

A facile stereoselective synthesis of (Z)-1,3-diaryl-2-(N-methylanilino)-2-propen-1-ones

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Abstract

The Claisen-Schmidt condensation of 1-aryl-2-(N-methylanilino)-1-ethanones with aromatic aldehydes in the presence of sodium hydroxide in aqueous alcohol led to the formation of hitherto unknown (Z)-1,3-diaryl-2-(N-methylanilino)-2-propen-1-ones. The structure and stereochemistry of the products were elucidated from ^1H , ^{13}C and 2D NMR spectroscopic data and nuclear Overhauser effect.

Keywords: 1-Ethanones, 2-propen-1-ones, configuration, NMR spectroscopic data, NOE, stereoselective synthesis

Introduction

1,3-Diaryl-2-propen-1-ones display many biological activities *viz.*, antiviral,¹ antipicornavirus,² anti-inflammatory,² antimicrobial,³ antimitotic,⁴ antitumor⁴ and antifungal,⁵ besides being synthons for the construction of diverse heterocycles like isoxazolines,⁶ isoxazoles,⁷ quinolinones,⁸ thienoquinolinones,⁹ thiadiazines,¹⁰ benzofuranones,¹¹ and flavones.¹²⁻¹⁴

It is pertinent to note that 1,3-diaryl-2-propen-1-ones with a variety of substituents in the (i) two aromatic rings and (ii) 2- and 3-positions are known. Surprisingly, there are only a very few reports on the synthesis of 2-amino-1,3-diaryl-2-propen-1-ones in the literature.¹⁵⁻¹⁸ Previously, 2-amino-1,3-diarylpropen-1-ones were obtained by: (i) the photooxidation of 2-morpholinocyclopropanols which provided a mixture of 2- and 3-aminoenones,¹⁵ (ii) the reaction of α,β -diaminoprop-3-en-1-one with Grignard reagent,¹⁶ (iii) the cathodic reduction of azidochalcones,¹⁷ and (iv) the reaction of 3-(methoxyamino)-1,3-diphenylpropan-1-one with sodium methoxide or potassium *t*-butoxide.¹⁸

As the electronic effects of the amino and carbonyl groups in 2-amino-3-diaryl-2-propen-1-ones could act in opposing directions, the reactivity of the α,β -unsaturated carbonyl system in chemical reactions could be fine-tuned by judicious selection of groups linked to nitrogen and the aryl rings. This prompted us to synthesise several new 1,3-diaryl-2-propen-1-ones with *N*-

