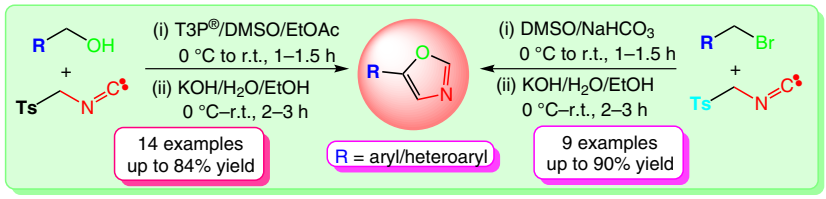
Synlett K. S. Vinay Kumar et al. Letter

A One-Pot Tandem Approach for the Synthesis of 5-(Het)aryloxazoles from Substituted (Het)aryl Methyl Alcohols and Benzyl Bromides

Koravangala S. Vinay Kumar
Toreshettahally R. Swaroop
Narasimhamurthy Rajeev
Ajjampura C. Vinayaka
Gejjalagere S. Lingaraju
Kanchugarakoppal S. Rangappa*
Maralinganadoddi P. Sadashiva*

Department of Studies in Chemistry, University of Mysore, Mysuru, Karnataka, India
mpsadashiva@gmail.com
rangappaks@gmail.com



Received 03.10.2015
Accepted after revision: 20.01.2016
Published online: 01.03.2016
DOI: 10.1055/s-0035-1561391; Art ID: st-2015-b0794-l

Abstract A new modified van Leusen strategy has been developed for the synthesis of biologically significant 5-substituted oxazoles by the reaction of (het)aryl methyl alcohols or benzyl bromides as precursors with tosylmethylisocyanide (TosMIC) under basic conditions. This method is efficient, takes place under mild reaction conditions, and is tolerant of various functional groups with high yield.

Key words oxazole, TosMIC, T3P®, DMSO, $NaHCO_3$

Oxazoles represents an important class of heterocyclic compounds because of their presence in natural products[1] and their versatile biological activities like antibacterial,[2] antifungal,[3] and others.[4] Besides, they are also utilized as a scaffold for the construction of many peptides, macrocyclic compounds, and polymers.[5] Hence, there is a great deal of interest for the development of new strategies for the synthesis of oxazoles. The available classical methods for the synthesis of substituted oxazoles are copper- and ruthenium-catalyzed cyclizations of 3-substituted-1,4,2-dioxazol-5-ones with phenylethenes or phenylacetylene,[6] Robinson–Gabriel cyclodehydration of α-acylaminoketones,[7] and rhodium-catalyzed reaction of diazocarbonyl compounds with nitriles.[8] The recently reported methods are *p*-toluenesulfonic acid catalyzed reaction of amides with propargyl alcohols,[9] *tert*-butyl hydroperoxide (TBHP)–I_2 mediated tandem oxidative cyclization of benzyl amines with alkenes,[10] α-aminoketones with aldehydes,[11] silver-catalyzed reaction of α-bromoketones with primary amides,[12] cycloaddition of alkynes with nitriles catalyzed by gold and copper,[13] and copper-catalyzed aerobic oxidative cyclization of aldehydes with amines.[14] Further, the functionalization to oxazole ring were accessed *via* transition-metal-catalyzed reactions.[15]

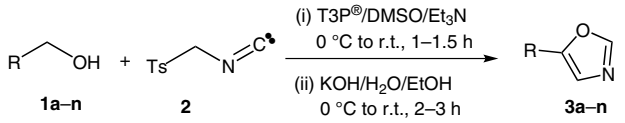
However, to synthesize biologically significant 5-(het)aryl oxazoles, TosMIC and aldehydes are widely used precursors for, for instance, van Leusen oxazole synthesis, which involves the reaction of TosMIC with aldehydes in the presence of potassium carbonate in methanol,[16] the modifications of van Leusen oxazole synthesis that involves the reaction of solid-phase equivalents of TosMIC with aldehydes,[17] quarternary ammonium hydroxide ion exchange resin catalyzed reaction of TosMIC with aldehydes,[18] reaction of TosMIC with aldehydes/acid chlorides followed by ultrasound-promoted desulfonation,[19] reaction of TosMIC with aldehydes in ionic liquid [bmim]Br,[20] reaction of aldehydes with benzotrizolylmethylisocyanide,[21] and other methods including Suzuki–Miyaura cross-coupling of aryl bromides with oxazoline-substituted potassium organotrifluoroborates[22] and asymmetric condensations for oxazolines.[23] Also, few pharmacologically relevant chemotypes have been synthesized through van Leusen strategy.[24] The literature survey reveals that an aldehyde precursor is most commonly used with TosMIC reagent to access van Leusen oxazoles.

