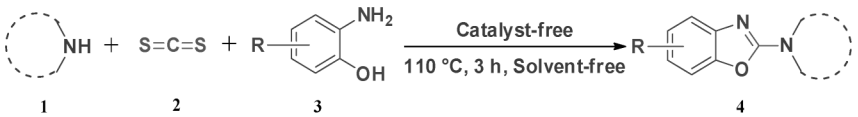
1a 2 3a 4a

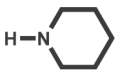
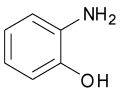
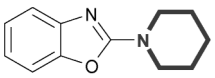
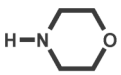
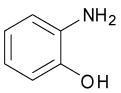
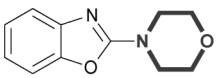
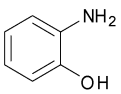
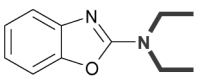
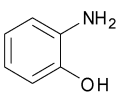
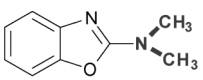
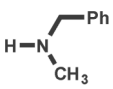
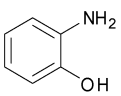
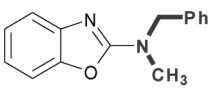
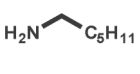
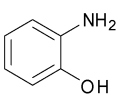
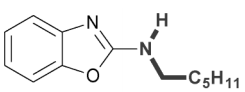
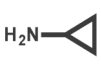
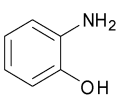
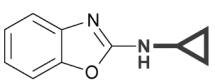
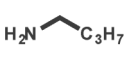
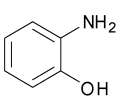
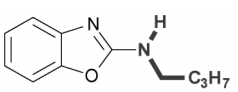
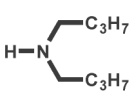
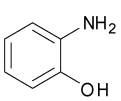
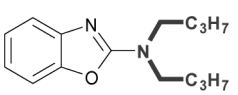
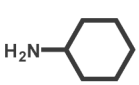
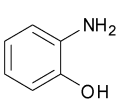
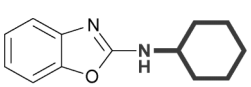
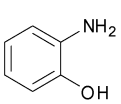
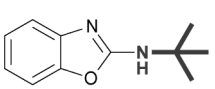
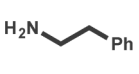
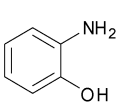
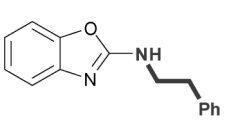
Entry	Base	Solvent	*T*/°C	Time (h)	Yield (%)[b]
1.	—	—	100	5	71
2.	—	—	**110**	**3**	**90**
3.	—	—	120	3	90
4.	K_2CO_3	—	110	3	89
5.	Na_2CO_3	—	110	3	90
6.	CS_2CO_3	—	110	3	87
7.	—	DMF	110	10	80
8.	—	CH_3CN	80	10	65
9.	—	THF	65	10	40
10.	—	1,4-Dioxane	100	10	68
11.	—	DCE	85	10	54
12.	—	DMSO	110	10	45
13.	—	H_2O	100	10	trace
14.	—	NMP	110	10	49
15.	—	Toluene	110	10	60

[a] Using **1a** (1.5 mmol), **2** (1.5 mmol) and **3a** (1 mmol). [b] Isolated yield based on 2-aminophenol.

