Chemistry of Heterocyclic Compounds, Vol. 43, No. 3, 2007

CONDENSATION OF 4-ARYL-4-OXOBUTANOIC ACIDS WITH BENZYLAMINES: SYNTHETIC AND STRUCTURAL STUDIES ON 1-ARYLMETHYL-3-[(*E*)-1-ARYLMETHYLIDENE]-5-PHENYL-2,3-DIHYDRO-1H-2-PYRROLONES

H. Surya Prakash Rao, S. Senthilkumar, K. Gopu, and Shaik Rafi

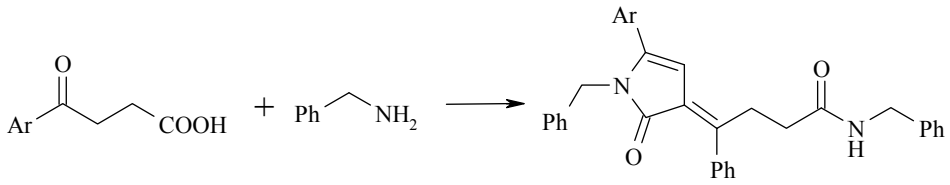
The microwave-mediated reaction of 4-aryl-4-oxobutanoic acids with benzylamines furnished 1-arylmethyl-3-[(E)-1-arylmethylidene]-5-phenyl-2,3-dihydro-1H-pyrrolones. This result is in contract to the earlier report on this reaction conducted under neat conditions. Structures for the products were assigned on the basis of spectral data and confirmed by independent synthesis.

Keywords: pyrrolones, domino reactions, microwave.

Multicomponent condensation reactions taking place either by design or by serendipity are attractive routes for the preparation of complex products from simple starting materials [1, 2]. In this context, the reaction of 4-oxo-4-phenyl-butanoic acid (**1a**) with amines has attracted the attention of organic chemists from the beginning of the 20th century because of the formation of orange-colored pyrrolone derivatives through multicomponent condensations following domino pathways [3-8]. In addition, pyrrolones with structural diversity are attractive targets for synthesis as they are expected to show impressive biological properties [9].

We have been interested in the synthesis of different nitrogen heterocycles *via* microwave-mediated multicomponent condensation reactions [10-13]. Recently we reported a facile multicomponent condensation involving 4-oxo-4-phenylbutanoic acid esters with ammonium formate [14]. In continuation of this study, we conducted the microwave-mediated solution-phase condensation of 4-oxo-4-phenylbutanoic acid (**1a**) with benzylamine **2a** with an intention to generate pyrrolidones of diverse structures. We anticipated that the reaction would furnish pyrrolidones of the type **3** as reported by Saeed [15] (Scheme 1).

Scheme 1



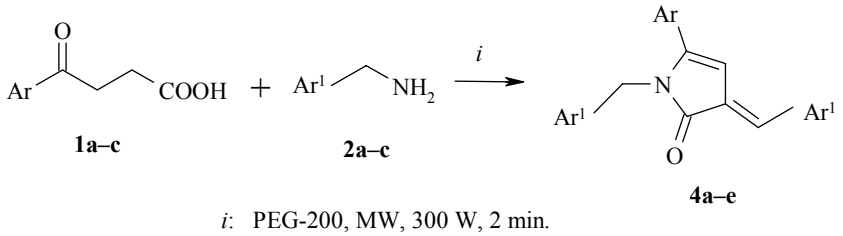
1a,b **2a** **3a,b**

1, 3 a Ar = Ph, **b** Ar = 4-ClC_6H_4

Department of Chemistry, Pondicherry University, Pondicherry 605 014, India; e-mail: hspr@yahoo.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 368-373, March, 2007. Original article submitted November 24, 2006.