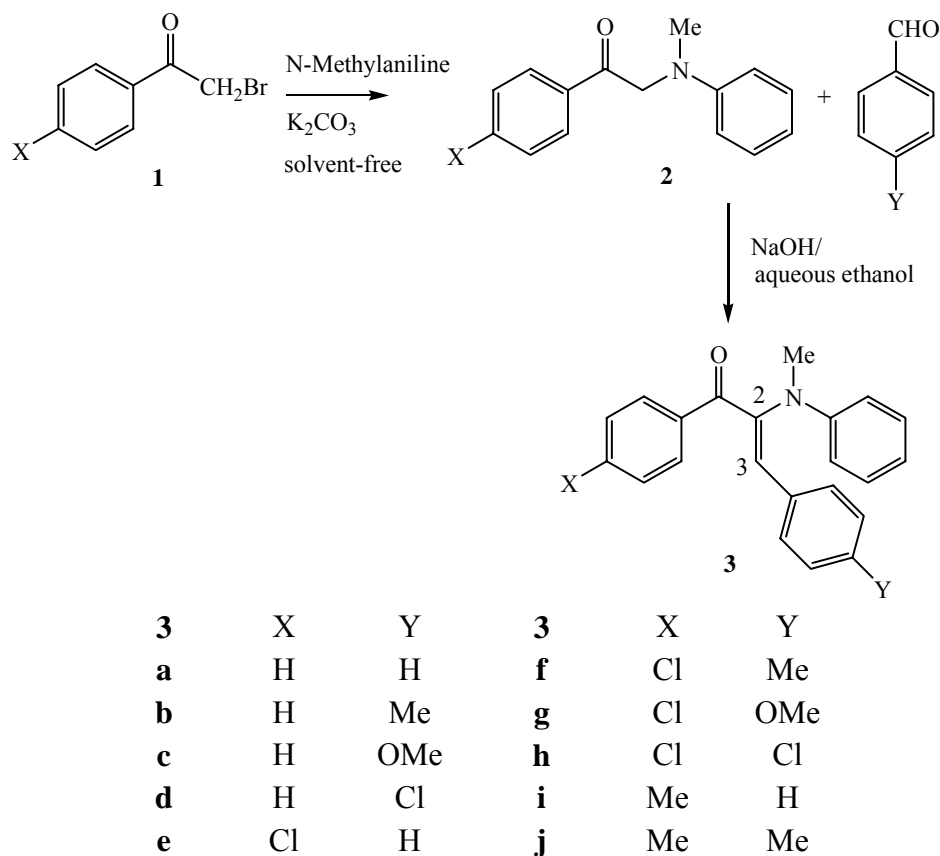
methylanilino group (-NMePh) at the 2-position (**3**) by the condensation of 1-aryl-2-(*N*-methylanilino)-1-ethanones with various aromatic aldehydes in the presence of sodium hydroxide in aqueous alcohol under mild conditions and report the results in this paper. These 2-amino-1,3-diarylpropen-1-ones, **3** can also be useful synthons in the construction of novel heterocycles.

Results and Discussion

In the present work, the condensation of 1-aryl-2-(*N*-methylanilino)-1-ethanones (**2**) with aromatic aldehydes in presence of sodium hydroxide in aqueous alcohol afforded (*Z*)-1,3-diaryl-2-(*N*-methylanilino)-2-propen-1-ones (**3a-3j**) (Scheme 1) in 54-78 % yields.

In general, the interaction of the lone pair of electrons on nitrogen with the double bond in enamines confers electrophilicity over the carbon attached to the nitrogen rendering the enamines prone to hydrolysis. Hence it was reasoned that if the amino group carries an aromatic ring, the availability of the lone pair of electrons on nitrogen for conjugation with the C=C bond would be diminished, as the lone pair could also interact mesomerically with the aryl ring attached to the nitrogen. Further, the steric interactions between the Me/aryl ring attached to nitrogen with the oxygen/3-aryl ring of the enone system of **3** could orient the nitrogen in such a way that the nitrogen lone pair is turned away from being parallel with the p-orbitals of the C=C bond, reducing the conjugation between the nitrogen and the C=C bond. The aforementioned nitrogen conjugation with the aromatic ring and the steric interactions diminishing the nitrogen conjugation with the C=C bond could, in turn, diminish the tendency of **3** to hydrolysis under the present reaction conditions involving aqueous alcoholic sodium hydroxide.

The 1-aryl-2-(*N*-methylanilino)-1-ethanones, **2** required for the synthesis of **3** were, in turn, obtained in excellent yields by the reaction of the appropriate phenacyl bromides, **1** with *N*-methylaniline (**Scheme 1**) in the presence of potassium carbonate under solvent-free conditions. The present methodology is simple, eco-friendly, rapid and efficient compared to literature methods.^{19,20} In earlier works, 1-aryl-2-(*N*-methylanilino)-1-ethanones **2** were synthesized from the reaction of phenacyl bromides with *N*-methylaniline under reflux in ethanol. The physical constants of these compounds are comparable with those reported in the literature. 2-(*N*-Methylanilino)-1-phenyl-1-ethanone (**2**, X = H), 1-(4-chlorophenyl)-2-(*N*-methylanilino)-1-ethanone (**2**, X = Cl) and 1-(4-methylphenyl)-2-(*N*-methylanilino)-1-ethanone (**2**, X = CH₃) were obtained in 88%, 91% and 90% yields respectively in the present work. It is pertinent to note that in our recent work²¹ on the synthesis of 2-arylindoles, we have obtained **2** as an intermediate under solvent-free conditions in presence of sodium bicarbonate and used it without purification in the next step and hence the yield of **2** could not be reported.



