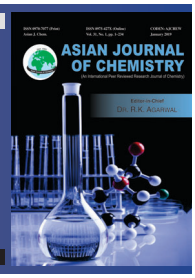
Asian Journal of Chemistry; Vol. 31, No. 1 (2019), 176-180

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2019.21622



# Novel Synthesis of 5-Oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate Derivatives in Non-Aqueous Medium

NITIN SRIVASTAVA* and M. SAXENA

Department of Chemistry, Amity University Uttar Pradesh, Lucknow Campus, Lucknow-226028, India

*Corresponding author: E-mail: nsrivastava1@lko.amity.edu

*Received*: 30 July 2018; *Accepted*: 27 September 2018; *Published online*: 30 November 2018; AJC-19179

A novel synthetic method of synthesis of 5-oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate (rhodanine) derivative is being reported using primary amines and acetylenic ester, carbon disufide and Triton-B in non-aqueous medium.

**Keywords: Carbon disulfide, Primary amine, Acetylenic ester, Triton-B.**

## INTRODUCTION

Rhodanine-based compounds have potential biological activities. The rhodanine derivatives have shown remarkable antifungal activity [1-4]. These compounds are also aggregators that can non-specifically interact with target proteins as well as Michael acceptors and interfere photometrically in biological assays due to their colour. They are found to inhibit targets like HCV NS3 protease [5] PMT1 mannosyltransferase [6] PRL-3 and JSP-1 phosphatase [7,8] and B lactamase [9]. After several years of research in drug discovery, they have gained a reputation as being pan assay interference compounds (PAINS) and frequent hitters in screening campaigns. Rhodanine-based compounds are also aggregators that can non-specifically interact with target proteins as well as Michael acceptors and interfere photometrically in biological assays due to their colour.

Gaikwad and Gautam [10] reported rhodanine derivatives as hypoglycemic agents which act as potent drugs to treat diabetes mellitus by lowering glucose levels in the blood. Most of them are administered orally. Shukla *et al.* [11] showed that substituted 3-aminomethylidene-4-thiazolidinone-2-thiones as potent antiviral agents. Classical methods for the synthesis of rhodanine is the several steps process and preparation of rhodanine structure and finally Knoevenagel condensation with aldehydes [12-16]. Taran *et al*. [17] proposed the synthesis of arylidene rhodanine derivatives *via* reaction between dithiocarbamates and aryl propiolates in the presence of $Bu_3P$ as catalyst in iPrOH. Earlier treatment of amine and its derivatives like dialkylacetylendicarboxylate and isocyante by Alizadeh *et al.* [18,19] at room temperature led to the formation of maleimide derivatives. The reaction product was separated using ethyl acetate as organic solvent [20]. Owing to the numerous biological activity involved in the rhodanine scaffold many researchers have given various process for its synthesis [21-24].

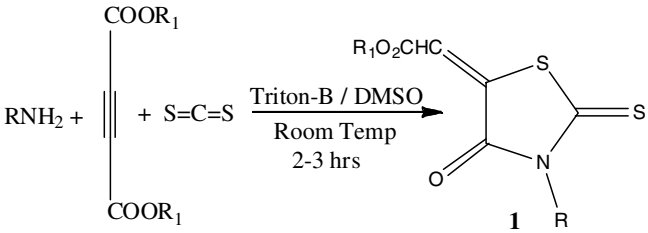
Alizadeh *et al*. [25] synthesized various rhodanine derivatives *via* reaction of acetylene carboxylate and alkyl halides in carbon disulphide. In present study, we used carbon disulfide under similar condition for synthesis of several 5-oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate derivative (rhodanine). Carbon disulfide is preferred over common organic solvents as it is easily available, cheap and less toxic. The one pot reaction between acetylene dicarboxylate in the presence of carbon disulfide and Triton-B gave several rhodanine derivatives. The use of phase transfer catalyst Triton-B made the easier workout of the synthesized compounds with better yield.

## EXPERIMENTAL

All the reagents used were of Merck, India. Identification of products was done by comparing their physical data and spectral data with the compounds already known. Infrared spectra (4000-200 $cm^{-1}$) were analyzed on a Bomem MB-FTIR spectrophotometer while NMR spectra were recorded on Bruker Advance DPX instrument spectrophotometer (400 MHz)

with $CDCl_3$ as solvent and tetramethylsilane as standard. Elemental analysis done by Carlo-Erba EA 1110 CHNOS analyzer which agreed comfortably with calculated ones. Characterization of all products was made by comparing their physical data with the reported data.

