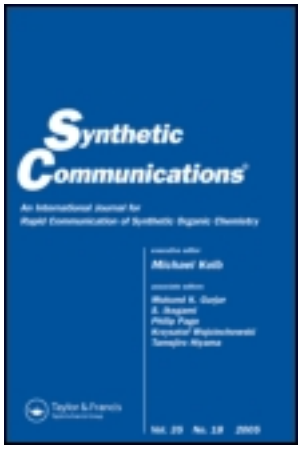


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Malonic Ester Amide Synthesis: An Efficient Methodology for Synthesis of Amides

Pankaj S. Mahajan [a] , Jyoti P. Mahajan [a] & Santosh B. Mhaske [a]

[a] National Chemical Laboratory (CSIR-NCL) , Division of Organic Chemistry , Pune , India

Accepted author version posted online: 26 Mar 2013.Published online: 03 Jun 2013.

To cite this article: Pankaj S. Mahajan , Jyoti P. Mahajan & Santosh B. Mhaske (2013): Malonic Ester Amide Synthesis: An Efficient Methodology for Synthesis of Amides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:18, 2508-2516

To link to this article: http://dx.doi.org/10.1080/00397911.2012.717671

Synthetic Communications®, 43: 2508–2516, 2013

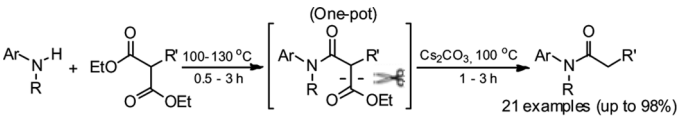
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.717671

Taylor & Francis
Taylor & Francis Group

MALONIC ESTER AMIDE SYNTHESIS: AN EFFICIENT METHODOLOGY FOR SYNTHESIS OF AMIDES

Pankaj S. Mahajan, Jyoti P. Mahajan, and Santosh B. Mhaske
National Chemical Laboratory (CSIR-NCL), Division of Organic Chemistry, Pune, India

GRAPHICAL ABSTRACT



Abstract *A general methodology "malonic ester amide synthesis" has been demonstrated, which uses α-substituted/unsubstituted diethyl malonates for the decarboxylative acylation of various aromatic/heteroaromatic primary/secondary amines to form one-carbon homologated amides, thus providing easy access to amides with odd/even chain lengths and an array of substituents on the alkyl/aryl part while avoiding use of acyl chlorides or peptide coupling reagents.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Amide synthesis; aromatic amines; condensation; decarboxylation; diethyl malonates

INTRODUCTION

Amide bond formation is one of the most important and regularly utilized reactions in organic synthesis.[1–4] It is used in the synthesis of 65% of the drug candidates surveyed[5] and 16% of industrial processes investigated.[6] Amides are present in more than 50% of reported medicinal compounds. Constable et al.[5] identified amide bond formation as one of the most utilized transformation in the pharmaceutical industry and also emphasized that it is one of 12 very high priority research areas. Diethyl malonate (DEM), found in fruits such as grapes, pineapples, and strawberries, is extensively used in the famous reaction, malonic ester synthesis (MES); however, application of α-substituted/unsubstituted DEM for the synthesis of amides never emerged as a general and efficient methodology. In this context, we

Received July 13, 2012.
Address correspondence to Santosh B. Mhaske, National Chemical Laboratory (CSIR-NCL), Division of Organic Chemistry, Pune 411 008, India. E-mail: sb.mhaske@ncl.res.in

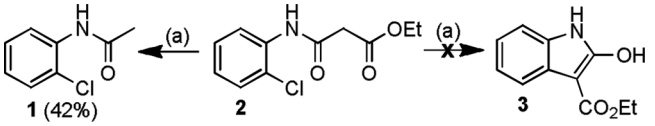
herein report a general methodology, malonic ester amide synthesis (MEAS), for the synthesis of various amides.