However, to our surprise, in contrast to the findings of Saeed, the reaction furnished pyrrolone **4a** instead of **3a** (Scheme 2). Similarly, unlike the findings of Saeed, the reaction of the acid **1c** with benzylamine **2a** furnished pyrrolone **4c** rather than anticipated pyrrolone **3b**. We have now re-investigated this interesting reaction in detail and report the results of this study.

Scheme 2



1a–c **2a–c** **4a–e**

i: PEG-200, MW, 300 W, 2 min.

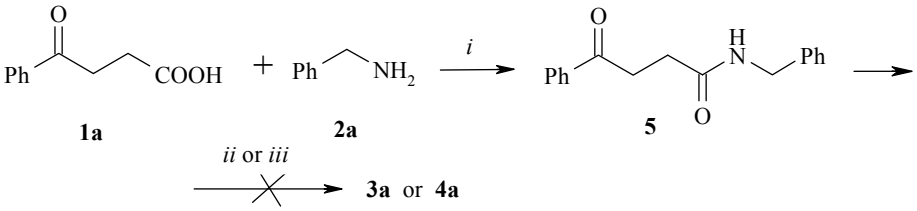
1,2 a Ar = Ar^1 = Ph; **b** Ar = Ar^1 = 4-Me-C_6H_4, **c** Ar = Ar^1 = 4-ClC_6H_4;
4 a Ar = Ar^1 = Ph, **b** Ar = 4-MeC_6H_4, Ar^1 = Ph; **c** Ar = 4-ClC_6H_4, Ar^1 = Ph, **d** Ar = Ph, Ar^1 = 4-MeC_6H_4, **e** Ar = Ph, Ar^1 = 4-ClC_6H_4

The microwave-mediated reaction of keto acid **1a** with benzylamine **2a** leads to the formation of 1-benzyl-5-phenyl-3-[(*E*)-1-phenylmethylidene]-2,3-di- hydro-1H-2-pyrrolone (**4a**) exclusively in 78% yield. The structure of pyrrolone **4a** was confirmed on the basis of spectral and analytical data. The UV spectrum of **4a** showed two λ_{max} at 310 (logε4.24) and 410 nm (logε2.11) due to cinnamoyl-type and diphenylbutadiene moieties present in the molecule. The IR spectrum of **4a** showed a band at ν 1701 cm^{-1} due to the presence of five-membered amide carbonyl. As anticipated from its structure, **4a** displayed three singlets in the ^{1}H NMR spectrum at δ 4.79, 6.20, and 7.46 ppm assignable to N–CH_2Ph, alkenic hydrogen on C(4), and methylidene hydrogen, respectively. The ^{13}C NMR spectrum of **4a** showed eighteen signals, which included one aliphatic, sixteen aromatic/olefinic, and one carbonyl carbons. The mass spectrum of **4a** displayed *m/z* peak at 337 in support of molecular formula $C_{24}H_{19}NO$. It is clear from spectral studies that the product **4a** was formed by the condensation of the two units of benzylamine **2a** and one unit of 4-oxo-4-phenylbutanoic acid (**1a**) [16]. The stereochemistry at the methylidene group was assigned on the basis of comparison of spectral data with compounds of similar structure [17].

Transformation of keto acid **1a** and benzylamine to **4a** also took place under normal thermal conditions at 140°C in 2 h. However, the rate of transformation was faster under microwave irradiation. Thus, as anticipated, there was an about 100-fold increase in the rate of pyrrolidone **4a** generation under the influence of microwaves. In this context, we repeated the reaction of keto acid **1a** with benzylamine **2a** under the conditions reported by Saeed by heating them together without solvent in a preheated oil bath. The reaction furnished two products, **3a** and **4a,** in the ratio of 1:4, *i.e*., even under direct heating without any solvent, pyrrolone **3a** was the minor product. The structure for **3a** was assigned on the basis of spectral data. Even though most of the signals in ^{1}H NMR spectrum of **3a** prepared by us match the reported values, there were some differences (see Experimental).

