ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 5058–5060

www.rsc.org/chemcomm

COMMUNICATION

Regioselective *N*-alkylation of 2-aminobenzothiazoles with benzylic alcohols†

Feng Li,* Haixia Shan, Qikai Kang and Lin Chen

Received 31st January 2011, Accepted 4th March 2011
DOI: 10.1039/c1cc10604j

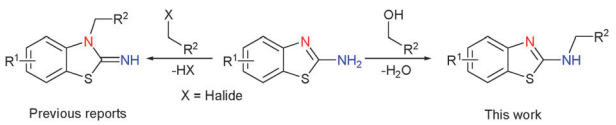
The preparation of 2-(*N*-alkylamino)benzothiazoles *via* regioselecive *N*-alkylation of 2-aminobenzothiazoles has been accomplished by using benzylic alcohols as alkylating agents.

The *N*-alkylation of amines is one of the most fundamental and important C–N bond-forming transformations in organic synthesis.[1] Traditionally, the *N*-alkylation of amines was performed with alkyl halides using stoichiometric bases. Recently, much attention has been paid to the *N*-alkylation of amines with alcohols as alkylating agents based on transition metal-catalyzed "hydrogen autotransfer (or hydrogen-borrowing) process".[2] Such methods are apparently attractive because of highly atom efficiency and the formation of water as the only side product. However, most studies were focused on using alcohols as benign alkylating agents instead of alkyl halides.[3] The potential of alcohols as alkylating agents other than alkyl halides on regioselectivity remains unrealized.

2-(*N*-alkylamino)benzothiazoles are very important structural units in many biologically active compounds,[4] and they also exhibit a wide range of pharmacological and physiological activities.[5] As a result, several transition metal-catalyzed methods have been developed for the preparation of 2-(*N*-alkylamino)benzothiazoles, including cyclization of *ortho*-halobenzothioureas,[6] oxidative C–H funcationalization of benzothioureas,[7] and oxidative decarbonylative coupling of benzothiazoles with formamides.[8] However, these procedures usually suffer from the multistep preparation of the starting materials, use of expensive metal catalysts and low functional group tolerance. Very recently, Ma and co-workers reported an Ullmann-type three-component method available for the synthesis of 2-(*N*-alkylamino)benzothiazoles from easily accessible 2-haloanilines in the presence of stoichiometric or excess amount of copper salts and bases.[9] The preparation of 2-(*N*-alkylamino)benzothiazoles *via* simple *N*-alkylation of 2-aminobenzothiazoles is still a challenge in organic synthesis.

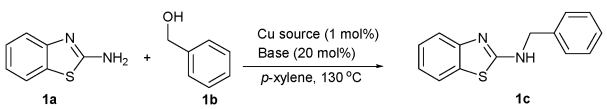
It was well documented that the *N*-alkylation of 2-aminobenzothiazoles with alkyl halides occurs on the most basic endocyclic nitrogen, affording *N*-endosubstituted 3-alkyl-2-iminobenzothiazolines as products (Scheme 1, left).[10] Herein, we wish to describe our efforts towards regioselective *N*-alkylation of 2-aminobenzothiazoles to *N*-exosubstituted 2-(*N*-alkylamino)benzothiazoles using alcohols as alkylating agents (Scheme 1, right). The copper/base was selected as the catalytic system here because it is cost-effective and has emerged for the *N*-alkylation of sulfonamides with alcohols.[2e,f]

Initially, the *N*-alkylation of 2-aminobenzothiazole **1a** with benzyl alcohol **1b** was chosen as a model to explore the feasibility of the reaction. The reaction was carried out in the presence of a copper salt (1 mol%) and NaOH (20 mol%) at 130 °C. When Cu(II) source was used as the catalyst, only low to moderate yields of the desired product **1c** were obtained (Table 1, entries 1–3). The reaction proceeded to afford **1c** with



Scheme 1 Regioselective *N*-alkylation of 2-aminobenzothiazoles with alkyl halides and alcohols.