**General procedure:** Amine (0.386 mL) was added to Triton-B and stirred for 10 min followed by the addition of $CS_2$ (0.321 mL) dropwise. Then dimethyl acetate carboxylate was added again dropwise. The mixture was stirred for 2.5 h. TLC plate showed the formation of some new compound. The reaction was seen continuously and formation of product was monitored with TLC. After the completion, the reaction mixture was drained into distilled water and extraction was done three times using ethyl acetate (**Scheme-I**). IR, NMR and elemental analysis data of selected compounds are given below:




**Scheme-I**

**2-[4-Oxo-3-(*m*-trifluoromethylphenylmethyl)-2-thioxo-1,3-thiazolidine-5-yliden]ethanoate (1):** Yield 75 %, m.p.: 76 °C, yellow powder. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1720 (C=O), 1680 (C=C), 1342, 1187 (C=S). $^1H$ NMR: (400 MHz, $CDCl_3$): δ 7.5 (multiplet arom. H), 6.8-7.0 (singlet δ vinylic H), δ 5.4 (singlet 2H adj. to N), 3.9 (singlet 3H of $CH_3O$). Elemental analysis calcd. (found) % for $C_{14}H_{10}NO_3S_2F_3$: C 47.9 (46.8), H 2.84 (2.64), O 13.6 (14.4), S 18.2 (17.2), F 16.2 (15.9).

**2-[4-Oxo-3-(*p*-trifluoromethylphenylmethyl)-2-thioxo-1,3-thiazolidine-5-yliden]ethanoate (2):** Yield 77 %, m.p.: 82 °C, yellow powder. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1720 (C=O), 1683 (C=C), 1330, 1187 (C=S). $^1H$ NMR: (400 MHz, $CDCl_3$): δ 7.5 (multiplet arom. H), 6.8-7.0 (singlet δ vinylic H), δ 5.4 (singlet 2H adj. to N), 3.9 (singlet 3H of $CH_3O$). Elemental analysis calcd. (found) % for $C_{14}H_{10}NO_3S_2F_3$: C 47.8 (47.6), H 2.90 (2.98), O 13.70 (13.86), S 18.0 (18.25), F 16.6 (17.6).

**2-[4-Oxo-3-(propylphenylmethyl)-2-thioxo-1,3-thiazolidine-5-yliden]ethanoate (3):** Yield 80 %, m.p.: 128 °C, yellow powder. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1725 (C=O), 1685 (C=C), 1330, 1187 (C=S). $^1H$ NMR: (400 MHz, $CDCl_3$): δ 4.5 (2H arom.), δ 4.0 (singlet $OCH_3$), δ 3.0 (2H arom.), δ 2.0 (4H multiplet), δ 1.9 (1H singlet). Elemental analysis calcd. (found) % for $C_{15}H_{15}NO_3S_2$: C 56.07 (55.20), H 4.6 (4.8), N 4.36 (4.10), O 14.9 (14.2), S 19.9 (20.2).

**2-[4-Oxo-3-(1′-methylethyl)-2-thioxo-1,3-thiazolidine-5-yliden]ethanoate (4):** Yield 80 %, m.p.: 12 °C, yellow oil. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1725 (C=O), 1670 (C=C), 1315, 1187 (C=S). $^1H$ NMR: (400 MHz, $CDCl_3$): δ 1.54 (6H doublet) , δ 3.88.0 (3H singlet $OCH_3$), δ 5.20 (1H septet CH-$CH_3$), δ 6.77 (1H, singlet ethylenic H), δ 1.9 (1H singlet). Elemental analysis calcd. (found) % for $C_9H_{11}NO_2S_2$: C 44.08 (46.4), H 4.48 (5.02), N 5.71 (6.24), O 15.59 (14.8), S 26.12 (27.02).