To test the generality of the three-component condensation involving one molecule of oxo acid **1** and two molecules of benzylamine **2**, the reaction was carried out with keto acids having electron-releasing (CH_3, **1b**) and electron- withdrawing (Cl, **1c**) groups located on the C(4) position of the aryl ring. Thus, on reaction with benzylamine **2a** two butanoic acids **1b** and **1c** were smoothly transformed into corresponding pyrrolone derivatives **4b** and **4c** in 67 and 83% yield, respectively (Scheme 2). Similarly, benzylamines **2b** and **2c** having electron-releasing (CH_3, **2b**) and electron-withdrawing (Cl, **2c**) groups reacted with keto acid **1a** smoothly to furnish pyrrolones **4d** and **4e** in 74 and 79% yield, respectively. Structures for pyrrolones **4b-e** were assigned on the basis of spectral and analytical data, which are well comparable with the parent compound **4a**.

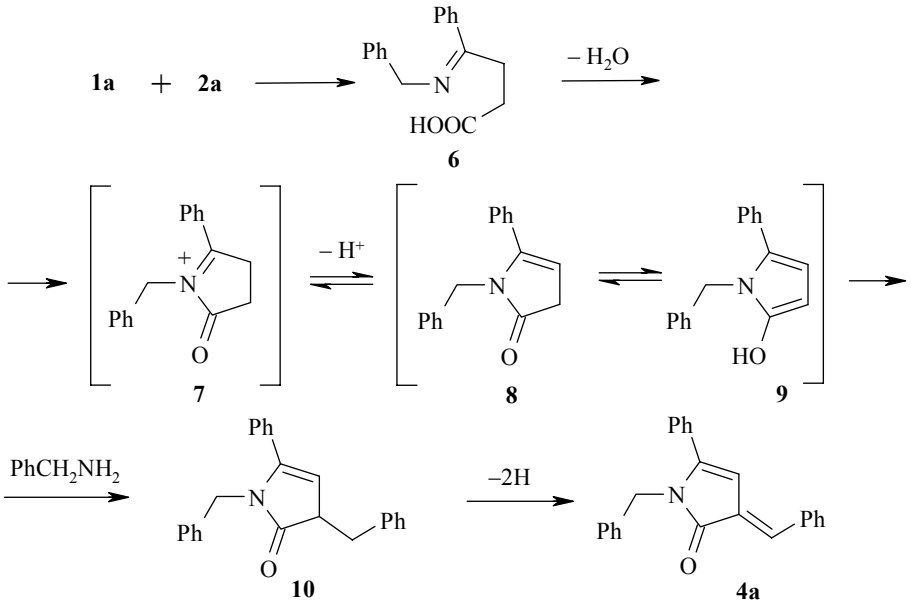
Scheme 3



i: DCC, DCM, rt, 95%, *ii:* P_2O_5, benzene or toluene, reflux, or *iii:* conc. H_2SO_4, DCM, rt.

Saeed reported isolation of the amide **5** as a by-product in the reaction of **1a** and **2a** and its isolation was taken as a mechanistic evidence for the formation of pyrrolone **3a**. We have now prepared the amide **5** by an independent route by dehydrocondensation of keto acid **1a** and benzylamine **2a** using DCC (Scheme 3). The amide **5** failed to undergo cyclization to pyrrolone **3** or **4** under a variety of microwave/thermal conditions.