Overall, the synthesis of oxazoles from classical and conventional methods are associated with several disadvantages, such as need of harsh reaction conditions like high temperature, toxic metal as catalyst, less stable precursor (aldehyde), and difficulties to synthesize pre-functionalized intermediates. As a part of our ongoing research on the development of new synthetic methods for heterocyclic compounds,[25] we report herein a new approach for the synthesis of 5-aryl oxazoles from TosMIC with alcohols or benzyl bromides oxidized in propylphosphonic anhydride (T3P®)–dimethyl sulfoxide (DMSO) or DMSO media, respectively, for the first time.

In the beginning of our study, we selected the oxidation of benzyl alcohol to benzaldehyde in T3P®–DMSO and reaction of in situ generated benzaldehyde with TosMIC in the

presence of base as a model reaction. Our initial attempts failed in the presence of bases like triethylamine, Hünig's base, $NaHCO_3$, and K_2CO_3. The reason might be that the less basic strength and strong alkaline media must be required to neutralize the acidity of T3P®. Therefore, we have selected aqueous–alcoholic NaOH and KOH as base in excess. The reaction took place smoothly to give product 5-phenyloxazole (**3a**).[26] However, from the point of view of reaction time and yield aqueous–alcoholic KOH is the suitable base for this reaction (83% yield, Table 1, entry 1). In addition, the slight excess of aqueous–alcoholic KOH did not affect during the course of the reaction.

Table 1 Synthesis of 5-(Het)aryl Oxazoles from (Het)aryl Methyl Alcohols



1a–n **2** **3a–n**

Entry	**1**, **3** R	**3**	Yield (%)
1	Ph	**3a**	83
2	4-MeC_6H_4	**3b**	84
3	4-*t*-BuC_6H_4	**3c**	80
4	4-$MeOC_6H_4$	**3d**	65
5	4-$O_2NC_6H_4$	**3e**	68
6	4-FC_6H_4	**3f**	74
7	4-ClC_6H_4	**3g**	72
8	4-BrC_6H_4	**3h**	70
9	2-naphthyl	**3i**	82
10	2-thienyl	**3j**	69
11	2-furyl	**3k**	61
12	pyridin-2-yl	**3l**	71
13	quinolin-3-yl	**3m**	75
14	2-methoxystyryl	**3n**	78

With this optimized reaction conditions, we extended the protocol for the synthesis of 5-(*p*-tolyl)-, 5-(4-*tert*-butylphenyl)-, 5-(4-methoxy)phenyl-, and 5-(4-nitrophenyl)oxazoles **3b**–**e** bearing electron-donating and electron-withdrawing groups from the corresponding substituted aryl methyl alcohols in 65–84% yield (Table 1, entries 2–5). Similarly, the methodology is equally extended to benzyl alcohols bearing different halogen atoms, which furnished respective 5-aryl oxazoles **3f**–**h** in 70–74% yield (Table 1, entries 6–8). Likewise, the protocol is compatible with fused aryl-like 2-naphthylmethyl alcohol, which give 5-(2-naphthyl)oxazole **3i** in 82% yield (Table 1, entry 9). The protocol succeeded equally well with 2-thienylmethyl alcohol, furfurol, pyridine-2-yl methyl, and quinolin-3-yl methyl alcohols, which gave the corresponding 5-(het)aryl oxazoles **3j**–**m** in 61–75% yields (Table 1, entries 10–13). Interestingly, allylic alcohol 3-(2-methoxyphenyl)prop-2-en-1-ol also underwent smooth oxidation and cyclization with TosMIC to give 5-(2-methoxystyryl)oxazole (**3n**) in 78% yield (Table 1, entry 14).