Scheme 1. Synthesis of (Z)-1,3-diaryl-2-(N-methylanilino)-2-propen-1-ones.

All the 1,3-diaryl-2-(N-methylanilino)-2-propen-1-ones **3** have been characterized using elemental analysis, IR, ^1H , ^{13}C and 2D NMR spectroscopic data. The IR spectrum (a KBr pellet) of **3a** showed a strong absorption at 1630 cm^{-1} due to the carbonyl group.

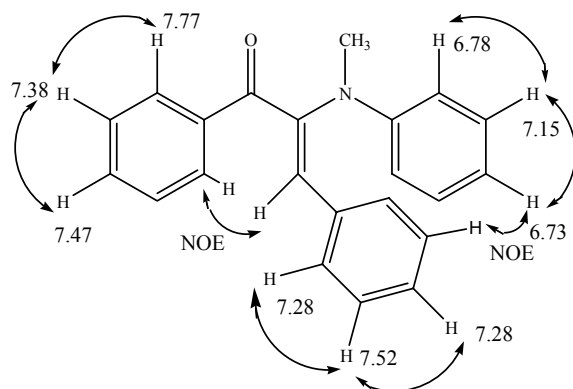


Figure 1. H,H-COSY and NOESY correlations of **3a**.

The structure of the enones is also consistent with the ^1H and ^{13}C NMR spectroscopic data as illustrated for 2-(*N*-methylanilino)-1,3-diphenyl-2-propen-1-one (**3a**). The three-protons singlet at 3.12 ppm and one-proton singlet at 6.97 ppm are assigned to *N*-methyl and benzylidene protons respectively. The distinct assignment of the signals of the benzene rings of **3** was made from the chemical shift of signals, multiplicity and H,H-COSY spectrum of **3** (Fig. 1). For instance, the doublet occurring far downfield at 7.77 ppm integrating for two protons with a *J* value of 8 Hz is assigned to the *ortho* hydrogens of the benzoyl ring. This signal correlates with a triplet at 7.38 ppm (*J* = 8 Hz) in the H,H-COSY spectrum which enables its assignment to the *meta* hydrogens of the benzoyl ring. Similarly, the signal of the *meta* hydrogens at 7.38 ppm correlates with the triplet at 7.47 ppm with a *J* value of 8 Hz. By similar considerations, the protons of remaining two phenyl rings have also been assigned. Other enones also showed similar features in their ^1H NMR spectra. The configuration of the double bond of **3** was found to be (*Z*) by nuclear Overhauser effect (NOE) experiment, wherein (i) the benzylidene proton at 6.97 ppm has a NOE correlation with the *ortho* hydrogens of the benzoyl ring and (ii) the *para* proton of the *N*-aryl ring appearing at 6.73 ppm also shows a NOE correlation with the *meta* protons of the 3-aryl ring that appears at 7.52 ppm.

The ^{13}C NMR spectrum of **3** show that the carbonyl carbons, C-1, give signals in the range of 196.1-197.2 ppm, while the aromatic carbons give signals in the range of 113.1-147.9 ppm. Among the aromatic signals, the *ipso* carbons give less intense signals in the region of 136.5-147.9 ppm. The signals in the region of 38.2-39.5 ppm are assigned to the methyl carbon attached to the nitrogen.

Conclusions

In conclusion, the present work describes a simple, rapid and efficient method for the stereoselective synthesis of novel 1,3-diaryl-2-(*N*-methylanilino)-2-propen-1-ones (**3**) under mild reaction conditions.