Table 1 *N*-alkylation of 2-aminobenzothiazole **1a** with benzyl alcohol **1b** under various conditions[a]



Entry	Cu source	Base	Yield%[b]
1	$CuCl_2{\cdot}2H_2O$	NaOH	27
2	$CuBr_2$	NaOH	66
3	$Cu(OAc)_2$	NaOH	75
4	CuCl	NaOH	96
5	CuBr	NaOH	94
6	CuI	NaOH	93
7	CuCl	KOH	80
8	CuCl	Na_2CO_3	10
9	CuCl	K_2CO_3	21
10	CuCl	*t*BuONa	43
11	CuCl	*t*BuOK	37

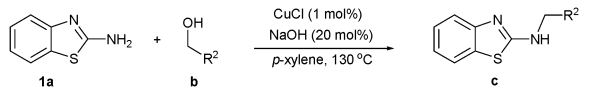
[a] Reaction conditions: 1 mmol amine, 1.2 mmol alcohol, 0.01 mmol Cu source, 0.2 mmol base, 130 °C, 12h. [b] Isolated yield.

School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, P. R. China.
E-mail: fengli@mail.njust.edu.cn; Fax: +86-25-84431939;
Tel: +86-25-84317316

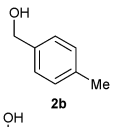
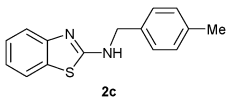
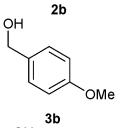
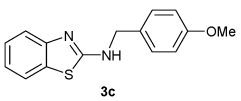
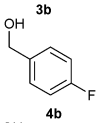
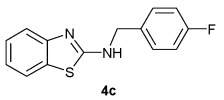
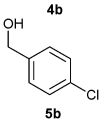
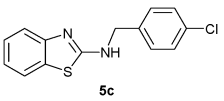
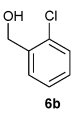
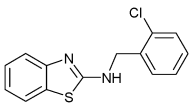
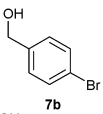
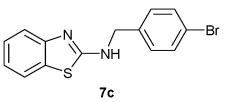
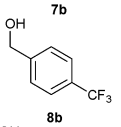
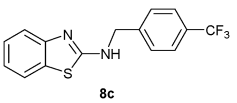
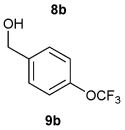
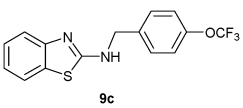
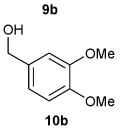
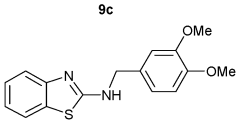
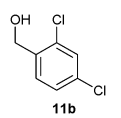
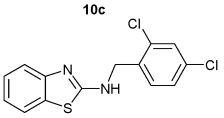
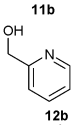
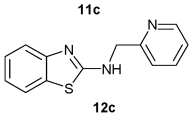
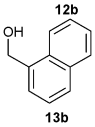
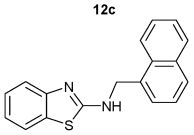
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for **1–20c**. See DOI: 10.1039/c1cc10604j

almost quantitative yields when Cu(I) source was used as the catalyst (entries 4–6). Among Cu(I) sources, CuCl was chosen as the catalyst for further research (entry 4). Using KOH, Na_2CO_3, K_2CO_3, *t*BuONa or *t*BuOK as alternative base for the reaction, decreases in the yield were observed (entries 7–11).

Table 2 *N*-alkylation of 2-aminobenzothiazole **1a** with various alcohols[a]



1a b c

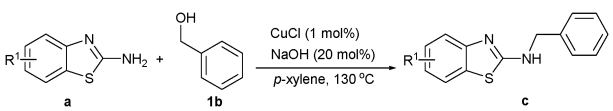
Entry	Alcohol	Product	Yield%[b]
1	 2b	 2c	97
2	 3b	 3c	92
3	 4b	 4c	94
4	 5b	 5c	90
5	 6b	 6c	91
6	 7b	 7c	98
7	 8b	 8c	85
8	 9b	 9c	75
9	 10b	 10c	81
10	 11b	 11c	83
11	 12b	 12c	85
12	 13b	 13c	80

[a] Reaction conditions: 1 mmol amine, 1.2 mmol alcohol, 0.01 mmol CuCl, 0.2 mmol NaOH, 130 °C, 12 h. [b] Isolated yield.