The structure of one of the oxazoles, 5-(quinolin-3-yl)oxazole (**3m**) was confirmed by single-crystal X-ray diffraction studies (CCDC reference number 1429231),[27] and its ORTEP diagram is shown in Figure 1.

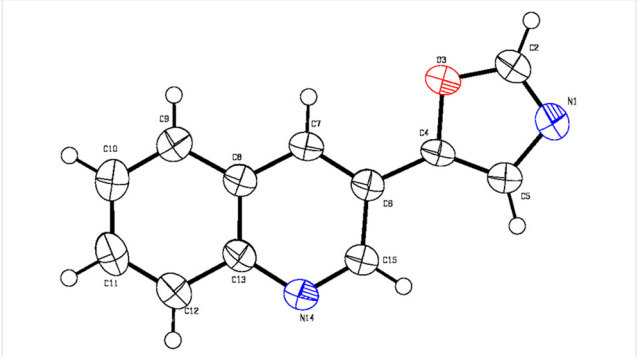
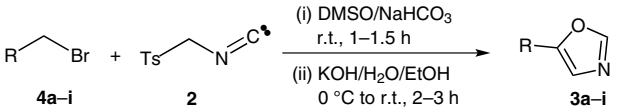


Figure 1 ORTEP diagram of 5-(quinolin-3-yl)oxazole (**3m**)

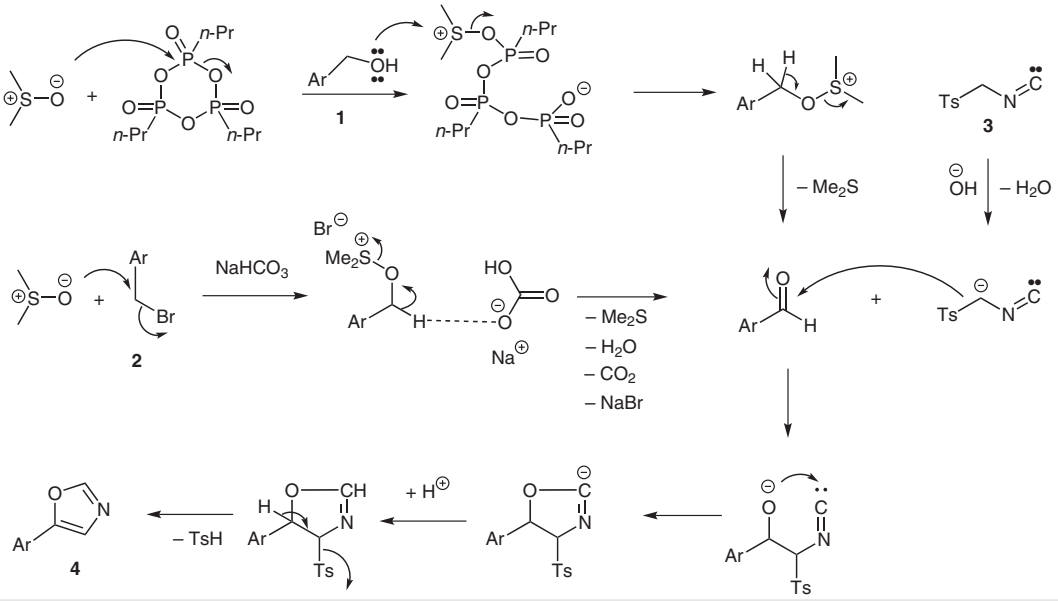
Further, we have focused our attention to synthesize 5-aryl oxazoles from benzyl bromides via oxidation in DMSO media in the presence of base. Oxidation of benzyl bromide to benzaldehyde was carried out in the presence of $NaHCO_3$ and DMSO, followed by cyclization with TosMIC in the presence of various bases like triethylamine, Hünig's base, $NaHCO_3$, K_2CO_3, aqueous–alcoholic NaOH and KOH. It was found that KOH is the best base with respect to reaction time and yield of **3a** (Table 2, entry 1).[28] In a parallel study,

