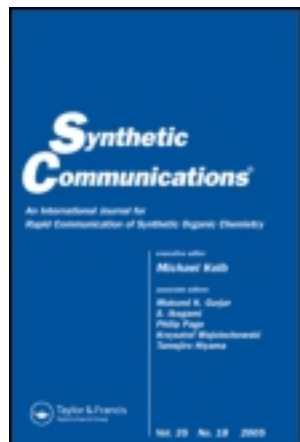




Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

Triflic Anhydride: A Mild Reagent for Highly Efficient Synthesis of 1,2-Benzisoxazoles, Isoxazolo, and Isothiazolo Quinolines Without Additive or Base

Rajesh G. Kalkhambkar^a & H. Yuvaraj^b

^a Department of Chemistry, Karnatak University's Karnatak Science College, Dharwad, Karnatak, India

^b School of Display and Chemical Engineering, Yeungnam University, Gyeongsan, Gyeongbuk, Republic of Korea
Published online: 27 Dec 2013.

To cite this article: Rajesh G. Kalkhambkar & H. Yuvaraj (2014) Triflic Anhydride: A Mild Reagent for Highly Efficient Synthesis of 1,2-Benzisoxazoles, Isoxazolo, and Isothiazolo Quinolines Without Additive or Base, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:4, 547-555, DOI: [10.1080/00397911.2013.821617](https://doi.org/10.1080/00397911.2013.821617)

To link to this article: <http://dx.doi.org/10.1080/00397911.2013.821617>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

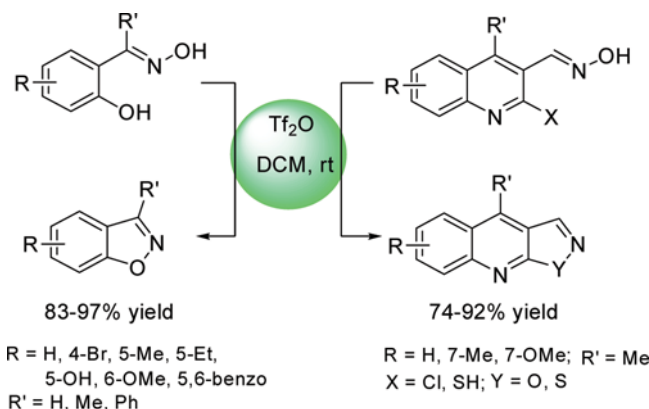
TRIFLIC ANHYDRIDE: A MILD REAGENT FOR HIGHLY EFFICIENT SYNTHESIS OF 1,2-BENZISOXAZOLES, ISOXAZOLO, AND ISOTHIAZOLO QUINOLINES WITHOUT ADDITIVE OR BASE

Rajesh G. Kalkhambkar¹ and H. Yuvaraj²

¹Department of Chemistry, Karnatak University's Karnatak Science College, Dharwad, Karnatak, India

²School of Display and Chemical Engineering, Yeungnam University, Gyeongsan, Gyeongbuk, Republic of Korea

GRAPHICAL ABSTRACT



Abstract The synthetic utility of trifluoromethanesulphonic anhydride (triflic anhydride, TA) without additive or base for the high-yielding synthesis of a wide variety of 1,2-benzisoxazoles from 2-hydroxyaryl aldoximes and ketoximes under mild conditions has been carried out for the first time. As a continuation of our study, syntheses of isoxazolo and isothiazolo quinolones have also been demonstrated using triflic anhydride under similar conditions. This method is simple and has benefits from the easy way to isolate the products in excellent yields.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource(s): Full experimental and spectral details.]

Keywords Aldoximes; 1,2-benzisoxazoles; isothiazolo quinolones; isoxazolo quinolones; ketoximes; triflic anhydride

Received April 24, 2013.