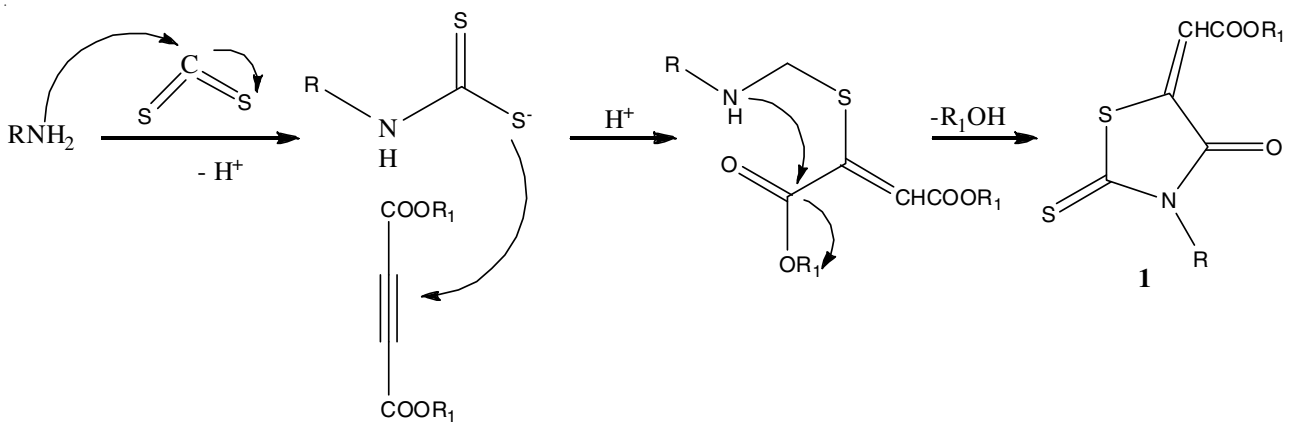
**2-[4-Oxo-3-(2′-methylpropyl)-2-thioxo-1,3-thiazolidine-5-yliden]ethanoate (5):** Yield 80 %, m.p.: 8 °C, pale yellow oil. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1715 (C=O), 1690 (C=C), 1315, 1187 (C=S). $^1H$ NMR (400 MHz, $CDCl_3$): δ 2.25-2.30 (1H multiplet $CH_2CH$ -$CH_3$), δ 3.87 (3H singlet $OCH_3$), δ 3.93 [2H doublet $CH_2CH$-$(CH_3)_2$]. Elemental analysis calcd. (found) % for $C_{10}H_{13}NO_3S_2$: C 46.66 (45.86), H 4.28 (4.04), N 5.44 (5.24), O 18.67 (19.07), S 24.90 (25.20).

## RESULTS AND DISCUSSION

One pot synthesis of rhodanine derivatives having coveted biological and pharmacological activities using Triton-B, carbon disulfide at room temperature is reported. The reaction of carbon disulfide with several amines in presence of dialkyl-acetylenedicarboxylate was spontaneous at room temperature in DMSO/ Triton-B. Also these reactions were completed in 2-3 h (Table-1).

