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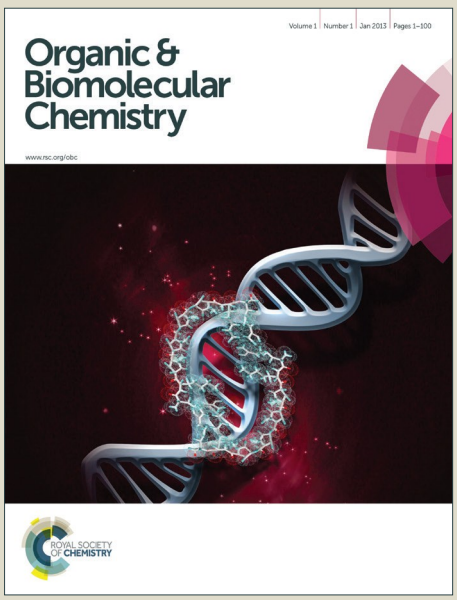

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ARTICLE TYPE

Copper-Catalyzed One-pot, Three-component Tandem Conjugative Alkynylation/6-*endo* Cyclization Sequence: Access to Pyrano[2,3-*d*]pyrimidines

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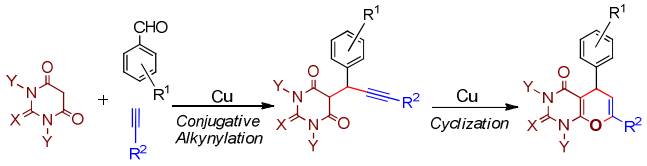
A copper catalyzed one-pot, three component reaction between barbituric acid, aldehydes and terminal alkynes has been developed for the construction of pyrano[2,3-*d*]pyrimidines *via* tandem conjugative alkynylation/6-*endo* cyclization pattern. Screening of barbituric acid derived organic acceptor in conjugative alkynylation reaction and synthetic applicability of conjugative addition product in one-pot conditions was documented for the first time.

Conjugative addition of terminal alkynes to organic acceptors is one of the powerful methods for the construction of C-C bonds.[1] As the reaction is believed to progress *via* metal alkynylide species, classical methods for conjugative alkynylation rely on the use of stiochiometric amounts of metal alkynylides[2], which leads to the generation of excess metallic wastes. In recent years, transition metal catalyzed direct addition of terminal alkynes[3] to acceptors alkenes *via in situ* generated metal alkynylide species has gained tremendous interest to avoid excess metallic wastes. In particular, copper[4] has shown remarkable ability to trigger the direct conjugative alkynylation process. Inspired by copper promoted direct conjugative alkynylation results, we envisioned that the *in situ* progress of conjugative alkynylation and synthetic elaboration of conjugative addition product could be achieved under one-pot copper catalyzed conditions. Further synthetic elaboration of conjugative addition product under one-pot conditions is an unmet goal, which is highly attractive due to the presence of potential alkyne functionality. On the other hand, the examples so far documented are limited to use organic acceptors like acrylates, meldrum acid-derived acceptors, and β-unsubstituted acyclic enones.[2-4] In an effort to extend the versatility of conjugative alkynylation process, we have been interested in screening the potential of *in situ* generated pyrimidine related Michael acceptor. Hence, we hypothesized that the three simple starting materials like barbituric acid, aldehydes and terminal alkynes would undergo conjugative alkynylation under copper catalyzed conditions to generate conjugative addition intermediate,[4] which, upon activation of triple bond with copper, further undergoes 6-*endo* cyclization to furnish targeted pyrano[2,3-*d*]pyrimidines (Scheme 1).

Importance of pyrimidine moiety is well known,[5] as it exists in wide range of biologically active molecules and serves as versatile building blocks of numerous natural products and purine bases of DNA and RNA. As a part of our research interest on



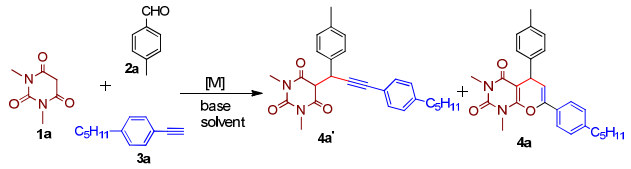
Scheme 1 Copper catalyzed one-pot tandem strategy