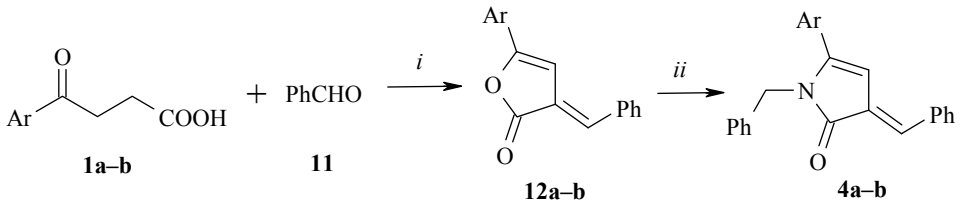
Scheme 4



Based on the accumulated results, a possible mechanism for the formation of pyrrolones **4** from 4-keto acids **1** and benzylamines **2** is given in Scheme 4. Initial dehydrocondesation of **1a** with benzylamine **2a** furnished imine **6**, which on cyclization led to formation of pyrrolone **8** *via* **7**. 2-Pyrrolones of the type **8** are highly reactive intermediates and they could exist in equilibrium between structures **8** and **9**. Further reaction of **9** with benzylamine led to the formation of **10**, which on oxidative dehydrogenation furnished highly conjugated pyrrole **4a**.

To further ascertain the structure and to support the mechanism for the formation of **4a** the pyrrolones **4a,b** were synthesized independently by a two-step sequence as shown in Scheme 5. The keto acids **1a,b** were condensed with benzaldehyde **11** under dehydrating conditions to yield lactones **12a,b** [18], which on treatment with benzylamine **2a** furnished pyrrolones **4a,b** in quantitative yield.

Scheme 5



i: Ac_2O/Et_3N, reflux, 95%; *ii*: $PhCH_2NH_2$, 100%; **1,4,12 a** Ar = Ph, **b** Ar = 4-MeC_6H_4

In conclusion, we have shown that both under microwave irradiation and normal thermal solution-phase conditions, the reaction of 4-oxo-4-phenylbutanoic acids **1** with benzylamines **2** furnish pyrrolones **4**.

EXPERIMENTAL

All solvents required for this study were distilled before use. Thin-layer chromatography (TLC) was performed with silica gel-G (SRL, India) or silica gel GF-254 (E-Merck) using hexane/ethyl acetate as eluent, and the plates were visualized with iodine vapors or UV light. Column chromatography was accomplished on silica gel (100-200 mesh, Acme synthetic chemicals) packed by the slurry method using EtOAc-hexane as eluent. IR spectra were recorded as KBr solutions or neat using an ABB Bomem MB 104 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with Brucker (300 and 75 MHz respectively) NMR spectrometers using TMS and the center line of the chloroform-D triplet (77.0 ppm) as internal standard, respectively. Melting points were recorded using a Gallenkamp melting point apparatus and were uncorrected. Mass spectra were recorded on a Finnigan MAT 8230 mass spectrometer. The microwave reactions were carried out using a BPL-Sanyo microwave oven, India; mono-mode, multipower, power source: 230 V, 50 Hz, microwave frequency: 2450 MHz. The starting materials, 4-oxo-4-phenylbutanoic acids **1,** were prepared by the Friedel-Crafts acylation of aromatic hydrocarbons with succinic anhydride according to the literature procedure [19].

Preparation of pyrrolones 4 (General procedure).