Table 2 Synthesis of 5-Aryl Oxazoles from Benzyl Bromides



4a–i **2** **3a–i**

Entry	**4**, **3** R	**3**	Yield (%)
1	Ph	**3a**	90
2	4-MeC_6H_4	**3b**	86
3	4-*t*-BuC_6H_4	**3c**	84
4	4-$MeOC_6H_4$	**3d**	77
5	4-$O_2NC_6H_4$	**3e**	80
6	4-FC_6H_4	**3f**	82
7	4-ClC_6H_4	**3g**	78
8	4-BrC_6H_4	**3h**	75
9	2-naphthyl	**3i**	78



Scheme 1 The plausible mechanism for the synthesis of 5-aryl oxazoles from benzyl alcohols and benzyl bromides.

this protocol was compared with benzyl chloride instead of benzyl bromide, which results in longer reaction time and low yield.

Thus, with these optimized reaction conditions, we examined the generality of the protocol by carrying the reaction out with *p*-tolyl-, 4-*tert*-butylbenzyl-, 4-methoxybenzyl-, and 4-nitrobenzylbromide (Table 2, entries 2–5) to furnish the corresponding 5-aryl oxazoles **3b**–**e** in 77–86% yield. Similarly, 4-flurophenyl-, 4-chlorophenyl-, and 4-bromophenyl oxazoles **3f**–**h** were obtained from the corresponding halogen-substituted benzyl bromides in 75–82% yield (Table 2, entries 6–8). This method can be equally extended for the synthesis of 5-(2-naphthyl) oxazole (**3i**) from 2-naphthylmethyl bromide in 78% yield (Table 2, entry 9). Notably, 5-(het)aryl oxazoles could not be synthesized due to nonavailability of precursors and difficulties in their preparation.

The probable mechanism for oxidation of alcohols[25d] and benzyl bromides[29] to aldehydes and van Leusen cyclization[16a] is given in Scheme 1.

In conclusion, we have developed a new strategy for the synthesis of 5-(het)aryl oxazoles from substituted (het)aryl methyl alcohols and benzyl bromides via oxidation in T3P®–DMSO and DMSO media, respectively, followed by the cyclization of in situ generated aldehyde with TosMIC in the presence of aqueous–alcoholic KOH with an excellent yield, mild, and eco-friendly protocols. It should be noted that these methods are the first substrate-modified green van Leusen oxazole synthesis methods. The noteworthy features of this developed protocol for the tandem reaction are less reaction time, broad functional-group tolerance, and ease of product purification.

Acknowledgment

K.S.V. thanks UGC-BSR for providing a fellowship, M.P.S. thanks UGC-SAP Phase-III, New Delhi for funding and N.R. thanks UGC-RGNF for a fellowship. The authors are grateful to IOE, University of Mysore for XRD facility and spectral characterization.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561391.

References and Notes

(1) (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382. (b) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143.

(2) (a) Cocito, C. *Microbiol. Rev.* **1979**, *43*, 145. (b) Moura, K. C. G.; Carneiro, P. F.; Pinto, M. do.. C. F. R.; da Silva, J. A.; Malta, V. R. S.; de Simone, C. A.; Dias, G. G.; Jardim, G. A. M.; Cantos, J.; Coelho, T. S.; Almeida da Silva, P. E.; da Silva, E. N. Jr. *Bioorg. Med. Chem.* **2012**, *20*, 6482.

(3) (a) Antonio, J.; Molinski, T. F. *J. Nat. Prod.* **1993**, *56*, 54. (b) Ryu, C. K.; Lee, R. Y.; Kim, N. Y.; Kim, Y. H.; Song, A. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5924.

(4) (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (b) Riego, E.; Hermandez, D.; Albericio, F.; Alvarez, M. *Synthesis* **2005**, 1907. (c) Liu, X. H.; Lv, P. C.; Xue, J. Y.; Song, B. A.; Zhu, H. L. *Eur. J. Med. Chem.* **2009**, *44*, 3930. (d) Kumar, D.; Kumar, N. M.; Sundaraee, S.; Johnson, E. O.; Shah, K. *Eur. J. Med. Chem.* **2010**, *45*, 1244.