Address correspondence to Rajesh G. Kalkhambkar, Department of Chemistry, Karnatak University's Karnatak Science College, Dharwad, Karnatak 580001, India. E-mail: rgkalkhambkar@gmail.com

INTRODUCTION

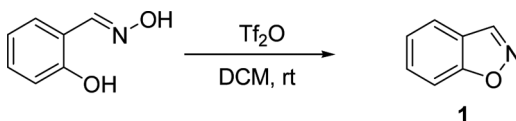
Because of their profound biological and pharmacological applications, 1,2-benzisoxazoles are useful intermediates in medicinal chemistry.^[1–6] In view of their extensive biological and pharmacological applications, many synthetic methods have been developed to construct these nitrogen–oxygen heterocycles,^[7] such as cycloaddition of benzyne and nitrile oxides,^[8] copper-catalyzed cyclization of Z-oximes,^[9] and the reaction of hydroxylamine-*o*-sulfonic acid with 2-hydroxyphenyl carbonyl compounds.^[10] In the past decade, many catalysts have also been developed for the synthesis of 1,2-benzisoxazoles, which includes the base-catalyzed cyclization of 2-hydroxyaryl aldoximes and ketoximes with Ac₂O,^[11,12] SOCl₂,^[13] Ga(OTf)₃,^[14] Ph₃P,^[15] and trichloroacetyl isocyanate.^[16] Although some benefits are there for each of the reported methods, the limitations and drawbacks associated with the synthesis of 1,2-benzisoxazoles in these reports,^[17,18] directed us to find a new and simple way of accessing the target molecules.

Generally, many benzo/hetero fused isoxazole derivatives and isothiazole derivatives exhibit a wide variety of pharmacological properties, as the structural units of many molecules consisting of 1,2-benzisoxazole moiety.^[20] In particular, isothiazolo quinolines are known to possess antibacterial activity.^[21] A number of methods are available in the literature for the synthesis of these heterocycles because of their great synthetic and medicinal importance.^[22–26] However, triflic anhydride-mediated simple synthesis of isoxazolo and isothiazolo quinolines without additive or base has not been reported yet. Recently, we have demonstrated the synthesis of simple 1,2-benzisoxazole by the utility of N-triflylimidazole, an in situ-generated reagent by the reaction of triflic anhydride and imidazole,^[19] which prompted us to synthesize a series of such compounds in the absence of imidazole. Hence, in continuation of our work on the use of triflic anhydride (TA), we now report the synthesis of 1,2-benzisoxazoles, isoxazolo quinolines, and isothiazolo quinolines under mild and neutral reaction conditions at room temperature without the formation of any side products.

RESULTS AND DISCUSSION

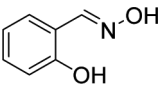
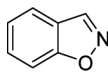
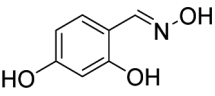
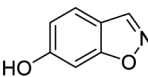
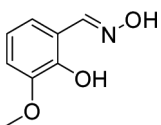
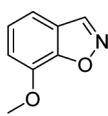
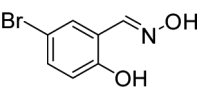
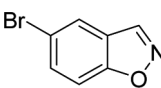
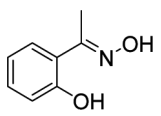
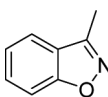
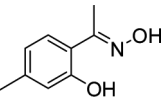
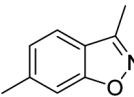
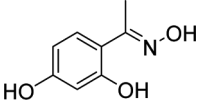
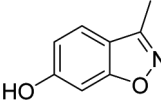
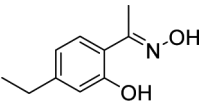
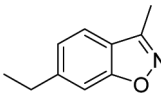
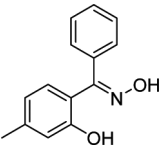
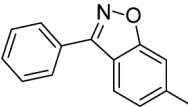
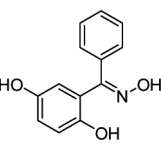
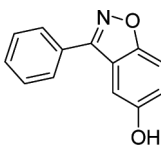
To optimize the reaction conditions such as temperature, solvent, and amount of reagent, and to study the feasibility of TA-mediated synthesis of 1,2-benzisoxazoles, the cyclization of salicylaldoxime to its corresponding 1,2-benzisoxazole (Scheme 1) was selected as a model.

The reaction was carried out at room temperature with equivalent amount of TA in dichloromethane (DCM). Addition of the TA produced the corresponding 1,2-benzisoxazole at rt in moderate yield in 4 h (Table 1, entry 1). The successful synthesis of 1,2-benzisoxazole derivatives via the cyclization of different aldoximes



Scheme 1. Synthesis of 1,2-benzisoxazole (**1**) from salicylaldoxime using TA.

