ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 2951

Received 19th January 2014,
Accepted 28th January 2014

DOI: 10.1039/c4cc00454j

www.rsc.org/chemcomm

Functionalization of an sp^3 C–H bond *via* a redox-neutral domino reaction: diastereoselective synthesis of hexahydropyrrolo[2,1-*b*]oxazoles†

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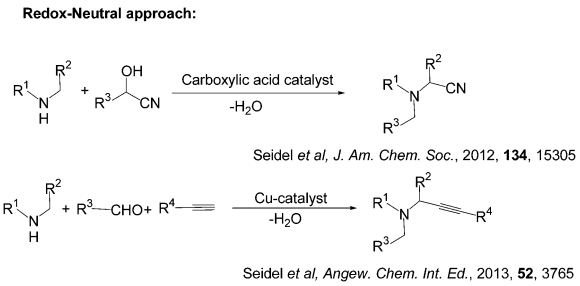
A diastereoselective synthesis of pyrrolidinooxazolidines was achieved by a metal-free, base-promoted reaction of pyrrolidine and aromatic aldehydes under microwave irradiation. The rare functionalization of an sp^3 C–H bond probably results from an *in situ* generated azomethine ylide that undergoes cycloaddition with aldehydes.

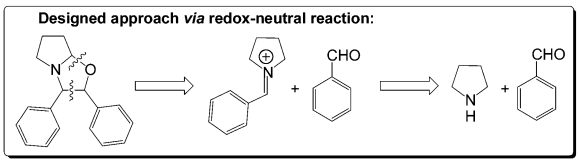
Functionalization of C–H bonds into C–C and/or C–X bonds (X = O, N, halogen, *etc.*) is an important area of organic synthesis for the construction of biologically active complex molecules.[1] Direct formation of a C–heteroatom bond *via* sp^3 C–H bond activation is a challenging task due to the strength of the sp^3 C–H bond, and it is difficult for a metal to form a sterically hindered C–H bond.[2] In this context, some promising catalytic systems for the selective functionalization of sp^3 C–H bonds have been developed during the last few years.[3] Generally functionalizations of sp^3 C–H bonds are carried out either by transition metal catalysis or by internal redox processes under thermal conditions. Recently much attention has been focussed on redox-neutral reactions for the formation of a fused ring as no external oxidant is required for this transformation.[4] However, the utilities of redox-neutral domino reactions in stereoselective syntheses of bioactive molecules have not been extensively explored so far. Recently, Seidel *et al.* reported a few redox-neutral approaches for the α-functionalization of secondary amines (Scheme 1).[5]

Pyrrolidinooxazolidines are the key intermediates in synthetic as well as in pharmaceutical chemistry and are important building blocks for the syntheses of various biologically active nitrogen containing heterocycles.[6] In addition, these are the core structures of some naturally occurring alkaloids.[7] As a consequence, substantial attention has been paid to develop efficient methods for their syntheses.[8] One notable strategy for the construction of this scaffold is the cycloaddition reaction between aldehyde and the *in situ* generated azomethine ylide from L-proline through decarboxylation.[8a,b] But the formation of azomethine ylide from the inactivated secondary amine is not easy due to the strong sp^3 C–H bonds. So the replacement of L-proline with pyrrolidine is a challenging task.



Scheme 1 Example of the redox-neutral approach.

The development of an efficient method for the stereo-controlled construction of fused heterocycles from basic chemicals is a demanding task in synthetic chemistry. The domino reaction is one of the major strategies for the construction of novel heterocycles from easily available starting materials.[9] It also offers more advantages over the step-wise reaction as there is no need for isolation of the intermediate. Microwave-assisted organic synthesis (MAOS) has drawn tremendous attention in recent times and has a great impact on C–H functionalization as microwave irradiation often enables the rapid attainment of high temperature necessary for inert C–H bond activation.[10] Taking a clue from the work of Seidel[5] we thought that the pyrrolidinooxazolidines could be synthesized by employing the iminium ion under suitable conditions (Scheme 2). Based on our previous experiences in microwave-assisted syntheses[11] and C–H functionalization,[12] herein we present a new diastereoselective synthesis of hexahydropyrrolo[2,1-*b*]oxazole through a redox-neutral



Scheme 2 Strategy for the synthesis of hexahydropyrrolo[2,1-*b*]oxazole.