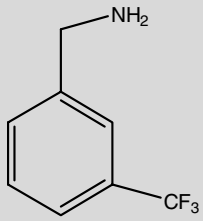
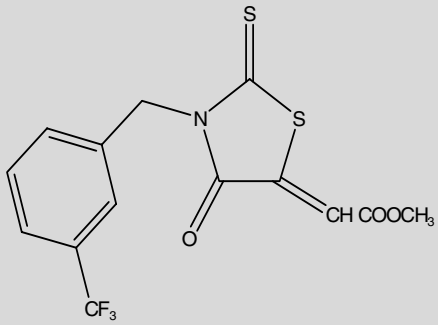
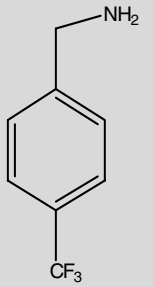
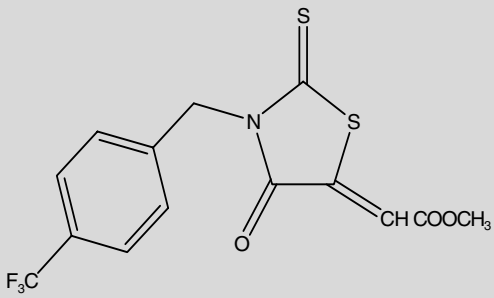
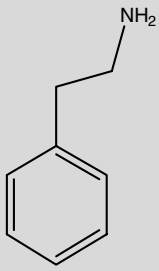
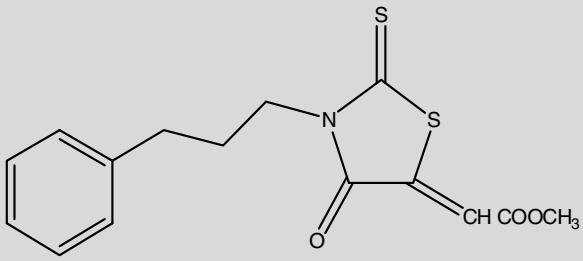
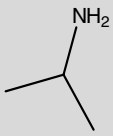
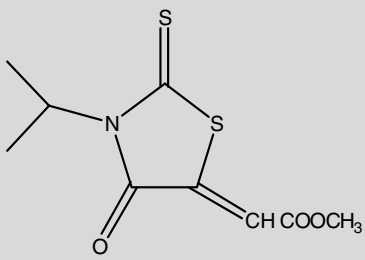
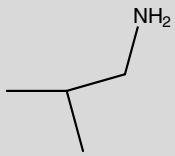
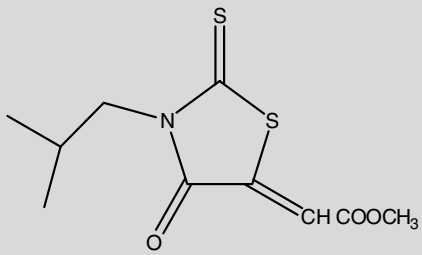
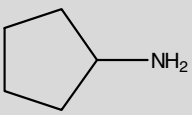
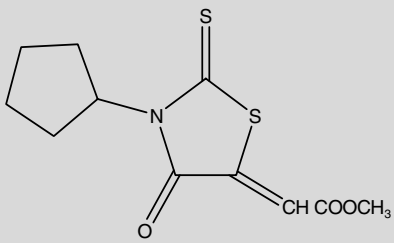
The synthesized compounds formed were identified by their elemental analysis, IR and $^1H$ NMR spectra. The $^1H$ NMR spectra of compound **1** exhibited 3 sharp singlets which were thought to be due to $OCH_3$ group (δ = 3.9), methylene protons (δ = 5.32) and vinylic proton at (δ = 6.85). The phenyl group gave characteristic aromatic signals in the NMR spectrum.

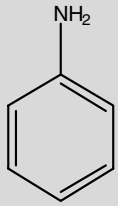
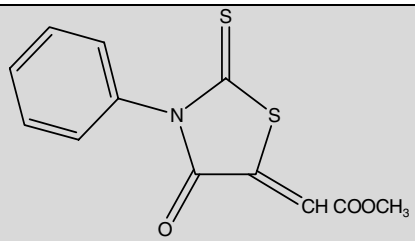
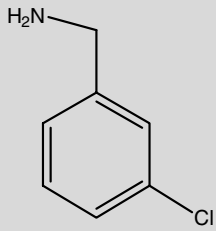
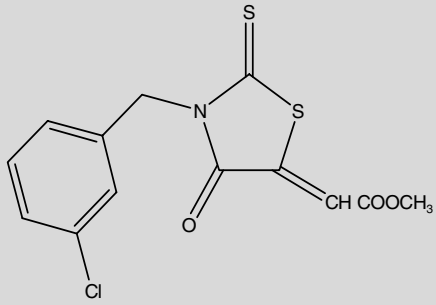
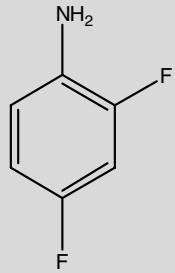
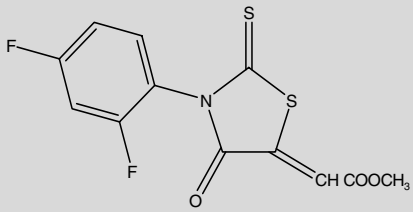
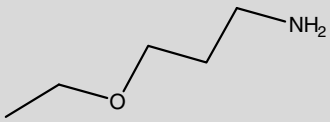
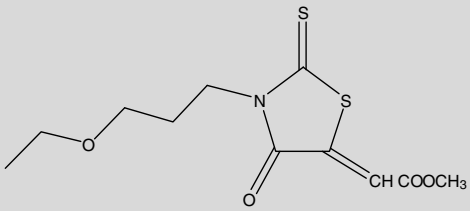
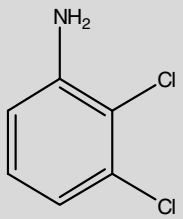
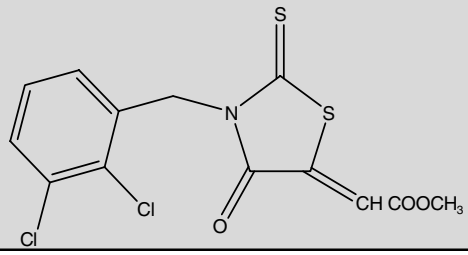
A possible mechanism of the reaction between carbon disulfide and amine in the presence of Triton-B is being put forward in **Scheme-II**. Compound **1** could results from initial addition of carbon disulfide to amine and subsequent attack of alkylammoniumcarbothioate on acetylenic ester to yield intermediate. Cyclization of intermediate and subsequent loss of $R_1OH$ lead to the formation of compound **1** (**Scheme-II**).