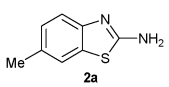
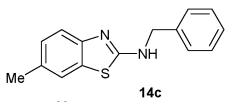
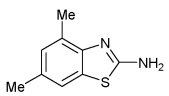
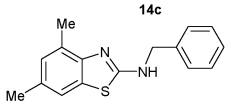
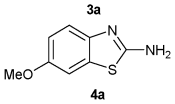
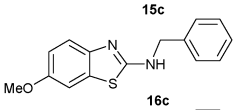
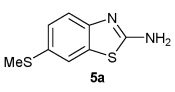
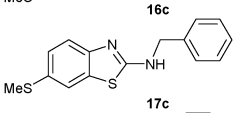
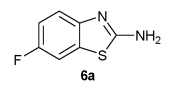
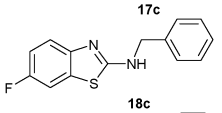
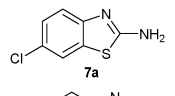
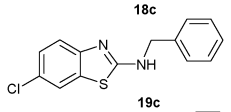
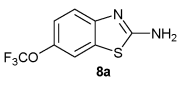
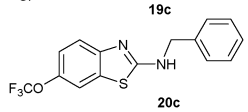
To expand the scope of the reaction, the *N*-alkylation of **1a** with various alcohols **b** was examined under the optimal conditions (Table 1, entry 4), and the results are summarized in Table 2. Similar to the case of **1b**, the *N*-alkylation of benzylic alcohols bearing a donating group, such as methyl **2b** and methoxyl **3b**, gave the corresponding products **2–3c** with 97% and 92% yields, respectively (Table 2, entries 1–2). The *N*-alkylation with benzylic alcohols bearing a halogen atom **4–7b** proceeded to give the corresponding products **4–7c** with excellent yields as well (entries 3–6). Benzylic alcohols bearing an electron-withdrawing group, such as trifluoromethyl **8b** and trifluoromethoxy **9b**, were successfully utilized to afford the desired products **8–9c** with 85% and 75% yields, respectively (entries 7–8). Further, reactions with benzylic alcohols bearing two substituted groups **10–11b** showed high activities and the corresponding products **10–11c** were obtained with 81% and 83% yields, respectively (entries 9–10). The reaction was also applied to 2-pyridylmethanol **12b** and 2-naphthalenemethanol **13b**, affording the desired products **12–13c** with 85% and 80% yields, respectively (entries 11–12). However, no reaction took place in the *N*-alkylation with aliphatic alcohols such as 1-butanol and cyclohexanol under the same conditions.

The *N*-alkylation of a variety of substituted 2-aminobenzothiazoles with **1b** was then investigated. As shown in Table 3, the *N*-alkylation of 2-aminobenzothiazoles bearing one or two

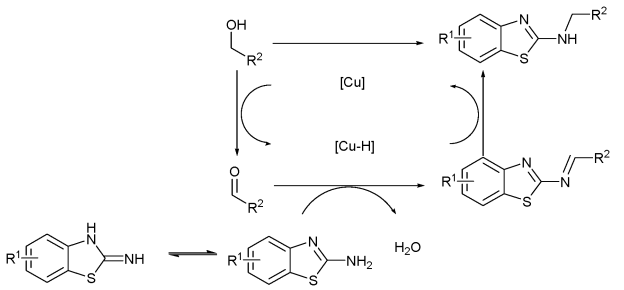
Table 3 *N*-alkylation of a variety of substituted 2-aminobenzothiazoles with benzyl alcohol **1b**[a]



a 1b c

Entry	Amine	Product	Yield%[b]
1	 2a	 14c	92
2	 3a	 15c	94
3	 4a	 16c	88
4	 5a	 17c	96
5	 6a	 18c	98
6	 7a	 19c	93
7	 8a	 20c	87[c]

[a] Reaction conditions: 1 mmol amine, 1.2 mmol alcohol, 0.01 mmol CuCl, 0.2 mmol NaOH, 130 °C, 12 h. [b] Isolated yield. [c] 160 °C.