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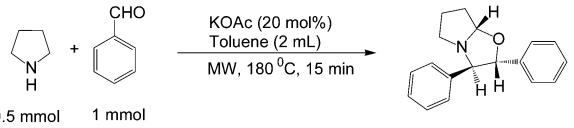
† Electronic supplementary information (ESI) available. CCDC 950404. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00454j

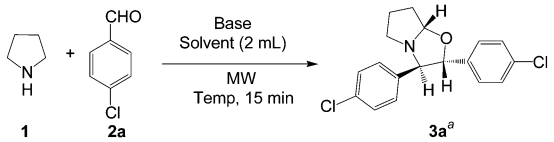


Scheme 3 Synthesis of hexahydropyrrolo[2,1-*b*]oxazole.

domino reaction under microwave irradiation (Scheme 3). The overall process becomes redox-neutral due to the combination of reductive *N*-alkylation and oxidative α-functionalization.

Initially we started our work by using pyrrolidine (1 equiv.) and 4-chlorobenzaldehyde (2 equiv.) as the model substrates under microwave irradiation for 15 min (optimized, see ESI†) in toluene. We noticed the formation of the expected product in 26% yield (Table 1, entry 1) as a single diastereomer in which two phenyl groups are in a *trans* arrangement and the structure of this diastereomer was confirmed by nOe experiments as well as by comparing the NMR result with the literature value.[8a] We felt that the base could accelerate the yield. When 20 mol% DABCO was used, the yield was increased to 62% (Table 1, entry 2). Next we tried to optimize the reaction conditions by varying the bases, solvents and temperature. Among the common bases such as DABCO, DBU, pyridine, K_2CO_3, KOAc, NaOH, and Cs_2CO_3, KOAc was found to be the most efficient affording 72% yield (Table 1, entries 2–8). No significant change in the yield was observed when the amount of base was increased to 30 mol% (Table 1, entry 9). The choice of solvents was important as the other solvents such as DCB, DMF, DMSO, and xylene were not so effective (Table 1, entries 10–13). A lower amount of the desired product was obtained when the temperature was decreased to 150 °C (Table 1, entry 14). However, when the reaction was carried out with conventional heating under refluxing conditions, only 24% of the desired product was afforded even after 24 hours (Table 1, entry 15). Finally, we chose the optimized reaction conditions as 20 mol% KOAc in toluene at 180 °C under microwave irradiation (Table 1, entry 6).

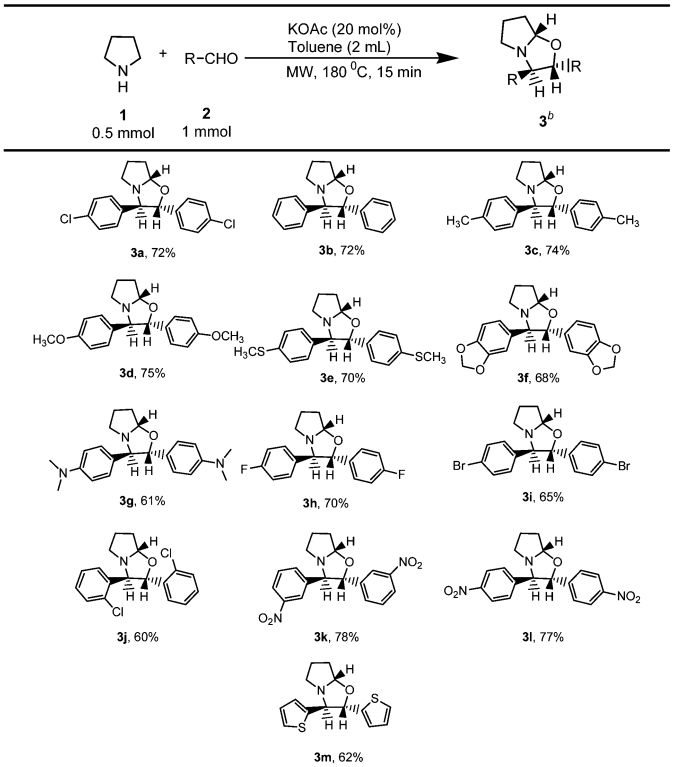
Table 1 Optimization of reaction conditions