Experimental Section

General Procedures. The melting points reported in this work are uncorrected. The ^1H and ^{13}C NMR spectra of the (*Z*)-1,3-diaryl-2-(*N*-methylanilino)-2-propen-1-ones (**3a-3j**) were measured at 300 and 75 MHz respectively using Bruker (Avance) NMR instrument in CDCl_3 and the chemical shifts referenced to tetramethylsilane. Standard Bruker software was employed to obtain both the one- and two-dimensional NMR spectra. The various phenacyl bromides were synthesized using literature procedures.^{22,23} Elemental analyses of **3** were performed on a Perkin Elmer 2400 Series II Elemental CHNS Analyser available in our institution.

Preparation of 1-aryl-2-(*N*-methylanilino)-1-ethanones (2). Phenacyl bromide (0.25 g, 1.25 mmol) was taken in a clean, dry test tube and a pinch of anhydrous potassium carbonate was added. To this, distilled *N*-methylaniline (0.17 g, 1.57 mmol) was added and the reaction mixture mixed vigorously using a clean, dry glass rod. The reaction mixture got solidified immediately. Stirring was continued for a few more minutes. To the reaction mixture, ice-cold water was added and stirred well to remove the potassium carbonate present in the reaction mixture. The greenish yellow 2-(*N*-methylanilino)-1-phenyl-1-ethanone was filtered at the pump, washed several times with ice-cold water, dried and crystallised from ethanol.

Synthesis of (*Z*)-1,3-diaryl-2-(*N*-methylanilino)-2-propen-1-ones (3). To a mixture of sodium hydroxide (0.3 g) in water (3 ml), ethanol (2 ml) and 1-aryl-2-(*N*-methylanilino)-1-ethanone (5 mmol) kept at 0° C, pure aldehyde (5 mmol) was added. After the addition of alcohol was over, the temperature of the reaction mixture was raised to about 25°C and stirred vigorously until the mixture became a thick mass. Then the flask was placed in a refrigerator overnight, the solid separated was filtered, washed with cold water and cold ethanol (3 ml), dried and crystallized from ethanol.

(*Z*)-2-(*N*-Methylanilino)-1,3-diphenyl-2-propen-1-one (3a). This compound was obtained as a pale yellow crystals, yield 1.09 g (70 %) m.p. 109-10° C; IR (KBr): 1630 cm⁻¹; ¹H NMR: 7.77 (d, *J* = 8 Hz, 2H), 7.52 (m, 2H), 7.47 (t, *J* = 8 Hz, 1H), 7.38 (t, *J* = 8 Hz, 2H), 7.28 (m, 3H), 7.15 (t, *J* = 8 Hz, 2H), 6.97 (s, 1H), 6.78 (d, *J* = 8 Hz, 2H), 6.73 (t, *J* = 8 Hz, 1H), 3.12 (s, 3H). ¹³C NMR: 38.8, 113.8, 118.8, 128.2, 128.6, 128.9, 129.1, 129.4, 132.1, 134.0, 135.0, 138.1, 142.6, 147.0, 196.4. Anal. Calcd. for C₂₂H₁₉NO: C, 84.31; H, 6.11; N, 4.47, Found: C, 84.26; H, 6.09; N, 4.51.

(*Z*)-2-(*N*-Methylanilino)-3-(4-methylphenyl)-1-phenyl-2-propen-1-one (3b). This compound was obtained as a pale yellow oil, yield 0.96 g (59%), IR (KBr): 1635 cm⁻¹; ¹H NMR: 7.73 (d, *J* = 8 Hz, 2H), 7.45 (m, 5H), 7.17 (m, 4H), 6.99 (s, 1H), 6.79 (d, *J* = 8 Hz, 2H), 6.75 (t, *J* = 8 Hz, 1H), 3.14 (s, 3H), 2.35 (s, 3H). ¹³C NMR: 21.9, 39.2, 114.1, 119.1, 128.6, 129.5, 129.6, 129.9, 130.1, 131.6, 132.4, 136.5, 138.9, 140.4, 142.3, 147.6, 196.9. Anal. Calcd. for C₂₃H₂₁NO: C, 84.37; H, 6.46; N, 4.28, Found: C, 84.39; H, 6.49; N, 4.30.