(5) (a) Cuny, G.; Gamez-Montano, R.; Zhu, J. *Tetrhedron* **2004**, *60*, 4879. (b) Bertram, A.; Maulucci, N.; New, O. M.; Nor, S. M. M.; Pattenden, G. *Org. Biomol. Chem.* **2007**, *5*, 1541. (c) Joannesse, C.; Johnston, C. P.; Concellon, C.; Simel, C.; Philp, D.; Smith, A. B.

Angew. Chem. **2009**, *121*, 9076. (d) Dhara, M. G.; Banerjee, S. *Prog. Polym. Sci.* **2010**, *35*, 1022. (e) Hussein, M. A.; Asiri, A. M.; Aly, K. I. *Int. J. Polym. Mater.* **2012**, *61*, 154.

(6) (a) Zhong, C. L.; Tang, B. Y.; Yin, P.; Chen, Y.; He, L. *J. Org. Chem.* **2012**, *77*, 4271. (b) *Oxazoles: Synthesis, Reactions, and Spectroscopy*, In *The Chemistry of Heterocyclic Compounds, Palmer D. C*; Wiley: Hoboken, **2004**, Parts A and B, Vol. 60.

(7) (a) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167. (b) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1283. (c) Shaw, A. Y.; Xu, Z.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1998.

(8) (a) Moody, C. J.; Doyle, K. J. *Prog. Heterocycl. Chem.* **1997**, *9*, 1. (b) Linder, J.; Garner, T. P.; Williams, H. E. L.; Searle, M. S.; Moody, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 1044. (c) Xu, X.; Zavalij, P. Y.; Hu, W.; Doyle, M. P. *Chem. Commun.* **2012**, *48*, 11522.

(9) Pan, Y. M.; Zheng, F. J.; Li, H. X.; Zhan, Z. P. *J. Org. Chem.* **2009**, *74*, 3148.

(10) Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5561.

(11) Wan, C.; Gao, L.; Wang, Q.; Zhang, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 3902.

(12) Ritson, D. J.; Spiteri, C.; Moses, J. E. *J. Org. Chem.* **2011**, *76*, 3519.

(13) (a) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (b) Li, X.; Huang, L.; Chen, H.; Wu, W.; Huang, H.; Jiang, H. *Chem. Sci.* **2012**, *3*, 3463.

(14) Xu, Z.; Zhang, C.; Jiao, N. *Angew Chem.* **2012**, *124*, 11529.

(15) (a) Bellina, F.; Lessi, M.; Manzini, C. *Eur. J. Org. Chem.* **2013**, 5621. (b) Besselierre, F.; Mahuteau-Betzer, F.; Grierson, D. S.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278. (c) Primas, N.; Bouillon, A.; Lancelot, J. C.; Rault, S. *Tetrahedron* **2009**, *65*, 6348. (d) Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180. (e) Odani, R.; Hirano, K.; Sotoh, T.; Miura, M. *J. Org. Chem.* **2015**, *80*, 2384.

(16) (a) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *13*, 2369. (b) Saikachi, H.; Kitagawa, T.; Sasaki, H.; van Leusen, A. M. *Chem. Pharm. Bull.* **1979**, *23*, 793. (c) Sagud, I.; Faraguna, F.; Marinic, Z.; Sindler-Kulyk, M. *J. Org. Chem.* **2011**, *76*, 2904.

(17) Kulakarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5633.

(18) Kulakarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5637.

(19) Addie, M. S.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 527.

(20) Wu, B.; Wen, J.; Zhang, J.; Li, J.; Xiang, Y. Z.; Yu, X. Q. *Synlett* **2009**, 500.

(21) Katritzky, A. R.; Chen, Y. X.; Yannakopoulou, K.; Lue, P. *Tetrahedron Lett.* **1989**, *30*, 6657.

(22) Molander, G. A.; Febo-Ayala, W.; Jean-Gerard, L. *Org. Lett.* **2009**, *11*, 3830.