Entry	Base (mol%)	Solvent	Temperature (°C)	Yield (%)[b]
1	—	Toluene	180	26
2	DABCO (20)	Toluene	180	62
3	DBU (20)	Toluene	180	64
4	Pyridine (20)	Toluene	180	48
5	K_2CO_3 (20)	Toluene	180	32
6	**KOAc (20)**	**Toluene**	**180**	**72**
7	NaOH (20)	Toluene	180	38
8	Cs_2CO_3 (20)	Toluene	180	36
9	KOAc (30)	Toluene	180	70
10	KOAc (20)	DCB	180	48
11	KOAc (20)	DMF	180	42
12	KOAc (20)	DMSO	180	—
13	KOAc (20)	Xylene	180	64
14	KOAc (20)	Toluene	150	56
15	KOAc (20)	Toluene	Reflux[c]	24

[a] Only one enantiomer of the racemic product is presented. [b] Isolated yields. [c] In conventional heating under reflux for 24 h.

Table 2 Substrate scopes of the reaction[a]



[a] Isolated yields. [b] One enantiomer of the racemic product is presented.

With the optimized reaction conditions in hand we studied the general applicability of the reaction (Table 2). Pyrrolidine efficiently reacted with various aldehydes bearing electron-donating as well as electron-withdrawing substituents to afford the corresponding products under the optimized reaction conditions (**3a–m**) and in each case the formation of a single diastereomer was observed. Aldehydes with –Me, –OMe, –SMe functionalities gave products with high yields (**3c–e**). Piperonal also reacted well to afford the product in 68% yield (**3f**). A strong electron-donating substituent like $-N(Me)_2$ did not diminish the yield of the product (**3g**). Aldehydes bearing halogens such as –F, –Cl, –Br were employed and the desired products were obtained in moderate to high yields (**3h–j**). A strong electron-withdrawing group like $-NO_2$ in the phenyl ring also successfully produced the product (**3k, l**). A substituent at the *ortho* position of the phenyl ring also afforded the corresponding product with a comparable yield (**3j**). Single crystal X-ray diffraction analysis of **3k** was carried out for further confirmation of the stereochemistry of the product (Fig. 1).[13] 2-Thiophene carboxaldehyde was compatible in this reaction to give the desired product **3m** without polymerization.

This protocol is applicable to piperidine also. Piperidine successfully reacted with aldehydes through this domino reaction to afford the corresponding 2,3-disubstituted hexahydrooxazolo-[3,2-*a*]pyridines (Scheme 4). Both the products (**5a, 5b**) were obtained in moderate yields which are difficult to prepare through the conventional decarboxylative method. However, morpholine, L-prolinol and aliphatic aldehydes did not afford the desired product under the present reaction conditions.