With the optimized conditions in hand (Table 1, entry 2), the scope and versatility of the method was then extended to a variety of amine and 2-aminophenol partners. As shown illustrated in Table 2, a range of amines such as piperidine (**1a**), morpholine (**1b**), *N*,*N*-diethylamine (**1c**), *N*,*N*-dimethylamine (**1d**), *N*-methylbenzylamine (**1e**), n-hexylamine (**1f**), cyclopropylamine (**1g**), n-butylamine (**1h**), *N*,*N*-dibutylamine (**1i**), cyclohexylamine (**1j**), *tert*-butylamine (**1k**), 2-phenylethylamine (**1l**), benzylamine (**1m**) and *N*,*N*-dipropylamine (**1n**) underwent smooth reaction with carbon disulfide (**2**) and different 2-aminophenols *viz.* 2-aminophenol (**3a**), 4-methyl-2-aminophenol (**3b**) and 4-nitro-2-aminophenol (**3c**) to deliver a series of 2-aminobenzoxazole derivatives (**4a–4u**) in moderate to excellent yields (56–96%). An electron withdrawing substituent installed at the 4-position of 2-aminophenol increased the yield of the reaction considerably (Table 2, entries 18–21), while an electron-donating substituent decreased the yield of the reaction (Table 2, entries 15–17). Aromatic primary and secondary amines failed to produce the desired 2-aminobenzoxazoles. Anilines bearing different substituents ($-OCH_3$, $-CH_3$, and –Cl) were screened as reaction partners along with CS_2 and 2-aminophenol, but none of them afforded the desired product (entries 22–24). However, the formation of small amounts of symmetrically substituted thiourea was observed at 110 °C after 3 h. Reactions were also carried out with amino group-containing heterocycles, such as 2-aminopyridine and 2-aminothiophene, in the presence of CS_2, and 2-aminophenol, resulting in no desired product formation (entries 25 and 26). However, the formation of trace amounts of symmetrically substituted thiourea was observed in the case of 2-aminopyridine at 110 °C after 3 h. Heterocyclic secondary amines such as pyrrole, imidazole, and pyrazole were also tested as amine variants along with CS_2, and 2-aminophenol, with no corresponding product formation (entries 27–29). Aliphatic secondary amines participated more rapidly in these transformations. When aliphatic primary amines were used, formation of the corresponding symmetrically substituted thiourea was invariably observed as a side product, however, no such product formation was noticed in the case of secondary amines, in accordance with the reported literature.[13] Primary amines with a phenyl ring at α- or β- position demonstrated a marked yield loss (entries 12 and 13). It is interesting to note that the desired product was not formed at all in the case of cyclopropylamine (**1g**), rather 2-mercaptobenzoxazole (**6**) was observed as the main product along with the symmetrically substituted thiourea. To improve the environmental friendliness of our methodology, efforts were made to trap the evolved H_2S by using *N*,*N*′-dicyclohexylcarbodiimide (DCC). Unfortunately, the utilization of DCC significantly decreased the yield of the product, probably due to the formation of side products arising from the reaction of 2-aminophenol with DCC.

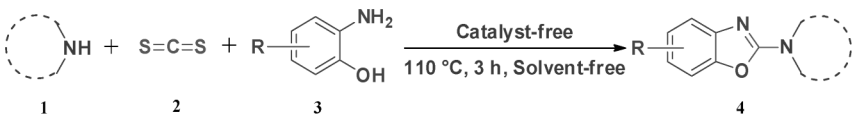
Table 2 Substrate scope for the one-pot synthesis of 2-amino benzoxazoles[a]



Entry	Amine (**1**)		One carbon surrogate (**2**)	2-Aminophenol (**3**)	Product (**4**)		Yield (%)[b]
1.		**1a**	CS_2	**2** 	**3a** 	**4a**	90
2.		**1b**	CS_2	**2** 	**3a** 	**4b**	87
3.		**1c**	CS_2	**2** 	**3a** 	**4c**	85
4.		**1d**	CS_2	**2** 	**3a** 	**4d**	80
5.		**1e**	CS_2	**2** 	**3a** 	**4e**	79
6.		**1f**	CS_2	**2** 	**3a** 	**4f**	75
7.		**1g**	CS_2	**2** 	**3a** 	**4g**	0
8.		**1h**	CS_2	**2** 	**3a** 	**4h**	75
9.		**1i**	CS_2	**2** 	**3a** 	**4i**	69
10.		**1j**	CS_2	**2** 	**3a** 	**4j**	67
11.		**1k**	CS_2	**2** 	**3a** 	**4k**	65
12.		**1l**	CS_2	**2** 	**3a** 	**4l**	60

[a] Using **1** (1.5 mmol), **2** (1.5 mmol) and **3** (1 mmol) at 110 °C for 3 h. [b] Isolated yield based on 2-aminophenol.