(23) Motoyama, Y.; Kawakami, H.; Shimozono, K.; Katsuyuki, A.; Nishiyama, H. *J. Org. Chem.* **2002**, *21*, 3408.

(24) (a) Moliner, F. D.; Hulme, C. *Org. Lett.* **2012**, *14*, 1354. (b) Moliner, F. D.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 5787.

(25) (a) Lingaraju, G. S.; Swaroop, T. R.; Vinayaka, A. C.; Sharath Kumar, K. S.; Sadashiva, M. P.; Rangappa, K. S. *Synthesis* **2012**, *44*, 1373. (b) Swaroop, T. R.; Roopashree, R.; Ila, H.; Rangappa, K. S. *Tetrahedron Lett.* **2013**, *54*, 147. (c) Swaroop, T. R.; Ila, H.; Rangappa, K. S. *Tetrahedron Lett.* **2013**, *54*, 5288. (d) Sharath Kumar, K. S.; Swaroop, T. R.; Harsha, K. B.; Narasimhamurthy, K. H.; Rangappa, K. S. *Tetrahedron Lett.* **2012**, *53*, 5619. (e) Vinayaka, A. C.; Sadashiva, M. P.; Wu, X.; Biryukov, S. S.; Stoute, J. A.; Rangappa, K. S.; Gowda, D. C. *Org. Biomol. Chem.* **2014**, *12*, 8555. (f) Bommegowda, Y. K.; Lingaraju, G. S.; Thamas, S.; Vinay Kumar, K. S.; Pradeepa Kumara, C. S.; Rangappa, K. S.; Sadashiva, M. P. *Tetrahedron Lett.* **2013**, *54*, 2693.

(26) To a solution of benzyl alcohol (4.6 mmol) in DMSO (2 mL), T3P® (5.5 mmol, 50% solution in EtOAc) was added at 0 °C followed by Et_3N (9.2 mmol) under nitrogen atmosphere. The mixture was stirred at r.t. for 1.5 h. After completion of the reaction (monitored by TLC), KOH (69.0–92.0 mmol) in H_2O–EtOH mixture (3 mL, 1:1, v/v) was added dropwise to the reaction mixture at 0 °C and stirred for 5 min followed by TosMIC (5.0 mmol) addition. The reaction was monitored by TLC and evaporated the EtOH from reaction mixture under reduced pressure, followed by dilution with EtOAc (2 × 25 mL). The organic layer was washed with H_2O (2 × 20 mL) and brine solution (2 × 20 mL). Then, the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford crude product. The crude was purified by column chromatography over silica gel (60–120 mesh) using hexane–EtOAc mixture as eluent (8:2) and obtained **3a** (83% yield) as pale yellow solid; mp 37–39 °C. FTIR: 3013, 3006, 2988, 2251, 1661, 1052, 1024, 1005, 658 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H, ArH), 7.65-7.62 (m, 2 H, ArH), 7.43–7.38 (m, 2 H, ArH), 7.34–7.30 (m, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 150.3, 128.9, 128.6, 127.7, 124.3, 121.4. HRMS: *m/z* calcd: 145.158; found: 146.703 $[M + H]^+$. Anal. Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65; O, 11.02. Found: C, 74.48; H, 4.89; N, 9.66.

(27) CCDC 1429231 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(28) The mixture of benzyl bromide (2.9 mmol) and $NaHCO_3$ (4.3 mmol) was stirred for 5 min followed by the addition of DMSO (1 mL) at r.t., and the reaction was monitored by TLC, followed by dropwise addition of KOH (4.3–5.8 mmol) in H_2O–EtOH mixture (3 mL, 1:1, v/v) at 0 °C. The reaction mixture was stirred for 5 min followed by the addition of TosMIC (5.0 mmol), then continued the stirring for 2–3 h. After completion of the reaction, EtOH was removed under reduced pressure; extracted and purified the crude product **3a** as mentioned the above procedure. The characterisation data were identical with the products isolated in the earlier protocol.

(29) Bratulescu, G. *Synth. Commun.* **2008**, *38*, 2748.