**Scheme-II**

TABLE-1

| S. No. | Amine used | $R_1$ | Structure of rhodanine derivatives | Yield (%) |
|---|---|---|---|---|
| 1 |  | —$CH_3$ |  | 71 |
| 2 |  | —$CH_3$ |  | 77 |
| 3 |  | —$CH_3$ |  | 80 |
| 4 |  | —$CH_3$ |  | 80 |
| 5 |  | —$CH_3$ |  | 80 |
| 6 |  | —$CH_3$ |  | 76 |

| | | | | |
|---|---|---|---|---|
| 7 |  | —$CH_3$ |  | 81 |
| 8 |  | —$CH_3$ |  | 70 |
| 9 |  | —$CH_3$ |  | 78 |
| 10 |  | —$CH_3$ |  | 84 |
| 11 |  | —$CH_3$ |  | 80 |

## Conclusion

In conclusion, carbon disulfide mediated synthesis has been reported for the synthesis of rhodanine derivatives and offers some notable and distinct advantages over usually employed procedure such as simplicity, room temperature conditions, simple work-up, high yield and cheap reagent.

## ACKNOWLEDGEMENTS

The authors gratefully acknowledge fruitful discussions with Dr. Devdutt Chaturvedi regarding the research and Amity University Uttar Pradesh Lucknow Campus, India for providing the infrastructure to conduct the research.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

## REFERENCES

1. Y. Inamori, Y. Okamoto, Y. Takegawa, H. Tsujibo, Y. Sakagami, Y. Kumeda, M. Shibata and A. Numata, *Biosci. Biotechnol. Biochem.*, **62**, 1025 (1998); https://doi.org/10.1271/bbb.62.1025.
2. J. Miao, C.-J. Zheng, L.-P. Sun, M.-X. Song, L.-L. Xu and H.-R. Piao, Med. Chem. Res., 22, 4125 (2013); https://doi.org/10.1007/s00044-012-0417-z.
3. P. Mitra and A.S. Mitra, *J. Indian Chem. Soc.*, **61**, 77 (1984).
4. A.A. Khalek, C.R. Ashby Jr., B.A. Patel, T.T. Talele and M.N. Seleem, *PLoS One*, **11**, e0164227 (2016); https://doi.org/10.1371/journal.pone.0164227.
5. W. Sing, C.L. Lee, S.L. Yeo, S.P. Lim and M.M. Sim, *Bioorg. Med. Chem. Lett.*, **11**, 91 (2001); https://doi.org/10.1016/S0960-894X(00)00610-7.
6. M.G. Orchard, J.C. Neuss, C.M. Galley, A. Carr, D.W. Porter, P. Smith, D.I.C. Scopes, D. Haydon, K. Vousden, C.R. Stubberfield, K. Young and M. Page, *Bioorg. Med. Chem. Lett.*, **14**, 3975 (2004); https://doi.org/10.1016/j.bmcl.2004.05.050.