pyrimidine core chemistry,[6] we have dedicated our efforts to generate pyrano[2,3-*d*]pyrimindines *via* tandem conjugative alkynylation/6-*endo* cyclization sequence. Only few reports regarding the synthesis of pyrano[2,3-*d*]pyrimidine derivatives was documented so far in literature. For example, Romenger's group[7] has developed a copper catalyzed inter/intramolecular oxo-Diels-Alder reaction of barbituric acid and salicylaldehyde derived alkynes. Although this method effectively access the target products, suffered some limitations of pre-requisite synthesis of alkynes from salicylaldehydes, less substrate scope, and terminal alkynes other than salicyladehyde derivatives was not tried. Moreover, all the existing methods revealed the fabrication of fused pyrano[2,3-*d*]pyrimidines but, none of the methods was successful to attain simple pyrano[2,3-*d*]pyrimidines. In this context, we disclose here a copper (II)triflate catalyzed one-pot, atom/step-economic, three component tandem conjugative alkynylation/6-*endo* cyclization process for the generation of pyrano[2,3-*d*]pyrimidines.

The intial design of our work was pioneered by choosing 1,3-dimethylbarbituric acid **1a**, *p*-tolualdehyde **2a**, and 1-ethynyl-4-pentyl benzene **3a** as model substrates. In the preliminary experiment, we carried out a model reaction between **1a** (1 mmol), **2a** (1 mmol), **3a** (1.2 mmol) and KO^{t}Bu (1.3 mmol) in DCE at 110 ^{o}C for 24 h employing 10 mol% copper(II) bromide as a catalyst. We were pleased to observe a mixture of conjugative addition product **4a'** and desired cyclized product **4a** in 11% and 15% yield. When we tried CuI instead of $CuBr_2$, yield of **4a'** and **4a** was observed as 10% and 22% respectively. Increase in **4a** yield (40%) along with trace amount of

conjugative addition product **4a'** was noted, when we switched the copper source from CuI to CuCl. To our delight, while we performed the model reaction employing copper(II) trifluoromethanesulfonate as a catalyst at 110 °C for 5 h afforded the targeted cyclized product in 67% yield with complete conversion of conjugative addition product **4a'**. Other copper catalysts *e.g.* $Cu(OAc)_2.H_2O$ had also provided the same result within 12 h, but ended up with lesser yield (Table 1, entry 5).

Table 1 Optimization of copper catalyzed tandem strategy[a,b]

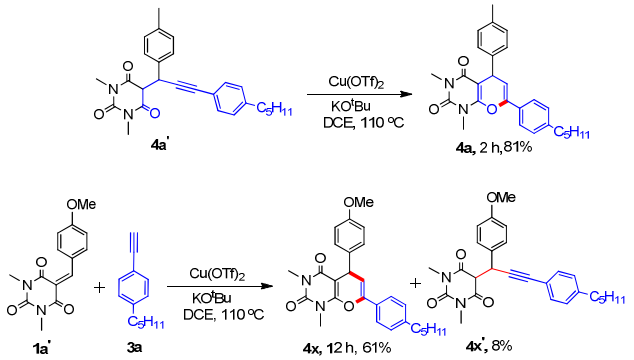


entry	catalyst	base	solvent	time (h)	Yield[b] (%) 4a'	4a
1	$CuBr_2$	KO^{t}Bu	DCE	24	11	15
2	CuI	KO^{t}Bu	DCE	24	10	22
3	CuCl	KO^{t}Bu	DCE	16	trace	40
4	$Cu(OTf)_2$	KO^{t}Bu	DCE	5	–	67
5	$Cu(OAc)_2.H_2O$	KO^{t}Bu	DCE	12	–	46
6	$Zn(OTf)_2$	KO^{t}Bu	DCE	24	trace	22
7	$In(OTf)_3$	KO^{t}Bu	DCE	24	51	5
8	$Yb(OTf)_3$	KO^{t}Bu	DCE	24	37	7
9	$BF_3.Et_2O$	KO^{t}Bu	DCE	24	28	4
10	$Cu(OTf)_2$	Et_3N	DCE	24	11	15
11	$Cu(OTf)_2$	K_2CO_3	DCE	16	–	46
12	$Cu(OTf)_2$	KO^{t}Bu	toluene	8	trace	21
13	$Cu(OTf)_2$	KO^{t}Bu	MeOH	14	NR	NR
14[c]	$Cu(OTf)_2$	KO^{t}Bu	DCE	20	4	47
15[d]	$Cu(OTf)_2$	KO^{t}Bu	DCE	10	–	55

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3a** (1.2 mmol), base (1.3 mmol) and 10 mol% metal catalyst were reacted in solvent (8 ml) at 110 °C. [b]Isolated yields. [c]5 mol% $Cu(OTf)_2$ was employed. [d]20 mol% $Cu(OTf)_2$ was used.