Table 1. Synthesis of 1,2-benzisoxazoles using TA

Entry	Compound	Substrate	Product	Time (h)	Isolated yield ^a (%)
1	1			4	72
2	2			3	93
3	3			3	90
4	4			3	88
5	5			5	97
6	6			4	90
7	7			4	86
8	8			3	91 (88 ^b)
9	9			3	86 (82 ^b)
10	10			2	85

(Continued)

Table 1. Continued

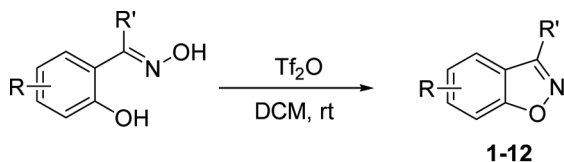
Entry	Compound	Substrate	Product	Time (h)	Isolated yield ^a (%)
11	11			2	83
12	12			4	94

^aIsolated yields of pure products.^bThe reaction was carried out in EDC.

prompted us to investigate the applicability of this procedure for the generation of other 1,2-benzisoxazoles via the cyclization of variety of ketoximes (Scheme 2).

A similar trend of reaction was observed in the cyclization of oxime of 2-hydroxyacetophenone to the corresponding 1,2-benzisoxazoles (Table 1, entry 5). The reaction was completed in 5 h at rt with 96% isolated yield. Thus, the cyclization of a wide range of structurally varied 2-hydroxyaryl aldoximes and ketoximes in the presence of TA was carried out under the optimized reaction conditions described previously. The results (Table 1) show that a variety of structurally varied 2-hydroxyaryl aldoximes and ketoximes cyclized smoothly in DCM to give the corresponding 1,2-benzisoxazoles in excellent yield (82% to 96%) and purity.

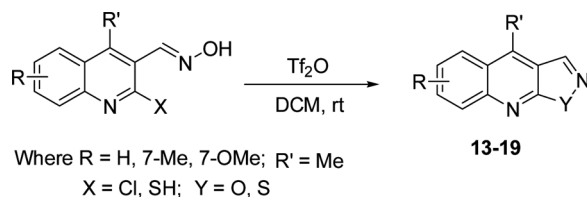
To evaluate the reactivity of the system with another solvent, we also carried out the reaction using ethylene dichloride (EDC). With EDC, in two different experiments the cyclization was completed in 3 h at rt with 88 and 82% yields (Table 1, entries 8 and 9 respectively) and almost the same results were obtained at 80 °C. Because the results obtained with EDC in terms of reaction time and isolated yield were not so encouraging in comparison with those of DCM and because EDC is potentially carcinogenic (cat. 1B), we thought to demonstrate the cyclization in DCM. As shown in Table 1, the use of this method at room temperature and under



Where R = H, 4-Br, 5-Me, 5-Et, 5-OH, 6-OMe, 5,6-benzo

R' = H, Me, Ph

Scheme 2. Synthesis of various substituted 1,2-benzisoxazoles (**1-12**) from 2-hydroxyaryl aldoximes and ketoximes using TA.



Scheme 3. Synthesis of various substituted isoxazolo and isothiazoloquinolines (**13–19**) using TA.

neutral conditions gave 83 to 94% yields of various substituted 1,2-benzisoxazoles (Table 1, entries 6, 7, and 10–12).

In view of the synthetic importance of isoxazolo and isothiazolo quinolines,^[20–22] and as a continuation of this work, we have also demonstrated the synthesis of a variety of isoxazolo and isothiazolo quinolines via the cyclization of variety of substituted oximes of 2-chloro-3-formylquinoline and 2-mercapto-3-formylquinoline in the presence of TA (Scheme 3).

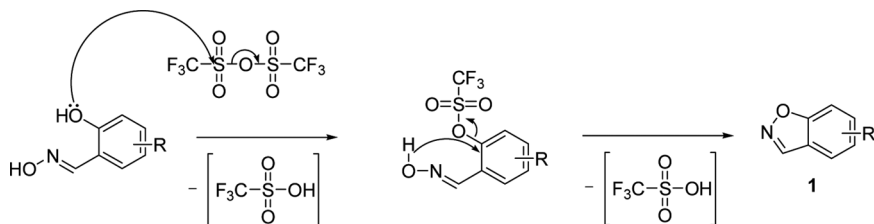
Under the present optimized reaction conditions, a comparatively long reaction time was observed with substrates such as the oximes of 2-chloro-3-formyl-7-methoxy-quinolin and 2-chloro-3-formyl-7-methyl-quinolin (Table 2, entries 3 and

Table 2. Synthesis of substituted isoxazolo and isothiazolo quinolines using TA

Entry	Compound	Substrate	Product	Time (h)	Isolated yield ^a (%)
1	13			6	84
2	14			6	92
3	15			8	84 (80 ^b)
4	16			7	84 (78 ^b)
5	17			6	74
6	18			5	85
7	19			5	90

^aIsolated yields of pure products.