Scheme 2 A possible mechanism for the regioselective *N*-alkylation reaction.

electron-donating substituents **2–5a** afforded the corresponding products **14–17c** with 88–96% yields (Table 3, entries 1–4). Similarly, 2-aminobenzothiazoles bearing a halogen atom **6–7a** were also converted into the corresponding products **18–19c** with excellent yields (entries 5–6). Further, the *N*-alkylation of 2-aminobenzothiazoles bearing an electron-withdrawing substituent **8a** afforded the desired product **20c** with 87% yields, though the elevated reaction temperature was required (entry 7).

In all case, no side product such as isomer 3-alkyl-2-iminobenzothiazoline and over-alkylated 2-(*N*-dialkylamino)-benzothiazoles was observed. Clearly, the reaction exhibited complete regioselectivity. It was also noteworthy that the substituent such as halide, methoxyl, thiomethyl, trifluoromethyl or trifluoromethoxy group on either benzyl alcohols or 2-amino-benzothiazoles could be tolerated under this reaction conditions.

Based on the experimental results and the known "hydrogen autotransfer (or hydrogen-borrowing) methodologies", a possible mechanism for the regioselective *N*-alkylation reaction is as follows (Scheme 2): the alcohols are first dehydrogenated to form the aldehydes with the generation of copper hydride species in the presence of bases.[11] Obviously, the exocyclic nitrogens are favored over endocyclic nitrogens in the process of the condensation of 2-aminobenzothiazoles with the resulting aldehydes, affording imine intermediates. Finally, the imine intermediates undergo the transfer hydrogenations to afford the 2-(*N*-alkylamino)benzothiazoles with regioselectivity, and the copper hydride species are also consumed.

In summary, we have developed a simple approach for the preparation of 2-(*N*-alkylamino)benzothiazoles *via* regioselective *N*-alkylation of 2-aminobenzothiazoles with benzylic alcohols. Notably, the research demonstrated new potential of alcohols as electrophiles. Efforts to elucidate the exact mechanism of reaction and expand the scope of reaction type are currently under way in our laboratory.

We are grateful to National Natural Science Foundation of China (No. 20902046) and Natural Science Foundation of Jiangsu Province (No. BK2009384) for financial support of this research. The project is also supported by the State Key Laboratory of Fine Chemicals, Dalian University of Technology (Grant No. KF0911).