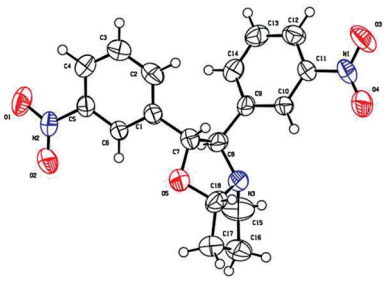
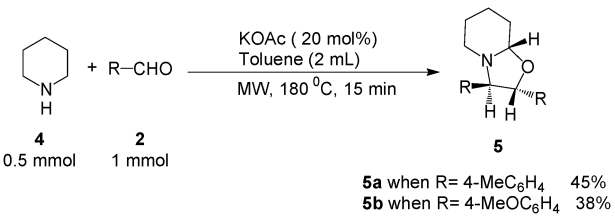
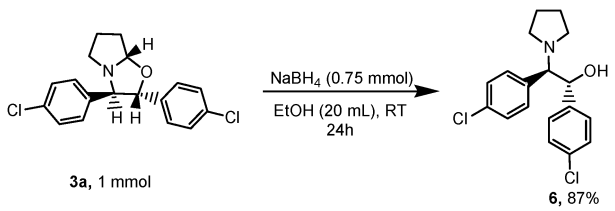


Fig. 1 The single crystal XRD structure of compound **3k**.



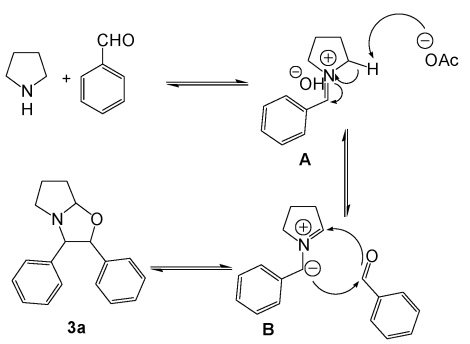
Scheme 4 Synthesis of 2,3-disubstituted-hexahydro-oxazolo[3,2-*a*]pyridine.



Scheme 5 Synthesis of amino alcohol from the pyrrolidinooxazolidine.

Diastereoselective amino alcohol can be easily prepared from the synthesized pyrrolidinooxazolidine. Reduction of **3a** with $NaBH_4$ gave 1,2-bis-(4-chloro-phenyl)-2-pyrrolidin-1-yl-ethanol (**6**) in 87% yield as a single diastereoisomer as determined by ^1H and ^{13}C NMR spectroscopy (Scheme 5).

A plausible reaction mechanism for this domino reaction is outlined in Scheme 6. The first step is the formation of the iminium ion (**A**) by the reaction between pyrrolidine and aldehyde. Then this iminium ion **A** transformed into azomethine ylide **B** *via* iminium α-deprotonation by the carboxylate anion.[5a] The [3+2] cycloaddition reaction between another equivalent of the aldehyde and the generated azomethine ylide **B** afforded the corresponding product selectively[8a] in high yield.



Scheme 6 A probable mechanism.

In summary, we have developed a conceptually new method for the direct functionalization of the unreactive sp^3 C–H bond of a cyclic amine *via* the redox-neutral domino reaction. Microwave-assisted hexahydropyrrolo[2,1-*b*]oxazoles were synthesized diastereoselectively in high yields. A simple operation, atom-efficient, transition metal-free and environmentally benign reaction conditions are the attractive features of this one-step protocol. Several aryl and heteroaryl aldehydes were found to be suitable substrates for this base promoted transformation. Piperidine also reacted well under the present reaction conditions. This present mechanistically different approach provides a useful alternative to the existing decarboxylative method. We believe that our present protocol will open up an expedient synthetic pathway for the synthesis of bioactive fused oxazolidine analogues.

A.H. acknowledges the financial support from CSIR, New Delhi. A.K.B and S.M. thank CSIR and UGC for their fellowship. We thank Dr T. K. Paine, IACS, Kolkata, for XRD analysis.