^bThe reaction was carried out in EDC.



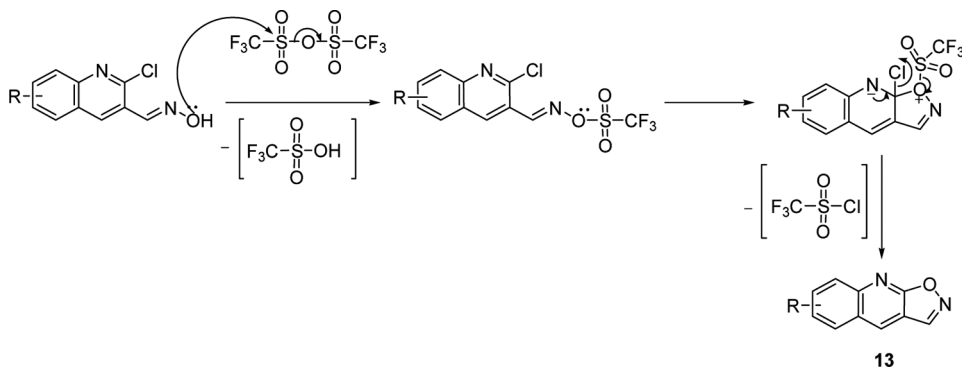
Scheme 4. Plausible mechanism of formation of 1,2-benzisoxazole (**1**) using TA.

4 respectively). Nevertheless, all the oximes of quinoline are cyclized in 5 to 8 h with excellent yields of 74 to 92%. In comparison with the observed yield of various products as depicted in Table 2, excellent yields of products are obtained when the oximes of 2-chloro-3-formyl-4-methyl quinoline (Table 2, entry 2) and 2-mercapto-3-formyl-7-methyl quinoline (Table 2, entry 7) are subjected to cyclization.

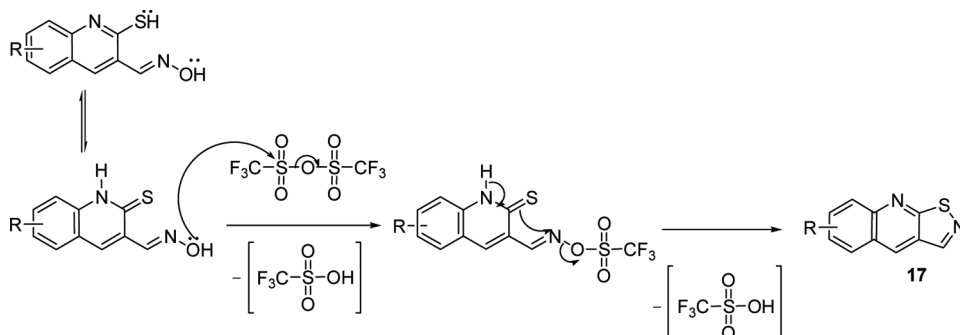
The plausible mechanism of formation of various 1,2-benzisoxazoles is depicted in Schemes 4–6. The initial step is the reaction between phenolic OH and Ta_2O_5 , which is favored because of high nucleophilicity of phenolic OH and facile cleavage of the S–O bond. The resulting phenyl trifluoromethyl sulfonate acts as a better leaving group and facilitates an intramolecular ipso attack by the oxime hydroxyl group, leading to the expulsion trifluoromethane sulfonic acid and the formation of 1,2-benzisoxazole **1** (Scheme 4).