(*Z*)-3-(4-Methoxyphenyl)-2-(*N*-methylanilino)-1-phenyl-2-propen-1-one (3c). This compound was obtained as a pale yellow oil, yield 0.97 g (57%). IR (KBr): 1638 cm⁻¹; ¹H NMR: 7.78 (d, *J* = 8 Hz, 2H), 7.46 (t, *J* = 8 Hz, 1H), 7.37 (t, *J* = 8 Hz, 2H), 7.26 (m, 2H), 7.18 (t, *J* = 8 Hz, 2H), 6.95 (s, 1H), 6.88 (m, 5H), 3.71 (s, 3H), 3.12 (s, 3H). ¹³C NMR: 39.2, 55.1, 113.1, 113.8, 114.4, 119.8, 128.4, 129.5, 129.7, 129.9, 131.8, 132.6, 136.7, 139.4, 142.6, 147.9, 196.4. Anal. Calcd. for C₂₃H₂₁NO₂: C, 80.44; H, 6.16; N, 4.08, Found: C, 80.48; H, 6.18; N, 4.07.

(*Z*)-3-(4-Chlorophenyl)-2-(*N*-methylanilino)-1-phenyl-2-propen-1-one (3d). This compound was obtained as a pale yellow oil, yield 0.93 g (53 %); IR (KBr): 1630 cm⁻¹; ¹H NMR: 7.71 (d, *J* = 8 Hz, 2H), 7.52 (m, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.32 (t, *J* = 8 Hz, 3H), 7.17 (t, *J* = 8 Hz, 2H), 6.77 (s, 1H), 6.75 (m, 3H), 3.12 (s, 3H). ¹³C NMR: 38.9, 114.0, 119.2, 128.3, 128.9, 129.0, 129.2, 130.6, 132.2, 132.6, 133.1, 135.1, 138.0, 143.0, 146.8, 196.3. Anal. Calcd. for C₂₂H₁₈ClNO: C, 75.97; H, 5.22; N, 4.03, Found: C, 75.99; H, 5.18; N, 4.02.

(Z)-1-(4-Chlorophenyl)-2-(N-methylanilino)-3-phenyl-2-propen-1-one (3e)

This compound was obtained as pale yellow crystals, yield 1.35 g (78%) m.p. 108-09° C; IR (KBr): 1630 cm⁻¹; ¹H NMR: 7.70 (d, *J* = 8 Hz, 2H), 7.54 (m, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.33 (m, 3H), 7.12 (t, *J* = 8 Hz, 2H), 6.91 (s, 1H), 6.78 (d, *J* = 8 Hz, 2H), 6.73 (t, *J* = 8 Hz, 1H), 3.12 (s, 3H). ¹³C NMR: 38.5, 113.6, 118.7, 128.3, 128.8, 129.1, 129.3, 129.6, 132.5, 134.3, 135.2, 138.5, 142.5, 147.2, 196.8. Anal. Calcd. for C₂₂H₁₈ClNO: C, 75.97; H, 5.22; N, 4.03, Found: C, 75.94; H, 5.24; N, 4.01.

(Z)-1-(4-Chlorophenyl)-2-(N-methylanilino)-3-(4-methylphenyl)-2-propen-1-one (3f). This compound was obtained as pale yellow crystals, yield 1.34 g (74%) m.p. = 90-91° C.; IR (KBr): 1638 cm⁻¹; ¹H NMR: 7.75 (d, *J* = 8 Hz, 2H), 7.52 (m, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.32 (m, 3H), 7.17 (t, *J* = 8 Hz, 2H), 6.95 (s, 1H), 6.78 (d, *J* = 8 Hz, 2H), 3.14 (s, 3H), 2.21 (s, 3H). ¹³C NMR: 21.1, 38.5, 114.5, 119.2, 128.1, 128.7, 129.1, 129.4, 129.8, 132.9, 134.7, 135.8, 138.8, 142.7, 147.1, 196.4. Anal. Calcd. for C₂₃H₂₀ClNO: C, 76.34; H, 5.57; N, 3.87, Found: C, 76.30; H, 5.60; N, 3.84.