7. N.S. Cutshall, C. O' Day and M. Prezhdo, *Bioorg. Med. Chem. Lett.*, **15**, 3374 (2005); https://doi.org/10.1016/j.bmcl.2005.05.034.
8. J.H. Ahn, S.J. Kim, W.S. Park, S.Y. Cho, J.D. Ha, S.S. Kim, S.K. Kang, D.G. Jeong, S.-K. Jung, S.-H. Lee, H.M. Kim, S.K. Park, K.H. Lee, C.W. Lee, S.E. Ryu and J.-K. Choi, *Bioorg. Med. Chem. Lett.*, **16**, 2996 (2006); https://doi.org/10.1016/j.bmcl.2006.02.060.
9. E.B. Grant, D. Guiadeen, E.Z. Baum, B.D. Foleno, D.A. Montenegro, H. Jin, E.A. Nelson, K. Bush and D.J. Hlasta, *Bioorg. Med. Chem. Lett.*, **10**, 2179 (2000); https://doi.org/10.1016/S0960-894X(00)00444-3.
10. N.J. Gaikwad and P. Gautam, *Indian J. Heterocycl. Chem.*, **12**, 181 (2002).
11. S.K. Shukla, S.P. Singh, L.P. Awasthi and D.D. Mukherjee, *Indian J. Pharm. Sci.*, **44**, 153 (1982).
12. B.B. Lohray, V. Bhushan, P.B. Rao, G.R. Madhavan, N. Murali, K.N. Rao, G.R. Madhavan, N. Murali, K.N. Rao, K. Anantha Reddy, B.M. Rajesh, P. Ganpathy Reddy, R. Chakrabarti and R. Rajagopalan, *Bioorg. Med. Chem. Lett.*, **7**, 785 (1997); https://doi.org/10.1016/S0960-894X(97)00118-2.
13. S.P. Singh, S.S. Parmar, K. Raman and V.I. Stenberg, *Chem. Rev.*, **81**, 175 (1981); https://doi.org/10.1021/cr00042a003.
14. C.L. Lee and M.M. Sim, *Tetrahedron Lett.*, **41**, 5729 (2000); https://doi.org/10.1016/S0040-4039(00)00866-2.
15. F.C. Brown, *Chem. Rev.*, **61**, 463 (1961); https://doi.org/10.1021/cr60213a002.
16. W.-D. Rudorf and R. Schwarz, *Hetrocycles*, **24**, 3459 (1986); https://doi.org/10.3987/R-1986-12-3459.
17. S. Gabillet, D. Lecercle, O. Loreau, M. Carboni, S. Dezard, J. Gomis and M. Taran, *Org. Lett.*, **9**, 3925 (2007); https://doi.org/10.1021/ol701563e.
18. A. Alizadeh, F. Movahedi, H. Masrouri and L.-G. Zhu, *Synthesis*, 3431 (2006); https://doi.org/10.1055/s-2006-950234.
19. A. Alizadeh, F. Movahedi and A.A. Esmaili, *Tetrahedron Lett.*, **47**, 4469 (2006); https://doi.org/10.1016/j.tetlet.2006.04.040.
20. J. Liu, Y. Zhou, Y. Wu, X. Li and A.S.C. Chan, *Tetrahedron Asymm.*, **19**, 832 (2008); https://doi.org/10.1016/j.tetasy.2008.03.015.
21. D. Kaminskyy, A. Kryshchyshyn and R. Lesyk, *Expert Opin. Drug Discov.*, **12**, 1233 (2017); https://doi.org/10.1080/17460441.2017.1388370.
22. S.S. Alneyadi, *Heterocycles*, **96**, 803 (2018); https://doi.org/10.3987/REV-17-878.
23. T. Tomasic and L.P. Masiè, *Expert Opin. Drug Discov.*, **7**, 549 (2012); https://doi.org/10.1517/17460441.2012.688743.
24. T. Tomasic and L.P. Masiè, *Curr. Med. Chem.*, **16**, 1596 (2009); https://doi.org/10.2174/092986709788186200.
25. A. Alizadeh, S. Rostamnia, N. Zohreh and R. Hosseinpour, *Tetrahedron Lett.*, **50**, 1533 (2009); https://doi.org/10.1016/j.tetlet.2008.12.107.