In the reaction of 2-chloroquinoline-3-aldoxime, the oxime forms a trifluoromethane sulfonate, which again brings intramolecular ipso chloro displacement at C-2 of quinoline by the expulsion of trifluoromethane sulfonylchloride, leading to the formation of isoxazole-fused quinoline (**13**) (Scheme 5). Similar structurally analogous intramolecular reactions have been observed in the formation of pyrazoloquinolines.^[28]

In the reaction of 2-mercaptoquinoline-3-aldoximes, the free oxime acts as a better nucleophile than the tautomeric thiol. The oxime has now been converted into a better leaving group. The N–S bond formation is triggered by the deprotonation at the ring N and the nucleophilic attack on the azomethine nitrogen. The N–S bond formation is facilitates by the facile cleavage of the N–O bond with the loss of



Scheme 5. Plausible mechanism of formation of isoxazoloquinoline (**13**) using TA.



Scheme 6. Plausible mechanism of formation of isothiazoloquinoline (**17**) using TA.

trifluoromethane sulfonyl moiety, leading to the formation of isothiazole fused quinolines (**17**) (Scheme 6).

The common features in this reaction seem to be the formation of O-trifluoromethanesulfonate and the leaving ability favoring the formation of O-C and S-N bonds by an intramolecular ipso $S_N\text{-Ar}$ pathway.

EXPERIMENTAL

The reagents employed were high-purity commercial samples, which were used as received from vendors without further purification. Reactions were carried out in an oven-dried round-bottom flask. Column chromatography was performed on silica gel (200–400 mesh). Thin-layer chromatography (TLC) was performed on alumina silica gel 60F₂₅₄ (Fischer) detected by ultraviolet (UV) light (254 nm) and iodine vapors. The melting points were determined by open capillaries on a Buchi apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Nicolet-Impact-410 FT-IR spectrometer, using KBr pellets. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AC-300F 300-MHz, spectrometer in dimethylsulfoxide (DMSO-*d*₆) using tetramethylsilane (TMS) as an internal standard with ¹H resonance frequency of 300 MHz and ¹³C resonance frequency of 75 MHz. Gas chromatographic (GC) analyses were performed on an Nucon 5700 series gas chromatograph. GC-MS analyses were performed on a Shimadzu 2010 series mass selective detector instrument. Elemental analysis was carried out by using Heraeus CHN rapid analyzer. All the compounds gave C, H, and N analysis within $\pm 0.4\%$ of the theoretical values. Dry DCM and EDC were obtained from commercial sources by the standard procedure.^[27]

Typical Procedure for the Synthesis of 1,2-Benzisoxazole Using Triflic Anhydride

The desired 2-hydroxyarylaldoxime or ketoxime (2.0 mmol) in 5 mL dry DCM was taken in an oven-dried round-bottom flask. To the reaction mixture was added dropwise triflic anhydride (2.0 mmol) in DCM under nitrogen for 15 min. The reaction mixture was stirred at rt and the progress of the reaction was monitored by TLC

and GC-MS (Table 1). After completion of reaction, the contents were poured on to crushed ice (100 mL), neutralized with 10% NaHCO₃ solution (20 mL), and extracted with DCM (3 × 15 mL). The pure products were obtained by column chromatography with hexane–ethyl acetate mixture (80:20). All the 1,2-benzisoxazole derivatives were characterized by GC-MS, ¹H and ¹³C NMR, and elemental analysis, and the results are compared with authentic samples.

Supporting Information

Full experimental details, IR, ¹H and ¹³C NMR spectra, and elemental analysis can be found via the “Supplementary Content” section of this article’s Web page.

CONCLUSIONS

In conclusion, we have successfully demonstrated the mild, convenient method for the synthesis of a wide variety of 1,2-benzisoxazoles, from 2-hydroxyaryl aldoximes and ketoximes using triflic anhydride. Further we have also demonstrated the synthesis of different substituted isoxazolo and isothiazolo quinolines using triflic anhydride at room temperature. This practical and simple method led to good yields with high purity of 1,2-benzisoxazoles under mild conditions without addition of external base or additive. This protocol could serve as a valuable alternative to the known reaction systems.

Further work, including the development of synthetic applications of aryl and heteroaryl oximes and exploration of the enormous potential of triflic anhydride as a triflyl source in organic synthesis, is under way in our laboratory.

ACKNOWLEDGMENTS

The authors thank the University Sophisticated Instrument Center, KUD, for IR, GC, GC-MS, ¹H NMR, and ¹³C NMR and G. Aridoss for useful discussions.