In next attempt, model reaction was performed by employing various metal catalysts like $In(OTf)_3$, $Yb(OTf)_3$, $BF_3.Et_2O$ in DCE at 110 °C for 24 h. In all cases, conjugative addition took place and furnished the addition product **4a'** in 51%, 37%, 28% yields respectively, but poor conversion of **4a'** to **4a** was observed (Table 1: entries **7-9**). In contrast, when we introduced zinc (II)triflate as a catalyst, cyclization took place exclusively and furnished **4a** in 22% yield (Table 1, entry **6**). Hence, we found $Cu(OTf)_2$ as an efficient catalyst for the current tandem strategy. Later on, various bases and solvents were tested by considering $Cu(OTf)_2$ as optimal catalyst (Table 1: entries **10-13**). These studies revealed that employing 10 mol% $Cu(OTf)_2$ and KO^{t}Bu as base in DCE at 110 °C was the best condition, which was further screened in terms of catalyst loading. Decrease or increase in catalytic loading from 10 mol% $Cu(OTf)_2$ did not provide any fruitful results, and thus, employing 10 mol% $Cu(OTf)_2$ and KO^{t}Bu as base in DCE at 110 °C was considered as optimised condition.

In order to figure out the mechanism of present tandem strategy, we have conducted some control experiments before moving towards generalisation phase. Initially, cyclization of conjugative addition product under copper catalyzed conditions was investigated. When conjugative alkynylation product **4a'** reacted under optimised reaction conditions, cyclization took place exclusively within 2 h and afforded **4a** in 81% yield. It is important to mention that, complete conversion of **4a'** was observed. In the next instance, role of *in situ* generated organic acceptor was tested by conducting a two component reaction between pre-formed barbituric acid derived organic acceptor **1a'** and 1-ethynyl-4-pentyl benzene **3a** under standard reaction conditions. As we expected, tandem conjugative alkynylation/6-*endo* cyclization strategy was applicable, which furnished the target cyclised product **4x** in 61% yield along with trace amount of conjugative addition product **4x'** (See Scheme 2). These results suggest that the current three component reaction might progressed through conjugative addition of terminal alkynes to *in situ* generated barbituric acid derived acceptor, which is in turn, underwent cyclization process.