(Z)-1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-2-(N-methylanilino)-2-propen-1-one (3g).

This compound was obtained as pale yellow crystals, yield 1.34 g (71%). m.p. = 84-85° C, IR (KBr): 1634 cm⁻¹; ¹H NMR: 7.79 (d, *J* = 8 Hz, 2H), 7.38 (t, *J* = 8 Hz, 2H), 7.29 (m, 2H), 7.14 (t, *J* = 8 Hz, 2H), 6.91 (s, 1H), 6.84 (m, 5H), 3.76 (s, 3H), 3.11 (s, 3H). ¹³C NMR: 39.2, 55.1, 113.1, 113.8, 119.8, 128.4, 129.5, 129.7, 129.9, 130.5, 131.8, 132.6, 136.7, 139.4, 142.6, 147.9, 196.4. Anal. Calcd. for C₂₃H₂₀ClNO₂: C, 73.11; H, 5.33; N, 3.71, Found: C, 73.13; H, 5.36; N, 3.75.

(Z)-1,3-Bis(4-chlorophenyl)-2-(N-methylanilino)-2-propen-1-one (3h). This compound was obtained as pale yellow oil, yield 1.15 g (60%). IR (KBr): 1628 cm⁻¹; ¹H NMR: 7.72 (d, *J* = 8 Hz, 2H), 7.42 (m, 2H), 7.38 (t, *J* = 8 Hz, 2H), 7.29 (m, 2H), 7.18 (t, *J* = 8 Hz, 2H), 6.83 (s, 1H), 6.75 (m, 3H), 3.12 (s, 3H). ¹³C NMR: 39.1, 114.4, 119.8, 128.4, 128.7, 129.3, 129.5, 129.7, 130.5, 131.8, 132.6, 136.7, 139.4, 142.6, 147.9, 196.4. Anal. Calcd. for C₂₂H₁₇Cl₂NO: C, 69.12; H, 4.48; N, 3.66, Found: C, 69.09; H, 4.45; N, 3.69.

(Z)-1-(4-Methylphenyl)-2-(N-methylanilino)-3-phenyl-2-propen-1-one (3i). This compound was obtained as pale yellow crystals, yield 1.11 g (68%). m.p. = 95-96° C, IR (KBr): 1631 cm⁻¹; ¹H NMR: 7.79 (d, *J* = 8 Hz, 2H), 7.48 (m, 6H), 7.14 (m, 3H), 6.97 (s, 1H), 6.79 (d, *J* = 8 Hz, 2H), 6.69 (t, *J* = 8 Hz, 1H), 3.11 (s, 3H), 2.26 (s, 3H). ¹³C NMR: 21.3, 39.5, 114.5, 119.4, 128.7, 129.8, 129.9, 130.1, 130.4, 131.6, 132.4, 136.7, 138.6, 140.7, 142.8, 147.3, 196.1. Anal. Calcd. for C₂₃H₂₁NO: C, 84.37; H, 6.46; N, 4.28, Found: C, 84.41; H, 6.50; N, 4.24.