1-Benzyl-5-phenyl-3-[(*E*)-1-phenylmethylidene]-2,3-dihydro-1H-2-pyrrolone (**4a**). 4-Oxo-4-phenyl-butanoic acid (**1a**) (150 mg, 0.842 mmol) and benzylamine (**2a**) (214 mg, 2 mmol) were taken in a 25 ml conical flask, dissolved in 4 ml PEG-200, and allowed to keep under microwave irradiation at 300 W for 2 min. After completion of the reaction (TLC) the reaction mixture was cooled to room temperature and diluted with ice-cooled water (50 ml) and dichloromethane (20 ml). The organic layer was separated and washed with water (3×10 ml), brine solution (2×10 ml), dried (Na_2SO_4), and concentrated under *vacuo* to furnish the crude product, which was subjected to column chromatography (silica gel 100-200 mesh) using 10% EtOAc–hexane as an eluent to give compound **4a**. Yield 221 mg (78%), an orange solid, mp 140-142°C (lit. 142-143°C [5]), R_f 0.42 (10% EtOAc–hexane). UV spectrum (MeOH), λ_{max}, nm (logε): 310 (4.66), 410 (2.27). IR spectrum, ν cm^{-1}: 696, 737, 758, 1027, 1075, 1141, 1319, 1362, 1491, 1557, 1617, 1701, 3054. ^{1}H NMR spectrum (300 MHz, $CDCl_3$–CCl_4, 1:1), δ, ppm (*J*, Hz): 4.79 (2H, s); 6.20 (1H, s); 7.02 (2H, d, *J* = 6.3); 7.17-7.21 (2H, m); 7.25-7.39 (9H, m); 7.46 (1H, s); 7.62 (2H, d, *J* = 8.1). ^{13}C NMR spectrum (75 MHz, $CDCl_3$–CCl_4, 1:1), δ ppm: 44.69, 100.84, 127.22 (2C), 128.06, 128.52, 128.57, 128.85 (2C), 129.38, 129.98, 130.28, 131.61, 132.81, 136.10, 137.83, 149.59, 170.48. LRMS, *m/z* (*I*, %): 337 [M]$^+$ (37), 246 (6), 228 (10), 202 (14), 139 (10), 119 (20), 91 (100), 77 (10), 65 (28), 51 (8). Found, %: C 85.47; H 5.71; N 4.12. $C_{24}H_{19}NO$. Calculated, %: C 85.43; H 5.68; N 4.15.

1-Benzyl-5-(4-methylphenyl)-3-[(*E*)-1-phenylmethylidene]-2,3-dihydro-1H-2-pyrrolone (**4b**). Following the general procedure described above, the reaction of 4-(4-methylphenyl)-4-oxobutanoic acid (**1b**) (161 mg, 0.842 mmol) and benzylamine (**2a**) (214 mg, 1.56 mmol) in 6 ml PEG-200 gave compound **4b** which was purified by column chromatography. Yield 153 mg (52%), an orange solid, mp 154-156°C, R_f 0.39 (10% EtOAc–hexane). UV spectrum (MeOH), λ_{max}, nm (logε): 311 (4.36), 410 (2.32). IR spectrum, ν, cm^{-1}: 691, 737, 760, 822, 1026, 1141, 1319, 1360, 1449, 1494, 1610, 1701, 2903, 3027. ^{1}H NMR spectrum (300 MHz, $CDCl_3$–CCl_4, 1:1), δ, ppm (*J*, Hz): 2.38 (3H, s); 4.84 (2H, s); 6.22 (1H, s); 7.09 (2H, d, *J* = 6.6); 7.14-7.26 (8H, m); 7.33-7.44 (3H, m); 7.49 (1H, s); 7.65 (2H, d, *J* = 7.2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$–CCl_4, 1:1), δ ppm: 170.99, 149.66, 139.54, 137.77, 135.91, 132.49, 130.18 (2C), 129.90, 129.39, 129.28 (2C), 128.82 (2C), 128.45 (2C), 128.32, 127.85 (2C), 127.04, 126.99 (2C), 100.34, 44.59, 21.33. LRMS, *m/z* (*I*, %): 351 $[M]^+$ (100), 245 (6), 217 (12), 91 (56). Found, %: C 85.39; H 6.05; N 4.02. $C_{25}H_{21}NO$. Calculated, %: C 85.43; H 6.02; N 3.99.