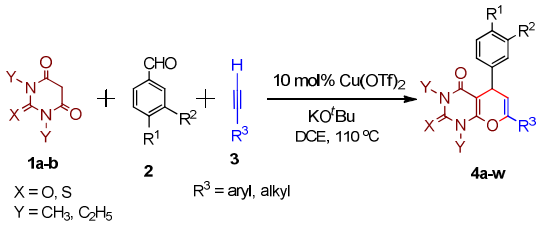


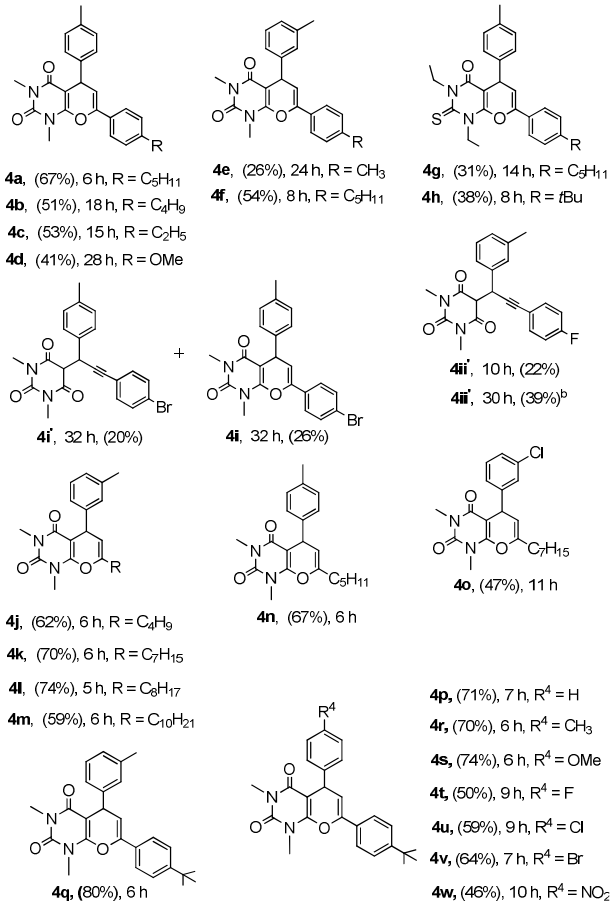
Scheme 2 Control experiments

With the optimisation and control experimental results in hand, we were dedicated to study the substrate scope of the reaction in detail. Intially, a wide range of aromatic terminal alkynes were tested under the standard reaction conditions and the results are summarized in Table 2. Various electron-donating substituted terminal alkynes were reacted smoothly with various barbituric acid partners and aldehydes under current copper catalyzed conditions to afford the target cyclized products in low to good range of yields *i.e.* 26-67% (See Table 2). In case of 4-ethynyl toluene and 4-ethynyl anisole the reaction was slow and it took 24-28 h for the complete conversion of conjugative addition product (Table 2: entries **4d** and **4e**). Meanwhile, when 1,3-diethyl-2-thio-barbituric acid **1b** was tried instead of **1a**, yields of the corresponding pyrano[2,3-*d*]pyrimidines were shifted towards the lower end *i.e.* 31% and 38% repectively (Table 2: entries **4g** and **4h**). It was quite encouraging that, in all cases complete conversion of conjugative addition product was observed. Subsequently, the effect of electron-withdrawing substituted terminal alkynes in present tandem three component reaction was tested. In case of bromo substituted terminal alkyne, the reaction was sluggish and generated a mixture of conjugative addition product **4i'** and cyclized product **4i** in 20% and 26% yields respectively (Table 2: entries **4i'** and **4i**). Presence of fluoro group in terminal alkyne had completely diminished the cyclization step and only conjugative addition product **4ii'** was

observed in 22% yield. Increase in reaction time or copper loading (25 mol%) did not provide favourable results in terms of consumption of conjugative addition product. 1-ethynyl-4-nitrobenzene was completely ineffective in the present study; even conjugative addition product was also not observed. Therefore, our present tandem conjugative alkynylation/6-*endo* cyclization strategy is highly compatible with electron-donating substituted terminal alkynes and presence of withdrawing groups in terminal alkynes has decreased the reactivity of conjugative addition product for cyclization step.

Table 2 Substrate scope[a]





[a]Reaction conditions: barbituric acid (1 mmol), aldehyde (1 mmol), alkyne (1.2 mmol), KO^{t}Bu (1.3 mmol) and 10 mol% $Cu(OTf)_2$ were allowed to react in DCE at 110 °C till the reaction is complete. [b]Reaction was carried out with 25 mol% $Cu(OTf)_2$.

In continuation, we next monitored aliphatic terminal alkynes as an alkyne partner under present reaction conditions. As illustrated in Table 2, a range of aliphatic alkynes were tested using optimised conditions. Aliphatic alkynes ranging from 1-hexyne to 1-dodecyne were well tolerated in this conversion and furnished the desired products in good to moderate yields (Table 2, entries **4j-4n**). Presence of halogen substituent on aldehyde decreases the conversion and shifted the yield towards moderate end (Table 2, entry **4o**).

In next attempt, the electronic effects on the *in situ* generated barbituric acid derived acceptor were studied by varying different electron-donating and electron–withdrawing groups in aldehydes (Table 2: **4p-4w**). For this, a set of experiments were conducted by treating wide range of aldehydes with 1,3-dimethyl barbituric acid **1a** and 4-*tert*-butyl phenylacetylene **3j** under present tandem conditions. In case of electron-donating groups on aldehyde, the reaction underwent smoothly in 6-10 h and returned the desired products in good range of yields *i.e.* 70-80% (Table 2: entries **4q-4s**). Good to moderate yields were observed when an electron-withdrawing group (halogen) is present on the aromatic ring of aldehydes (Table 2, **4t-4v**); fluoro, chloro and bromo substituted aldehydes afforded the corresponding pyrano[2,3-*d*]pyrimidines in 50%, 59%, and 64% yields respectively. Notably, 4-nitro benzaldehyde was also well tolerated under current copper catalyzed conditions and furnished the target product **4w** within 10 h in 46% yield.