Notes and references

1 (*a*) M. B. Smith and J. March, in *March's AdVanced Organic Chemistry*, Wiley-Interscience, New York, 2001, pp. 499-501; (*b*) B. M. Trost, T. Zhang and J. D. Sieber, *Chem. Sci.*, 2010, **1**, 427.
2 For selected reviews, see: (*a*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (*b*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753; (*c*) G. E. Dobereiner and R. H. Grabtree, *Chem. Rev.*, 2010, **110**, 681; (*d*) G. Guillena, D. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611.
3 (*a*) M. H. S. A. Hamid and J. M. J. Williams, *Chem. Commun.*, 2007, 725; (*b*) R. Yamaguchi, S. Kawagoe, C. Asai and K. I. Fujita, *Org. Lett.*, 2008, **10**, 181; (*c*) F. Shi, M. K. Tse, S. Zhou, M. M. Pohl, J. Radnik, S. Hubner, Klaus. J. A. Bruckner and M. Beller, *J. Am. Chem. Soc.*, 2009, **131**, 1775; (*d*) H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766; (*e*) F. Shi, M. K. Tse, X. Cui, D. Gördes, D. Michalik, K. Thurow, Y. Deng and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 5912; (*f*) X. Cui, F. Shi, M. K. Tse, D. Gördes, K. Thurow, M. Beller and Y. Deng, *Adv. Synth. Catal.*, 2009, **351**, 2949; (*g*) M. Zhu, K. Fujita and R. Yamaguchi, *Org. Lett.*, 2010, **12**, 1336.
4 (*a*) B. Cavalleri, M. Turconi, G. Tamborini, E. Occelli, G. Cietto, R. Pallanza, R. Scotti, M. Berti, G. Roman and F. Parenti, *J. Med. Chem.*, 1990, **33**, 1470; (*b*) J. Das, R. V. Moquin, J. Lin, C. Liu, A. M. Doweyko, H. F. Defex, Q. Fang, S. Pang, S. Pitt, D. R. Shen, G. L. Schieven, J. C. Barrish and J. Wityak, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2587; (*c*) S. R. Byeon, Y. J. Jin, S. J. Lim, J. H. Lee, K. H. Yoo, S. K. Jung, S. J. Ohb and D. J. Kim, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4022; (*d*) Z. Y. Sun, Z. Zhu, Y. Ye, B. McKittrick, M. Czarniecki, W. Greenlee, D. Mullins and M. Guzzi, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6801.
5 (*a*) I. D. Linney, I. M. Buck, E. A. Harper, S. B. Kalindjian, M. J. Pether, N. P. Shankley, G. F. Watt and P. T. Wright, *J. Med. Chem.*, 2000, **43**, 2362; (*b*) U. S. Sørensen, D. Strøbæk, P. Christophersen, C. Hougaard, M. L. Jensen, E. Nielsen, D. Peters, L. Teuber, U. S. Sørensen, D. Strøbæk, P. Christophersen, C. Hougaard, M. L. Jensen, E. Nielsen, D. Peters and L. Teuber, *J. Med. Chem.*, 2008, **51**, 7625; (*c*) S. N. Manjula, N. M. Noolvi, K. V. Parihar, S. A. M. Reddy, V. Ramani, A. K. Gadad, G. Singh, N. G. Kutty and C. M. Rao, *Eur. J. Med. Chem.*, 2009, **44**, 2923; (*d*) D. Cressier, C. Prouillac, P. Hernandez, C. Amourette, M. Diserbo, C. Lion and G. Rima, *Bioorg. Med. Chem.*, 2009, **17**, 5275.
6 (*a*) L. L. Joyce, G. Evindar and R. A. Batey, *Chem. Commun.*, 2004, 446; (*b*) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, *J. Org. Chem.*, 2009, **74**, 8719; (*c*) Q. Ding, X. He and J. Wu, *J. Comb. Chem.*, 2009, **11**, 587.
7 (*a*) K. Inamoto, C. Hasegawa, K. Hiroya and T. Doi, *Org. Lett.*, 2008, **10**, 5147; (*b*) L. L. Joyce and R. A. Batey, *Org. Lett.*, 2009, **11**, 2792.
8 S. H. Cho, J. Y. Kim, S. Y. Lee and S. Chang, *Angew. Chem., Int. Ed.*, 2009, **48**, 9127; Angew. Chem., 2009, 121, 9291.
9 D. Ma, X. Lu, L. Shi, H. Zhang, Y. Jiang and X. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1118.
10 (*a*) J. V. Metzger, *Thiazoles and their Benzo Derivatives. Comprehensive Heterocyclic Chemistry*, Pergamon Press Ltd, New York, 1984, vol. 6, pp. 235–331; (*b*) P. Jimonet, F. Audiau, M. Barreau, J. C. Blanchard, A. Boireau, Y. Bour, M. A. Coleno, A. Doble, G. Doerflinger, C. D. Huu, M. H. Donat, J. M. Duchesne, P. Ganil, C. Gueremy, E. Honore, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Laduron, J. L. Blevec, M. Meunier, J. M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, J. Rataud, M. Reibaud, J. M. Stutzmann and S. Mignani, *J. Med. Chem.*, 1999, **42**, 2828.
11 The process is supposed to be similar with the dehydrogenation of alcohols catalyzed by Ag/Al_2O_3-5, see: (*a*) K. Shimizu, K. Sugino and A. Satsuma, *Chem.–Eur. J.*, 2009, **15**, 2341; (*b*) K. Shimizu, R. Sato and A. Satsuma, *Angew. Chem., Int. Ed.*, 2009, **48**, 3982.