1-Benzyl-5-(4-chlorophenyl)-3-[(*E*)-1-phenylmethylidene]-2,3-dihydro-1H-2-pyrrolone (**4c**). Following the general procedure described above, the reaction of 4-(4-chlorophenyl)-4-oxobutanoic acid **1c** (150 mg, 0.71 mmol) and benzylamine **2a** (151 mg, 1.42 mmol) in 4 ml PEG-200 gave compound **4c,** which was purified by column chromatography. Yield 199 mg (76%), an orange solid, mp 160-162°C, R_f 0.41 (10% EtOAc–hexane). UV spectrum (MeOH), λ_{max}, nm (logε): 310 (4.84), 410 (2.13). IR spectrum, ν, cm^{-1}: 693, 737, 761, 836, 1091, 1141, 1317, 1361, 1451, 1488, 1617, 1702, 2902, 3024. ^{1}H NMR spectrum (300 MHz, $CDCl_3$–CCl_4, 1:1), δ, ppm (*J*, Hz): 4.79 (2H, s); 6.21 (1H, s); 7.04 (2H, d, *J* = 6.6); 7.18-7.26 (5H, m); 7.30-7.43 (4H, m); 7.50 (1H, s); 7.63 (2H, d, *J* = 6.6). ^{13}C NMR spectrum (75 MHz, $CDCl_3$–CCl_4, 1:1), δ, ppm: 44.81, 101.26, 127.09, 127.39, 128.69, 128.96, 129.31 (2C), 129.64, 129.71, 129.97, 130.35, 133.55, 135.63, 135.96, 137.67, 148.41, 170.50. LRMS, *m/z* (*I*, %): 373 $[M^+ + 2]$ (18), 371 $[M]^+$ (38), 245 (10), 228 (10), 202 (14), 91 (100), 65 (12). Found, %: C 77.56; H 4.91; N 3.79. $C_{24}H_{18}ClNO$. Calculated, %: C 77.52; H 4.88; N 3.77.

1-(4-Methylbenzyl)-3-[(*E*)-1-(4-methylphenyl)methylidene]-5-phenyl-2,3-dihydro-1H-2-pyrrolone (**4d**). Following the general procedure described above, the reaction of 4-oxo-4-phenylbutanoic acid **1a** (100 mg, 0.56 mmol) and 4-methylbenzylamine **2b** (121 mg, 0.99 mmol) in 6 ml PEG-200 gave compound **4d**. Yield 152 mg (74%), after purification by column chromatography (silica gel 100-200 mesh; eluent 20% ethyl acetate–hexane), an orange solid, mp 90°C, R_f 0.83 (20% ethyl acetate–hexane). UV spectrum (MeOH), λ_{max}, nm (logε): 317 (3.7). IR spectrum, ν, cm^{-1}: 698, 764, 812, 926, 1022, 1075, 1179, 1352, 1389, 1447, 1512, 1599, 1700, 3026. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.28 (3H, s); 2.38 (3H, s); 4.8 (2H, s); 6.24 (1H, s); 7.23 (2H, d, *J* = 7.8); 7.31 (2H, m); 7.33-7.39 (9H, m); 7.52 (1H, s); 7.64 (2H, d, *J* = 6.8). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 21.18, 21.65, 22.83, 29.45, 29.84, 30.17, 32.07, 44.53, 101.84, 127.25, 128.20, 128.70, 129.28, 129.42, 129.79, 130.46, 131.68, 133.20, 133.33, 134.92, 136.81, 140.15, 149.19, 171.16. Found, %: C 85.41; H 6.36; N 3.81. $C_{24}H_{23}NO$. Calculated, %: C 85.45; H 6.34; N 3.83.

1-(4-Chlorobenzyl)-3-[(*E*)-1-(4-chlorophenyl)methylidene]-5-phenyl-2,3-dihydro-1H-2-pyrrolone (**4e**). Following the general procedure described above, the reaction of 4-oxophenyl-4-butanoic acid **1a** (100 mg, 0.56 mmol) and 4-chlorobenzylamine **2c** (87 mg, 0.62 mmol) in 6 ml PEG-200 gave compound **4e** after purification by column chromatography. Yield 179 mg (79%), orange solid, mp 110°C, R_f 0.67 (20% ethyl acetate–hexane). IR spectrum, ν, cm^{-1} 693, 757, 758, 1029, 1141, 1318, 1362, 1491, 1555, 1617, 1701, 3053. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.85 (2H, s); 6.25 (1H, s); 7.07 (2H, d, *J* = 6.4); 7.19-7.21 (2H, m); 7.25-7.39 (7H, m); 7.52 (1H, s); 7.64 (2H, d, *J* = 6.8). Found, %: C 71.01; H 4.24; N 3.91. $C_{24}H_{17}NOCl_2$. Calculated, %: C 70.95; H 4.22; N 3.95.