Acetic acid, acetic anhydride, or acetyl chlorides are commonly used in the presence of base or acid catalysts to form corresponding amides. Long-chain substituted amides are usually formed via a reaction of activated carboxylic acid with an amine. The best known method, the Schotten–Baumann reaction, involves conversion of the acid to acid chlorides. A survey reveals[5] that 44% of the amide drug candidates are prepared from acid chloride intermediates. Carboxylic acids are also activated with a variety of catalysts, which include Lewis acids or peptide coupling agents. Approximately 36% of the amide bond-forming reactions in pharmaceutical industries are carried out by means of peptide coupling reagents.[5] Several other approaches for the amide bond formation including enzymatic catalysis,[7] metal catalysis,[8] activated carboxylic esters,[9] and *S*-nitrosothioacids[10] are also known. Every methodology has its own advantages/drawbacks, and despite a number of precedents, in view of its significance,[1] new methodologies for amide bond formation are always desired [1,5,6] and it is of contemporary interest.[2–4,11–15]

RESULTS AND DISCUSSION

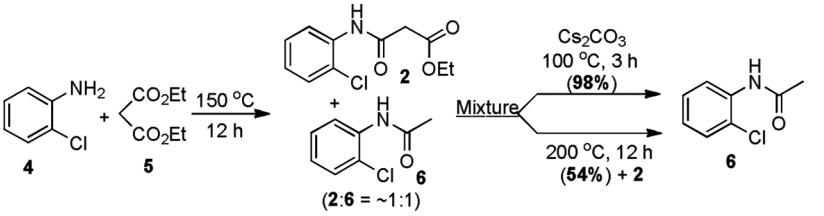
We were trying to develop a methodology for the synthesis of indole alkaloid[16] of type **3** starting from the substrate of type **2**[17] using intramolecular copper-catalyzed α-arylation of malonates.[18] We observed the formation of *N*-acetylated product **1** instead of alkaloid **3** in a reasonable yield (Scheme 1). Presented herein is the exploration of the serendipitous observation as a general methodology for amide bond formation.

The decarboxylation observed at milder conditions (Scheme 1) was well studied to identify the exact catalyst that is playing the role in this transformation. Formation of amide **1** was not observed even after heating the reaction mixture at 100 °C for several hours without the addition of any of the mentioned additives. It was found that the reaction using only CuI or 2-picolinic acid did not furnish amide **1**, but it was observed when Cs_2CO_3 was used in the reaction. Heating the reaction mixture containing 2-chloroaniline (**4**) and DEM (**5**) at 150 °C without any base for 12 h showed complete consumption of the amine (**4**), and the two new spots were isolated and characterized as intermediate **2** and the *N*-acetylated product **6** in ~1:1 ratio (Scheme 2). This experiment suggested that the decarboxylation can also be done at higher temperature without the use of Cs_2CO_3, but then it requires longer reaction time (incomplete consumption of intermediate **2**) and also gives lower yield. In one of the experiments, evaporating off DEM after consumption of amine (**4**) and neat heating of the residue containing compounds **2** and **6** shows complete disappearance



1 (42%) 2 3

Scheme 1. Indole methodology attempted and its result reactions conditions: (a) CuI (0.10 equiv.), 2-picolinic acid (0.20 equiv.), Cs_2CO_3 (3.00 equiv.), 1,4-dioxane, rt to 70 °C, 4 h.



Scheme 2. Initial optimization studies for amide formation.

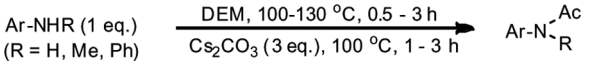
of the intermediate **2**, but the yield of the amide **6** reduces drastically with the formation of several other side products, which results in a poor-quality dark-colored product. When the mixture containing **2**, **6**, and DEM was heated (100 °C) in the presence of Cs_2CO_3 we got a quantitative yield of amide **6** (Scheme 2). Use of several other organic/inorganic bases instead of Cs_2CO_3 gave either poor conversion or a complex reaction mixture.