(Z)-1,3-Bis(4-methylphenyl)-2-(N-methylanilino)-2-propen-1-one (3j). This compound was obtained as pale yellow crystals, yield 1.09 g (64%). m.p. = 77-78° C, IR (KBr): 1634 cm⁻¹; ¹H NMR: 7.78 (d, *J* = 8 Hz, 2H), 7.46 (m, 5H), 7.18 (m, 3H), 6.94 (s, 1H), 6.78 (m, 2H), 6.70 (t, *J* = 8 Hz, 1H), 3.17 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H). ¹³C NMR: 21.1, 21.2, 39.2, 114.4, 119.8, 128.4, 129.6, 129.9, 130.1, 130.5, 131.7, 132.8, 136.8, 139.6, 140.9, 142.6, 147.8, 197.2. Anal. Calcd. for C₂₄H₂₃NO: C, 84.42; H, 6.79; N, 4.10, Found: C, 84.45; H, 6.83; N, 4.07.

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References and Notes

1. Bauer, D. J.; Selway, J. W. T.; Batchelor, J. F.; Tisdale, M.; Caldwell, I. C.; Young, D. A. B. *Nature* **1981**, *292*, 369.
2. Cody, V.; Middleton, E.; Harborne, J. B. *Plant Flavonoids in Biology and Medicine*, A. R. Liss, Inc.: New York, 1985; p 472.
3. Krishna, S. V.; Rajasekhar, A.; Reddy, T. K. K.; Naidu, M. S. R. *Curr. Sci.* **1988**, *57*, 1291.
4. Edwards, M. L.; Stemerick, D. M.; Sunkara, P. S. *J. Med. Chem.* **1990**, *33*, 1948.
5. Bilgin, A. A.; Palaska, E.; Abbabbasoglu, U. *FABAD Farm. Bilimler Derg.* **1991**, *16*, 81.
6. Katritzky, A.R.; Lagowski, J.H. *The Principles of Heterocyclic Chemistry*, Chapman and Hall Ltd: London, 1971; p 140.
7. Ciller, J. A.; Seoane, C.; Soto, J. L. *J. Heterocyclic Chem.* **1985**, *22*, 1663.
8. Donnelly, J. A.; Farrell, D. F. *J. Org. Chem.* **1990**, *55*, 1757.
9. Ombetta, J. E.; Lyet, S.; Xicluna, A.; Robert, J. F.; Panouse, J. J. *Ann. Pharm. Fr.* **1989**, *46*, 377.
10. Alberola, A.; Andres, J. M.; Gonzalez, A.; Pedrosa, R.; Vicente, M. *Synthesis* **1991**, 355.
11. Narasimhachari, N.; Narayanaswami, S.; Seshadri, T.R. *Proc. Indian Acad. Sci.* **1953**, *37A*, 104.
12. Algar, J.; Flynn, J.P. *Proc. Roy. Irish Acad.* **1934**, *42B*, I.
13. Oyamada, B. *J. Chem. Soc. Japan* **1934**, *55*, 1256.
14. Oyamada, T. *Bull. Chem. Soc. Japan* **1935**, *10*, 182.
15. Wiegel, W.; Henning, H.-G. *Chem. Commun.* **1997**, 1893.
16. Duhamel, P.; Duhamel, L.; Truxillo, V. *Tetrahedron Lett.* **1974**, 51.
17. Knittel, D.; Suryanarayana Rao, V. *Monatshefte fur Chemie* **1986**, *117*, 1185.
18. Reichel, L.; Pritze, P. *Justus Liebigs Ann. Chem.* **1974**, 120.
19. Allworth, K. L.; El-Hamamy, A. A.; Hesabi, M. M.; Hill, J. J. *Chem. Soc., Perkin Trans. 1* **1980**, 1671.
20. Crowther, A. F.; Mann, F. G.; Purdie, D. *J. Chem. Soc.* **1943**, *1*, 58.
21. Sridharan, V.; Perumal, S.; Avendano, C.; Menendez, J. C. *Synlett* **2006**, 91.
22. Cowper, R. M.; Davidson, L. H. *Organic Synthesis*, John Wiley: New York, 1943; *Coll. Vol. II*, 480.
23. Judefind, W. L.; Reid, E. E. *J. Am. Chem. Soc.* **1920**, *42*, 1043.