Table 2 (*Continued*)



1 2 3 4

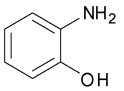
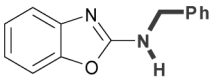
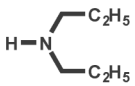
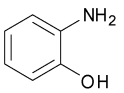
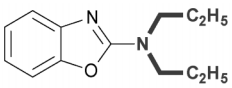
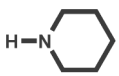
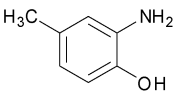
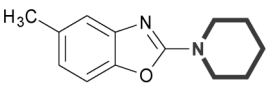
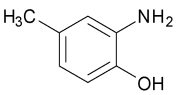
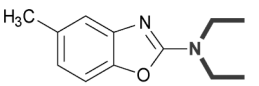
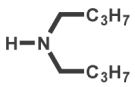
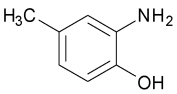
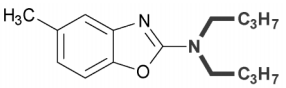
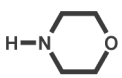
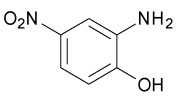
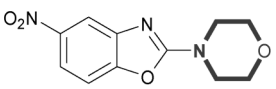
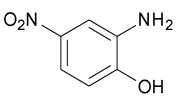
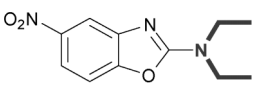
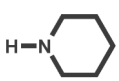
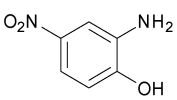
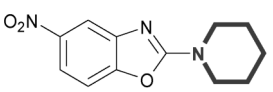
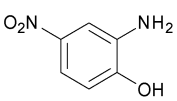
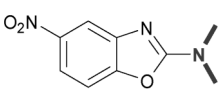
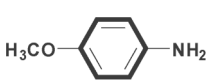
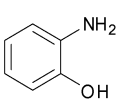
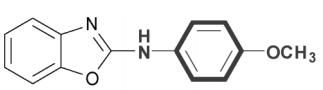
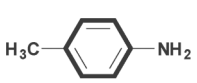
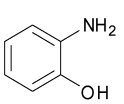
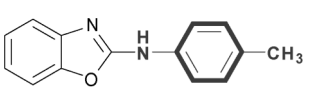
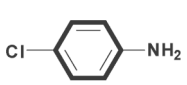
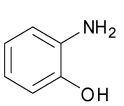
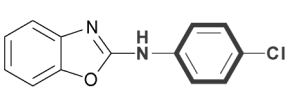
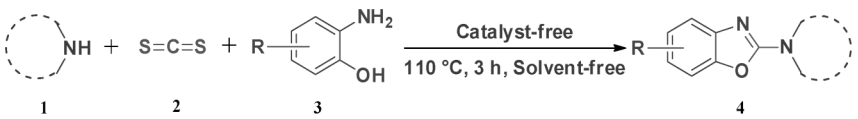
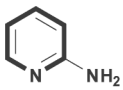
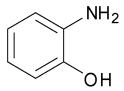
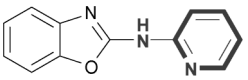
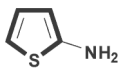
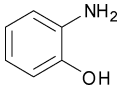
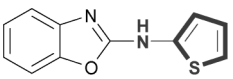
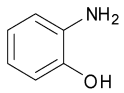
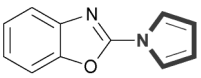
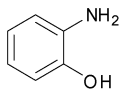
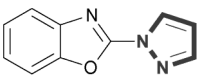
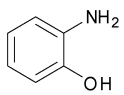
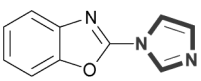
Entry	Amine (**1**)		One carbon surrogate (**2**)	2-Aminophenol (**3**)		Product (**4**)		Yield (%)[b]
13.		**1m**	CS_2	**2**		**3a**		**4m**	56
14.		**1n**	CS_2	**2**		**3a**		**4n**	75
15.		**1a**	CS_2	**2**		**3b**		**4o**	77
16.		**1c**	CS_2	**2**		**3b**		**4p**	70
17.		**1i**	CS_2	**2**		**3b**		**4q**	63
18.		**1b**	CS_2	**2**		**3c**		**4r**	94
19.		**1c**	CS_2	**2**		**3c**		**4s**	90
20.		**1a**	CS_2	**2**		**3c**		**4t**	96
21.		**1d**	CS_2	**2**		**3c**		**4u**	80
22.		**1o**	CS_2	**2**		**3a**		**4v**	0
23.		**1p**	CS_2	**2**		**3a**		**4w**	0
24.		**1q**	CS_2	**2**		**3a**		**4x**	0

Table 2 (*Continued*)



Entry	Amine (**1**)		One carbon surrogate (**2**)	2-Aminophenol (**3**)		Product (**4**)		Yield (%)[b]
25.		**1r**	CS_2	**2**		**3a**		**4y**	0
26.		**1s**	CS_2	**2**		**3a**		**4z**	0
27.		**1t**	CS_2	**2**		**3a**		**4aa**	0
28.		**1u**	CS_2	**2**		**3a**		**4ab**	0
29.		**1v**	CS_2	**2**		**3a**		**4ac**	0