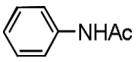
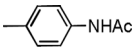
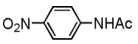
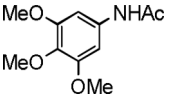
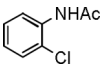
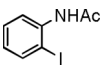
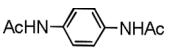
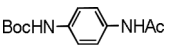
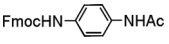
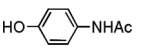
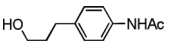
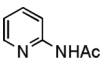
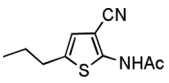
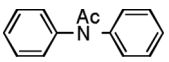
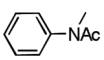
Further optimization studies using several permutations and combinations provided a better reaction condition, wherein the reaction mixture containing the amine (1.00 eq.) and DEM was heated (100–130 °C) until complete consumption (0.5–3 h) of amine followed by the addition of Cs_2CO_3 (3.00 eq.) at 100 °C and heating for another 1–3 h at the same temperature. Although the overall process has been observed occasionally[19–23] in fragmented forms previously in the literature using varying conditions and has been used in several industrial applications, generalization studies on its usefulness for amide synthesis have never been reported.

The optimized reaction condition was applied to various aromatic, hetero-aromatic, and aliphatic amines to study the reactivity pattern and generalization of the developed protocol. The methodology worked very well for aromatic/hetero-aromatic amines as seen in Table 1. Quantitative yield of corresponding amide in the case of 4-nitroaniline (Table 1, entry 3) and 70–75% yields in the case of aniline (Table 1, entry 1), *p*-toludine (Table 1, entry 2), and 3,4,5-trimethoxy aniline (Table 1, entry 4) were obtained. In the case of halogen-substituted substrates, we have observed that 2-chloroaniline (Table 1, entry 5) gave better yield than 2-iodoaniline (Table 1, entry 6), plausibly because of the steric reasons and tenacity of iodo compounds to decompose at higher temperature. *p*-Phenylenediamine (Table 1, entry 7) gave good yield as expected. Application of the protocol to an acid labile substrate (Table 1, entry 8) provided very good yield, which shows that this protocol can be used for such substrates too. However, in the case of base labile substrate (Table 1, entry 9) we have not observed any expected compound formation, but a trace amount of the same product as observed in the case of entry 7 (Table 1) was detected. Our study on amide formation of aromatic amine in the presence of competing phenolic -OH moiety (Table 1, entry 10) showed 100% selectivity and only the expected *N*-acetamide product was obtained in good yields.

The product of entry 10 (Table 1) is a widely used over-the-counter antipyretic and analgesic drug, Paracetamol, which is industrially prepared by acetylation of 4-aminophenol using acetic anhydride. In the case of amino-alcohol (Table 1, entry 11) along with the expected amide product a DEM transesterified (but not decarboxylated) product was also observed. After completion of the reaction, methanol

Table 1. Amide formation of various amines using DEM

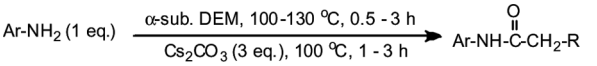


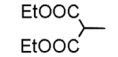
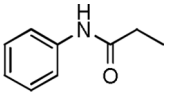
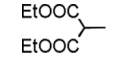
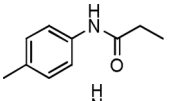
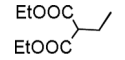
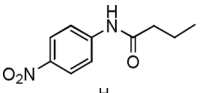
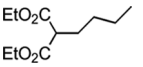
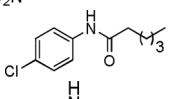
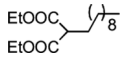
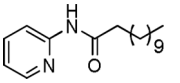
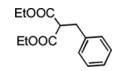
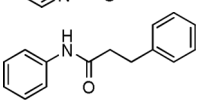
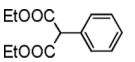
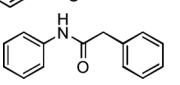
Entry	Product	Yield (%)
1		70
2		75
3		98
4		74
5		98
6		66
7		71
8		87
9		–
10		72
11		57
12[a]		87
13		65
14		92
15		90

[a]Single step, 120 °C, 1 h (Cs_2CO_3 was not necessary, self-catalyzed).