REFERENCES

1. (a) Quilico, A. *Isoxazoles and Related Compounds in the Chemistry of Heterocyclic Compounds*; A. Weissberger (Ed.); Interscience: New York, 1962; p. 17; (b) Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. *Adv. Heterocycl. Chem.* **1987**, 23, 103.
2. Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Davis, L.; Effland, R. C.; Ranbom, K.; Kitzen, J. M.; Wilker, J. C.; Novick, W. J. *J. Med. Chem.* **1982**, 25, 36.
3. Rangappa, K. S.; Basappa, S. J. *Phys. Org. Chem.* **2005**, 18, 773.
4. Veera Reddy, A.; Rajendiran, C.; Vaishali, N. WO Patent 2005/030738, Sep. 29, 2003; *Chem. Abstr.* **2005**, 142, 33849.
5. Struczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Glamkovski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. *J. Med. Chem.* **1985**, 28, 761.
6. Grunanger, P.; Vita-Finzi, P. *Isoxazoles in the Chemistry of Heterocyclic Compounds*; E. C. Taylor (Ed.); Interscience: New York, 1991; p. 49.
7. Smalley, R. K. *Methoden der organischen Chemie, Band E 8 a Heterene III*; Georg Thieme: Stuttgart, Germany, 1993; vol. 1, p. 226.
8. Crossley, J. A.; Browne, D. L. *Tetrahedron Lett.* **2010**, 51, 2271.

9. Udd, S.; Jokela, R.; Franzén, R.; Tois, J. *Tetrahedron Lett.* **2010**, *51*, 1030.
10. Suwinski, J.; Walczak, K. *Pol. J. Chem.* **1992**, *66*, 777.
11. Roman, G.; Comanita, E.; Comanita, B. *Tetrahedron* **2002**, *58*, 1617.
12. Jain, M.; Kwon, C. *J. Med. Chem.* **2003**, *46*, 5428.
13. Kalkote, U. R.; Goswami, D. D. *Aust. J. Chem.* **1977**, *30*, 1847.
14. Yan, P.; Batamack, P.; Surya Prakash, G. K.; Olah, G. A. *Catal Lett.* **2005**, *101*, 141.
15. Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. *Tetrahedron Lett.* **2006**, *47*, 8247.
16. Stokker, G. *J. Org. Chem.* **1983**, *48*, 2613.
17. Bode, J. W.; Uesuka, H.; Suzuki, K. *Org. Lett.* **2003**, *5*, 395.
18. Suwinski, J.; Walczak, K. *Pol. J. Chem.* **1993**, *67*, 1267.
19. Kalkhambkar, R. G.; Bunge, S. D.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 5184.
20. (a) Cutri, C. C. C.; Garozzo, A.; Siracusa, M. A.; Castro, A.; Tempera, G.; Sarva, M. C.; Guerrero, F. *Antiviral Res.* **2002**, *55*, 357; (b) Aebi, J.; Ackermann, J.; Dehmlow, H.; Maerki, H. P.; Morand, O. PCT Int. Appl. WO Patent 0236584, 2002.
21. Chu, D. T. W.; Ferandes, P. B.; Claiborne, A. K.; Shen, L.; Pernet, A. G. *Drugs Exp. Clin. Res.* **1998**, *14*, 378.
22. (a) Dieter, R. K.; Chang, H. J. *J. Org. Chem.* **1989**, *54*, 1088; (b) Laaman, S. M.; Meth-Cohn, O.; Rees, C. W. *Synthesis* **1999**, 757.
23. Zlotin, S. G.; Kislitsin, P. G.; Podgursky, A. I.; Samet, A. V.; Buchana, A. C.; Gakh, A. A. *J. Org. Chem.* **2000**, *65*, 8439.
24. Crenshaw, R. E.; Luke, G. M.; Siminoff, P. *J. Med. Chem.* **1976**, *19*, 262.
25. Choi, J. H.; Choi, E. B.; Pak, C. S. *Synlett* **2003**, 166.
26. Nadaraj, V.; Thamarai, S. S. *J. Chem. Pharm. Res.* **2012**, *4*(6), 2850.
27. Vogel, A. *Practical Organic Chemistry*; Longman: New York, 1989.
28. (a) Mali, J. R.; Pratap, U. R.; Jawale, D. V.; Mane, R. A. *Tetrahedron Lett.* **2010**, *51*, 3980; (b) Kedjadga, A.; Moussaoui, F.; Debache, A.; Rhouati, S.; Belfaith, A. *J. Soc. Alger. Chim.* **2004**, *14*, 225.