Based upon isolation of products and the existing literature, a plausible reaction pathway is outlined in Fig. 2. The formation of symmetrically substituted thiourea as a side product suggests the involvement of dithiocarbamate (**5**) as an intermediate. To confirm the presence of dithiocarbamate (**5**) during the course of reaction, a control experiment was conducted using a secondary amine (**1a**) and CS_2 alone under the optimized set of conditions, proving the formation of intermediate **5**. To further confirm the intermediacy of **5**, an additional experiment was carried out with a large excess of primary aliphatic amine **1l** and CS_2, which afforded the symmetrically substituted thiourea (**8**) as main product.

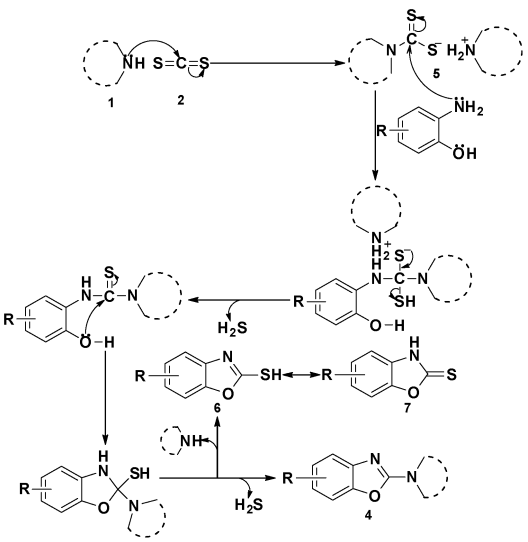


Fig. 2 Plausible mechanism of the reaction.

3. Experimental section

3.1 General remarks

^1H and ^{13}C NMR spectra were run on a JEOL AL300 FTNMR spectrometer at 300 MHz and 75 MHz respectively, at a temperature of 300 K. NMR chemical shifts are expressed in δ values with reference to tetramethylsilane (TMS) as an internal standard.

All reagents were procured from Aldrich, USA, and were used without further purification. The solvents were purified and dried according to standard methods prior to use. All reactions were carried out under an atmosphere of air. Reactions were monitored using thin-layer chromatography (TLC) carried out on silica gel 60/Kieselguhr F254 pre-coated on aluminium sheets (thickness 0.2 mm), commercially available from Merck, using ultra-violet light as the visualizing agent and I_2 as the developing agent.

3.2 General experimental procedure

A mixture of amine (**1**, 1.5 mmol) and CS_2 (**2**, 1.5 mmol), contained in a 25 mL round bottomed (R.B) flask with a magnetic stir bar, was stirred thoroughly for 60 min resulting in the formation of the intermediate dithiocarbamate (DTC). To it was then added 2-aminophenol (**3**, 1 mmol), and the flask containing the mixture equipped with a condenser, and heated at a temperature of 110 °C in an oil bath for 3 h. On completion of the reaction (by TLC), the resulting mixture was subsequently partitioned between ethyl acetate (5 mL) and water (10 mL). The aqueous layer was extracted thrice with ethyl acetate (5 mL) and the collected organic phases was dried (anhyd. Na_2SO_4), concentrated under vacuum and then purified by column chromatography on silica gel using mixtures of ethyl acetate and hexane as the eluting agent.

4. Conclusions

This novel approach offers advantages such as high efficiency, readily available starting materials, a simple experimental procedure, and good to excellent yields. In conclusion, we strongly believe that the versatility of this approach will open a new avenue for its application in heterocyclic chemistry.

Acknowledgements

We thank Council of Scientific and Industrial Research (CSIR), New Delhi and Department of Biotechnology (DBT), New Delhi for financial assistance.

Notes and references

1 (*a*) C. -J. Li and P. T. Anastas, *Chem. Soc. Rev.*, 2012, **41**, 1413; (*b*) P. J. Dunn, *Chem. Soc. Rev.*, 2012, **41**, 1452; (*c*) M. Philippe, B. Didillon and L. Gilbert, *Green Chem.*, 2012, **14**, 952; (*d*) R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437; (*e*) W. J. W. Watson, *Green Chem.*, 2012, **14**, 251.

2 Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95.