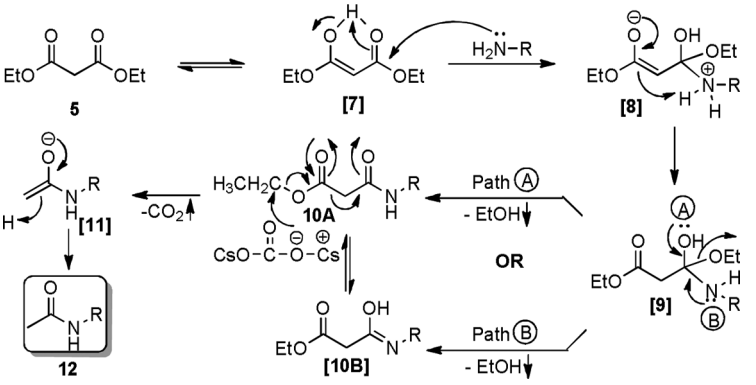
was added, and the reaction mixture was stirred at room temperature for 0.5 h to obtain exclusively the expected product in 57% yield. We also studied the acetylation reaction on hetero-aromatic amines. 2-Aminopyridine (Table 1, entry 12) gave an interesting result, wherein we could get the amide directly in a short time without the need for Cs_2CO_3. This indicates that the substrate itself catalyzed the further decarboxylation reaction. In view of this observation, attempts to optimize the protocol using pyridine or dimethylaminopyridine (DMAP) as a base did not work well. Further detailed studies on this novel organocatalytic process are warranted. Our methodology also worked well with a multisubstituted thioheterocyclic amine (Table 1, entry 13). Studies on the secondary amine also showed good results. Thus, diphenylamine (Table 1, entry 14) and *N*-methylaniline (Table 1, entry 15) provided corresponding amides in excellent yield proving the generality of the method for acetylation of variety of aromatic/heteroaromatic primary and secondary amines. However, our attempts to extend the MEAS protocol to aliphatic amines under the same conditions were not fruitful. The high reactivity of these aliphatic amines toward the ester moiety even at room temperature might be the cause, which plausibly leads to the formation of several other side products at higher temperature. Further studies in search of appropriate protocol for aliphatic amines are in progress.

Table 2. Amide formation using α-substituted DEM



Entry	α-Substituted DEM[a]	Product	Yield (%)
1			62
2			70
3			60
4[b]			68
5[c]			91
6			85
7			90

[a]α-Substituted DEM was purchased or prepared.[18,26–30]
[b]Step 1, 12 h. Step 2, 5 h.
[c]Single step, 120 °C, 1 h (Cs_2CO_3 was not required, self-catalyzed).



Scheme 3. Plausible mechanism for the MEAS methodology.

The MEAS methodology using DEM worked well with aromatic/heteroaromatic amines (Table 1); hence, we decided to broaden the scope by using α-substituted DEMs to prepare amides with a variety of one-carbon homologated acyl groups. Similar to the reaction pattern observed with DEM (Table 1, entries 1 and 2), aniline and *p*-toluidine reacted with α-methyl DEM, providing satisfactory yields (Table 2, entries 1 and 2). Contrary to the observation in Table 1 (entry 3), reaction of 4-nitro aniline with α-ethyl DEM provided lower yield. The reaction of 4-chloro aniline with α-butyl DEM (Table 2, entry 4) provided the expected amide in 68% yield. The plausible side reaction of malondiamide[24,25] formation might have contributed to the lower yield. With reasonable results in hand for α-methyl, α-ethyl, and α-butyl DEM, we decided to try our method on a longer chain α-substituted DEM.

We got very good yields (Table 1, entry 13) using 2-amino pyridine and DEM, without the need for Cs_2CO_3. Hence we used the same amine for the reaction with α -decyl DEM, and interestingly in this case also we obtained the same results and very good yield (Table 2, entry 5). The reaction of aniline with α-benzyl DEM (Table 2, entry 6) and α-phenyl DEM (Table 2, entry 7) gave excellent yields as compared to α-methyl DEM (Table 2, entry 1), probably because of the extended electron-withdrawing resonance and inductive effect of the benzene ring. A plausible mechanism for MEAS is depicted in Scheme 3.