Notes and references

1 (*a*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077; (*b*) H. M. L. Davies, *Angew. Chem., Int. Ed.*, 2006, **45**, 6422; (*c*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*d*) R. G. Bergman, *Nature*, 2007, **446**, 391; (*e*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*f*) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (*g*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094.
2 (*a*) K. R. Campos, *Chem. Soc. Rev.*, 2007, **36**, 1069; (*b*) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.–Eur. J.*, 2010, **16**, 2654.
3 G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726.
4 (*a*) N. Z. Burns, P. S. Baran and R. W. Hoffmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 2854; (*b*) T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010; (*c*) B. Peng and N. Maulide, *Chem.–Eur. J.*, 2013, **19**, 13274.
5 (*a*) L. Ma, W. Chen and D. Seidel, *J. Am. Chem. Soc.*, 2012, **134**, 15305; (*b*) D. Das, A. X. Sun and D. Seidel, *Angew. Chem., Int. Ed.*, 2013, **52**, 3765.
6 (*a*) C. Kadouri-Puchot and C. Agami, in *Asymmetric Synthesis of Nitrogen Heterocycles*, ed. J. Royer, Wiley-VCH, 2009, p. 223, and references cited therein; (*b*) A. I. Meyers, M. Harre and R. Garland, *J. Am. Chem. Soc.*, 1984, **106**, 1146; (*c*) A. I. Meyers, B. A. Lefker, T. J. Sowin and L. J. Westrum, *J. Org. Chem.*, 1989, **54**, 4243.
7 (*a*) J. J. Tufariello, H. BecLler and A. Smaratana, *Tetrahedron*, 1985, **41**, 3447; (*b*) P. Radford, A. B. Attygalle and J. Meinwald, *J. Nat. Prod.*, 1997, **60**, 755.
8 (*a*) F. Orsini, F. Pelizzoni, M. Forte, R. Destro and P. Gariboldi, *Tetrahedron*, 1988, **44**, 519; (*b*) H. Firouzabadi, N. Iranpoor, A. Ghaderi and M. Ghavami, *Tetrahedron Lett.*, 2012, **53**, 5515; (*c*) J. Alladoum, E. Vrancken, P. Mangeney, S. Roland and C. Kadouri-Puchot, *Org. Lett.*, 2009, **11**, 3746.
9 (*a*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*b*) L. F. Tietze, G. Brasche and G. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; (*c*) J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422; (*d*) D. M. D'Souza and T. J. J. Muller, *Chem. Soc. Rev.*, 2007, **36**, 1095.
10 (*a*) A. de la Hoz, A. Díaz-Ortiz and A. Moreno, *Chem. Soc. Rev.*, 2005, **34**, 164; (*b*) V. Polshettiwar and R. S. Varma, *Acc. Chem. Res.*, 2008, **41**, 629; (*c*) J. D. Moseley and C. O. Kappe, *Green Chem.*, 2011, **13**, 794; (*d*) C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250; (*e*) D. Kundu, S. Ahammed and B. C. Ranu, *Green Chem.*, 2012, **14**, 2024; (*f*) R. Kumar, C. Selvam, G. Kaur and A. K. Chakraborti, *Synlett*, 2005, 1401; (*g*) A. Sharma, D. Vacchani and E. V. der Eycken, *Chem.–Eur. J.*, 2013, **19**, 1158.
11 (*a*) M. Rahman, A. Majee and A. Hajra, *J. Chem. Res.*, 2009, 178; (*b*) M. Rahman, A. Majee and A. Hajra, *J. Heterocycl. Chem.*, 2010, **47**, 1230; (*c*) S. Das, S. Santra, A. Roy, S. Urinda, A. Majee and A. Hajra, *Green Chem. Lett. Rev.*, 2012, **5**, 97.
12 (*a*) M. Rahman, A. K. Bagdi, A. Majee and A. Hajra, *Tetrahedron Lett.*, 2011, **52**, 4437; (*b*) A. K. Bagdi, M. Rahman, S. Santra, A. Majee and A. Hajra, *Adv. Synth. Catal.*, 2013, **355**, 1741.
13 CCDC deposition code of compound **3k**: 950404.