Based on control experiments, a possible mechanism for the current transformation is illustrated in Figure 1. Intially, a base

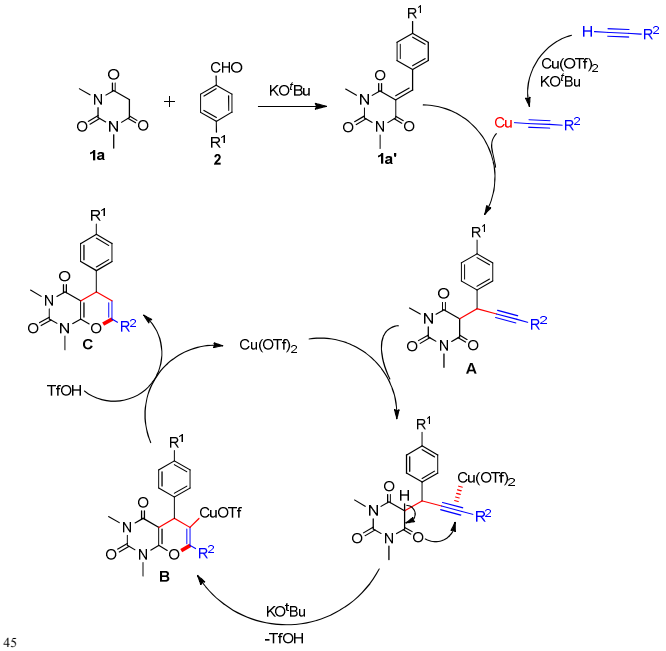


Fig. 1 Possible mechanism

promoted Knoevenagel condensation of barbituric acid and aldehyde takes place to produce 1,3-dimethyl-5-benzylidene pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **1a'**, which further acts as an organic acceptor and undergoes conjugative alkynylation step with copper alkynylide bond[3b] to generate the conjugative addition intermediate **A.** Later on, alkyne cyclization[8] of **A** can be initiated by the copper catalyzed activation of the triple bond in intermediate **A,** which enhances the electrophilicy of alkyne.

Deprotanation of **A** activates the nucleophilic attack of oxygen to generate intermediate **B**, which further undergoes demetallation to furnish the target pyrano[2,3-*d*]pyrimidines and regeneration of the catalyst for further cycle.

Conclusions

In conclusion, we have developed an efficient copper catalyzed one-pot, atom and step-economic three component method for the construction of pyrano[2,3-*d*]pyrimidines *via* tandem conjugative addition/6-*endo* cyclization sequence. *In situ* generation of organic acceptor, metal alkynylide, and synthetic utility of *in situ* genrated conjugative addition product under one-pot conditions are the attractive features, which makes this protocol valuable. Further studies are underway to explore new organic acceptors and synthetic applicability of conjugative alkynylation reaction towards value added products in one-pot conditions.

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Notes and references

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1 P. Perlmutter, *Conjugative Addition Reactions in Organic synthesis*, Tetrahedron Organic Series 9, Pergamon press, Oxford, 1992.

2 (a) R. Pappo and P. W. Collins, *Tetrahedron Lett., 1972*, **13**, 2627; (b) S. Kim and J. M. Lee, *Tetrahedron Lett.,* 1990, **31**, 7627; (c) S. Kim and J. H. Park, S. Y. Jon, *Bull. Korean Chem. Soc*., 1995, **16**, 783; (d) M. Eriksson, T. Iliefski, M. Nilsson, T. Olsson. *J. Org. Chem.,* 1997, **62**, 182; (e) T. R. Wu and J. M. Chong, *J. Am. Chem. Soc*., 2005, **127**, 3244; (f) O. V. Larionov and E. J. Corey, *Org. Lett.,* 2010, **12**, 300; (g) J. C. S. Woo, S. Cui, S. D. Walker, M. M. Faul, *Tetrahedron*, 2010, **66**, 4730.

3 (a) M. Picquet, C. Bruneau, P. H. Dixneuf, *Tetrahedron,* 1999, **55**, 3937; (b) S. Chang, Y. Na, E. Choi, S. Kim, *Org. Lett*., 2001, **3**, 2089; (c) T. Nishimura, Y. Washitake, Y. Nishiguchi, Y. Maeda, S. Uemura, *Chem. Commun.,* 2004, 1312; (d) J. Ito, K. Fujii, H. Nishiyama, *Chem. –Eur. J.* 2013, **19**, 601; (e) R. V. Lerum and J. D. Chisholm, *Tetrahedron Lett*., 2004, **45**, 6591; (f) E. Fillion and A. K. Zorzitto, *J. Am. Chem. Soc*., 2009, **131**, 14608; (g) T. Nishimura, T. Sawano, T. Hayashi, *Angew. Chem., Int. Ed.,* 2009, **48**, 8057; (h) T. Nishimura, T. Sawano, K. Ou, T. Hayashi, *Chem. Commun.,* 2011, **47**, 10142; (i) L. Chen and Chao-Jun. Li*, Chem. Commun.,* 2004, 2362; (j) L. Villarino, R. Garcia-Fandino, F. Lopez, J. L. Mascarenas, *Org. Lett.,* 2012, **14**, 2996; (k) G. Blay, L. Cardona, J. R. Pedro, A. Sanz-Marco, *Chem.–Eur. J.,* 2012, **18**, 12966; (l) G. Blay, M. C. Munoz, J. R. Pedro and A. Sanz-Marco, *Adv. Synth. Catal.,* 2013, **555**, 1071.