CONCLUSION

In conclusion, MEAS, a general and efficient methodology for amide bond formation has been demonstrated. It provides easy access to amides with odd/even chain lengths. Synthesis of amides with odd chain lengths is particularly important and noteworthy because most of the naturally occurring long-chain alcohols/acids (which are commonly used as starting materials) have even chain length. We believe that the MEAS methodology might become a suitable alternative in industries that are currently using acyl chlorides / anhydrides / peptide coupling reagents for this transformation. This method may potentially be useful for the preparation of polyamides. The work to improve the MEAS methodology in terms of broader substrate

scope, lower temperature, and less reaction time by developing a suitable 2-aminopyridine-based organocatalyst is under way.

EXPERIMENTAL

General Procedure

A two-neck, round-bottom flask (equipped with a distillation condenser and a magnetic stirring bar) contained a mixture of amine (1 eq.) and DEM/α-substituted. (To avoid the use of excess α-substituted DEM from economical point of view, only 10–20 eq. can be used and in the second step a small amount of 1,4-dioxane, just sufficient to avoid thick slurry formation, can be added. The results of both ways were comparable). DEM was heated (100–130 °C) until complete consumption (0.5–3 h) of the starting amine. The reaction mixture was allowed to cool down to 100 °C, and Cs_2CO_3 (3 eq.) was added [Cs_2CO_3 was not required for entry 12 (Table 1) and entry 5 (Table 2)]. Heating at 100 °C was continued until for 1–3 h until complete disappearance of the intermediate. Reaction progress was monitored by thin-layerchromatography.

N-(3,4,5-Trimethoxyphenyl)acetamide (CAS: 4304–24–9, Table 1, Entry 4)[31]

Mp 140–142 °C; IR (Nujol) ν_{max} 1212, 1695, 1758, 3395 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz, ppm): δ 2.00 (s, 3H), 3.60 (s, 3H), 3.72 (s, 6H), 6.94 (s, 2H), 9.84 (bs, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz, ppm): δ 24.3, 55.9, 60.3, 97.0, 133.5, 135.8, 153.0, 168.5; ESIMS (m/z): 248 (M + Na).

N-(3-Cyano-5-propylthiophen-2-yl)acetamide (Table 1, Entry 13)

Mp 108–110 °C; IR (Nujol) ν_{max} 1693, 2220, 3225, 3280 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 0.96 (t, $J = 7.1$ Hz, 3H), 1.62–1.73 (m, 2H), 2.29 (s, 3H), 2.68 (t, $J = 7.5$ Hz, 2H), 6.61 (s, 1H), 9.11 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 13.5, 22.9, 24.3, 31.4, 91.2, 115.0, 119.6, 137.6, 148.1, 167.2; ESIMS (m/z): 207 (M−1). Anal. calcd. for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.95; H, 5.68, N, 13.24.

N-(4-Nitrophenyl)butyramide (CAS: 54191–12–7, Table 2, Entry 3)[32]

Mp 143–145 °C; IR (Nujol) ν_{max} 1676, 3148, 3269 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.03 (t, $J = 7.32$ Hz, 3H), 1.75–1.79 (sext., $J = 7.5$, 2H), 2.41 (t, $J = 7.33$ Hz, 2H), 7.62 (bs, 1H), 7.73 (d, $J = 9.1$ Hz, 2H), 8.21 (d, $J = 9.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 13.7, 18.8, 39.7, 119, 125.1, 143.4, 143.8, 171.6; ESIMS (m/z): 207 (M−1).

N-(4-Chlorophenyl)hexanamide (CAS: 95843–76–8, Table 2, Entry 4)[33]

Mp 101–103 °C; IR (Nujol) ν_{max} 1654, 1706, 3302, 3412 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 0.91 (t, $J = 7.0$ Hz, 3H), 1.30–1.40 (m, 4H), 1.69–1.78

(m, 2H), 2.35 (t, $J = 7.8$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.27 (s, 1H), 7.46 (d, $J = 8.86$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 13.9, 22.4, 25.2, 31.4, 37.7, 121.0, 128.9, 129.1, 136.5, 171.5.