3 (*a*) P. S. M. Sommer, R. C. Almeida, K. Schneider, W. Beil, R. D. Süssmuth and H. -P. Fiedler, *J. Antibiot.*, 2008, **61**, 683; (*b*) Z. Li, P. Zhan, L. Naesens, E. Vanderlinden, A. Liu, G. Du, E. De Clercq and X. Liu, *Chem. Bio. Drug Des.*, 2012, **79**, 1024.

4 (*a*) M. A. Estiarte, R. J. Johnson, C. J. Kaub, S. Gowlugari, D. J. R. O'Mahony, M. T. Nguyen, D. E. Emerling, M. G. Kelly, J. Kincaid, F. Vincent and M. A. J. Duncton, *Med. Chem. Commun.*, 2012, **3**, 611; (*b*) l. K. Mangion, B. D. Sherry, J. Yin and F. J. Fleitz, *Org. Lett.*, 2012, **14**, 3458; (*c*) C. J. O'Donnell, B. N. Rogers, B. S. Bronk, D. K. Bryce, J. W. Coe, K. K. Cook, A. J. Duplantier, E. Evrard, M. Hajós, W. E. Hoffmann, R. S. Hurst, N. Maklad, R. J. Mather, S. McLean, F. M. Nedza, B. T. O'Neill, L. Peng, W. Qian, M. M. Rottas, S. B. Sands, A. W. Schmidt, A. K. Shrikhande, D. K. Spracklin, D. F. Wong, A. Zhang and L. Zhang, *J. Med. Chem.*, 2010, **53**, 1222.

5 (*a*) F. Delmas, A. Avellaneda, C. D. Giorgio, M. Robin, E. D. Clercq, P. Timon-David and J. -P. Galy, *Eur. J. Med. Chem.*, 2004, **39**, 685; (*b*) M. Yamato, Y. Takeuchi, K. Hattori and K. Hashigaki, *Chem. Pharm. Bull.*, 1984, **32**, 3053; (*c*) J. Köevér, T. Tímár and J. Tompa, *Synthesis*, 1994, 1124; (*d*) X. H. Qian, Z. B. Li, G. H. Song and Z. Li, *J. Chem. Res.*, 2001, **4**, 138; (*e*) N. Wishart, A. Rudolph and K. Ritter, US Patent, US2003/0109714A1; (*f*) J. Y. Kim, S. H. Cho, J. Joseph and S. Chang, *Angew. Chem. Int. Ed.*, 2010, **49**, 9903; (*g*) S. Wertz, S. Kodama and A. Studer, *Angew. Chem., Int. Ed.*, 2011, **50**, 11511.

6 J. Y. Hwang and Y. -D. Gong, *J. Comb. Chem.*, 2006, **8**, 297.

7 C. L. Cioffi, J. J. Lancing and H. Yüksel, *J. Org. Chem.*, 2010, **75**, 7942.

8 R. D. Carpenter and M. J. Kurth, *Nature*, 2010, **5**, 1731.

9 X. Zhang, X. Jia, J. Wang and X. Fan, *Green Chem.*, 2011, **13**, 413.

10 (*a*) N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso and A. F. Trindade, *Chem. Rev.*, 2009, **109**, 2703; (*b*) D. B. Ramachary and S. Jain, *Org. Biomol. Chem.*, 2011, **9**, 1277; (*c*) J. O. Metzger, *Angew. Chem., Int. Ed.*, 1998, **37**, 2975.

11 P. W. Miller and D. Bender, *Chem.–Eur. J.*, 2012, **18**, 433.

12 (*a*) R. Vanjari, B. K. Allam and K. N. Singh, *RSC Adv.*, 2013, **3**, 1691; (*b*) T. Guntreddi, B. K. Allam and K. N. Singh, *Synlett*, 2012, **23**, 2635; (*c*) B. K. Allam and K. N. Singh, *Tetrahedron Lett.*, 2011, **52**, 5851; (*d*) B. K. Allam and K. N. Singh, *Synthesis*, 2011, 1125; (*e*) R. Singh, B. K. Allam, D. S. Raghuvanshi and K. N. Singh, *Tetrahedron*, 2013, **69**, 1038; (*f*) D. S. Raghuvanshi, A. K. Gupta and K. N. Singh, *Org. Lett.*, 2012, **14**, 4326.

13 M. R. Maddani and K. R. Prabhu, *J. Org. Chem.*, 2010, **75**, 2327.