4 (a) A. S.-Marco, A. G.-Ortiz, G. Blay, J. R. Pedro, *Chem. Commun.,* 2014, **50**, 2275; (b) A. S.-Marco, A. G.-Ortiz, G. Blay, I. Fernandez, J. R. Pedro, *Chem. –Eur. J.,* 2014, **20**, 668; (c) R. Yazaki, N. Kumagai, M. Shibasaki, *Org. Lett.,* 2011, **13**, 952; (d) R. Yazaki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.,* 2010, **132**, 10275; (e) T. F. Knopfel, P. Zarotti, T. Ichikawa, E. M. Carreira, *J. Am. Chem. Soc.,* 2005, **127**, 9682; (f) T. F. Knopfel and E. M. Carreira, *J. Am. Chem. Soc.,* 2003, **125**, 6054.

5 (a) J. M. Blaney, C. Hansch, C. Silipo, A. Vittoria, *Chem. Rev*., 1984, **84**, 333; (b) J. Gut, In *Advances in Heterocyclic Chemistry*: Aza Analogs of Pyrimidine and Purine Bases of Nucleic Acids, Vol. 2 (Eds.: A. R. Katritzky), Academic Press: London, 1963, pp 189; (c) E. Lunt, In *Comprehensive Organic Chemistry*, Vol. 4 (Eds.: D. Barton, W. D. Ollis) Pergamon Press: London, 1974, pp 493; (d) R. N. Castle, S. D. Phillips, In *Comprehensive Heterocyclic Chemistry*; Vol. 3 (Eds.: A. R. Katritzky and C. W. Rees) Pergamon press: Oxford, 1984, pp 329.

6 (a) R. Sarma, M. M. Sarmah, D. Prajapati, *J. Org. Chem.,* 2012, **77**, 2018; (b) M. M. Sarmah, D. Bhuyan, D. Prajapati, *RSC Adv*., 2015, **5**, 12506. (c) M. M. Sarmah, R. Sarma, D. Prajapati, W. Hu, *Tetrahedron Lett.,* 2013, **54**, 267; (d) M. M.Sarmah, D. Prajapati, W. Hu, *Synlett*, 2013, **24**, 471; (e) M. M. Sarmah and D. Prajapati, *RSC Adv.*. 2014, **4**, 22955; (f) R. Sarma, K. J. Borah, Y. Dommaraju, D. Prajapati, *Mol. Divers.* 2011, **15**, 697; (g) D. Prajapati, M. Gohain, A. J. Thakur, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 3537; (h) D. Prajapati and A. J. Thakur, *Tetrahedron Lett.,* 2005, **46**, 1433; (i) D. Prajapati and S. Gadhwal, *Tetrahedron,* 2004, **60**, 4909.

7 (a) M. J. Khoshkholgh, S. Balalaie, R. Gleiter, F. Rominger, *Tetrahedron,* 2008, **64**, 10924; (b) M. J. Khoshkholgh, M. Lotfi, S. Balalaie, F. Rominger, *Tetrahedron,* 2009, **65**, 4228; (c) M. J. Khoshkholgh, S. Balalaie, H. R. Bijanzadeh, F. Rominger, J. H. Gross, *Tetrahedron Lett.,* 2008, **49**, 6965; (d) M. Jha, S. Juy, T-Y Chou, *Tetrahedron Lett.,* 2011, **52**, 4337; (e) K. P. Kumar, S. Satyanarayana, P. L. Reddy, G. Narasimhulu, N. Ravirala, B. V. S. Reddy, *Tetrahedron Lett.,* 2012, **53**, 1738; (f) R. Kumar, K. Raghu-vanshi, R. K. Verma, M. S. Singh, *Tetrahedron Lett*., 2010, **51**, 5933.

8 V. Belting and N. Krause, *Org. Biomol. Chem.,* 2009, **7**, 1221.