SUPPORTING INFORMATION

Full experimental detail, copies of ^{1}H and ^{13}C, and DEPT NMR spectra and literature references for known compounds can be found via the Supplementary Content section of this article's web page.

ACKNOWLEDGMENTS

P. S. M. and J. P. M. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for the research fellowship. S. B. M. thanks the Department of Science and Technology (DST), New Delhi for the Ramanujan fellowship award and DST-Science and Engineering Research Council (SERC) Fast-Track project research grant. S. B. M. also thanks CSIR, New Delhi, and S. Pal, director, National Chemical Laboratory Pune, for providing the infrastructure, constant support, and encouragement.

REFERENCES

1. Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.
2. Soule, J.-F.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18550.
3. Yamaguchi, K.; Kobayashi, H.; Oishi, T.; Mizuno, N. *Angew. Chem. Int. Ed.* **2011**, *51*, 544.
4. Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J. *Chem. Commun.* **2012**, *48*, 666
5. Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L. Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
6. Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.
7. Wang, M.-X. *Top. Catal.* **2005**, *35*, 117.
8. Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405.
9. Kim, B. R.; Lee, H.-G.; Kang, S.-B.; Sung, G. H.; Kim, J.-J.; Park, J. K.; Lee, S.-G.; Yoon, Y.-J. *Synthesis* **2012**, *44*, 42.
10. Pan, J.; Devarie-Baez, N. O.; Xian, M. *Org. Lett.* **2011**, *13*, 1092.
11. Wu, W.; Zhang, Z.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 14256.
12. Qin, C.; Zhou, W.; Chen, F.; Ou, Y.; Jiao, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 12595.
13. Kegnæs, S.; Mielby, J.; Mentzel, U. V.; Jensen, T.; Fristrup, P.; Riisager, A. *Chem. Commun.* **2012**, *48*, 2427.
14. Xiao, F.; Liu, Y.; Tang, C.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 984.
15. Morin, M. S. T.; Lu, Y.; Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2012**, *77*, 2013.
16. Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491.
17. Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802.
18. Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469.
19. Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249.
20. Scansetti, M.; Hu, X.; McDermott, B. P.; Lam, H. W. *Org. Lett.* **2007**, *9*, 2159.
21. Fioravanti, S.; Morreale, A.; Pellacani, L.; Ramadori, F.; Tardella, P. A. *Synlett* **2007**, 2759.

22. Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775.
23. Hargreaves, M.; Khan, M. *Monatsh. Chem.* **1978**, *109*, 799.
24. Ukrainets, I. V.; Bezugly, P. A.; Treskach, V. I.; Taran, S. G.; Gorokhova, O. V. *Tetrahedron* **1994**, *50*, 10331.
25. Sechi, M.; Azzena, U.; Delussu, M. P.; Dallocchio, R.; Dessì, A.; Cosseddu, A.; Pala, N.; Neamati, N. *Molecules* **2008**, *13*, 2442.
26. Wang, Y.; Deng, R.; Mi, A.; Jiang, Y. *Synth. Commun.* **1995**, *25*, 1761.
27. Yoon, J. H.; Park, Y. J.; Lee, J. H.; Yoo, J.; Jun, C.-H. *Org. Lett.* **2005**, *7*, 2889.
28. Keglevich, G.; Novák, T.; Vida, L.; Greiner, I. *Green Chem.* **2006**, *8*, 1073.
29. Poldy, J.; Peakall, R.; Barrow, R. A. *Tetrahedron Lett.* **2008**, *49*, 2446.
30. Peng, B.; Zhang, S.; Yu, X.; Feng, X.; Bao, M. *Org. Lett.* **2011**, *13*, 5402.
31. Sharma, P. K.; Dandiya, P. C.; Bose, B. C.; Vijayvargiya, R. *Ind. J. Med. Res.* **1965**, *53*, 1191.
32. Correa, A.; Elmore, S.; Bolm, C. *Chem. Eur. J.* **2008**, *14*, 3527.
33. Zhang, Y.; Zhang, Y. *J. Chem. Res.* **2004**, 596.