N-Benzyl-4-(1-benzyl-2-oxo-5-phenyl-2,3-dihydro-1H-3-pyrrolylidene)-4-phenylbutan- amide (3a). Compound **1a** (200 mg, 1.12 mmol) and benzylamine **2a** (120 mg, 1.12 mmol) were taken in a 5 ml RB and heated to reflux for 2 h in a preheated oil bath (180°C). The reaction mixture, cooled to room temperature, was diluted with dichloromethane (20 ml). The organic solution was washed with water (2×20 ml) and brine (20 ml). The solvent was removed after drying (Na_2SO_4), which was carried out under reduced pressure. The crude product

was subjected to column chromatography on SiO_2 and eluted with increasing amounts of ethyl acetate in hexane (1:9 to 2:8). Pooling of fractions having a clear product led to isolation of amide **3a**, yield 100 mg (18%) and compound **4a**, yield 272 mg (72%). The spectral data of **3a** generated in this experiment almost matched with previously prepared sample **3a** [15], orange solid, mp 160–162°C. IR spectrum, ν, cm^{-1}: 782, 1493, 1600, 1684, 1807, 1887, 1953, 2924, 3061, 3322. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.48 (2H, t, *J* = 7.8); 3.64 (2H, t, *J* = 7.8); 4.42 (2H, d, *J* = 6.0); 4.71 (2H, s); 5.68 (1H, s); 7.03 (2H, d, *J* = 8.1); 7.19-7.40 (18H, m). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 29.3, 35.81, 43.36, 44.53, 102.97, 126.92 (2C), 127.02, 127.12, 127.67 (2C), 127.94 (2C), 128.44 (6C), 128.87, 128.95, 129.06, 131.22, 137.67, 138.79, 140.00, 145.00, 153.87, 169.50, 171.80.

HSPR thanks University Grants Commission, India, for the Special Assistance Program (SAP-DRS), the Council of Scientific Industrial Research, India, and the Department of Science and Technology, India, for financial assistance. S. Rafi thanks CSIR for the Junior Research Fellowship awarded in the major research project awarded to HSPR. We thank Prof. A. Srikrishna, Sophisticated Instrumentation Facility and Sophisticated Analytical Instrumentation Center, for generously recording NMR spectra.

REFERENCES

1. J. Azizian, A. R. Karimi, H. Arefrad, A. A. Mohammadi, and M. R. Mohammadizadeh, *Molecular Diversity*, **6**, 223 (2003).
2. D. Lee, J. K. Sello, and S. L. Schreiber, *Org. Lett.*, **2**, 709 (2000).
3. M. T. Kolb, *Bull. Chim. Soc. Fr.*, **19**, 389 (1898).
4. B. Love, R. B. Greenwald, M. M. Goodman, and C. L. Zirkle, *J. Med. Chem.*, **14**, 849 (1971).
5. E. V. Safaryan, G. V. Grigoryan, and S. G. Agbalyan, *Arm. Khim. Zh.*, **39**, 38 (1986); *Chem. Abstr.*, **106**, 67037 (1987).
6. H. Fiesselmann and W. Ehmann, *Chem. Ber.*, **91**, 1713 (1958).
7. B. Love, R. B. Greenwald, M. M. Goodman, and C. L. Zirkle, *J. Med. Chem*, **14**, 849 (1971).
8. A. Treibs, K. Jacob, and A. Diel, *Liebigs Ann. Chem.*, **702**, 112 (1967).
9. W. I. Awad, A. I. Hashem, and K. Ei-Badny, *Indian J. Chem.*, **13**, 1139 (1975).
10, H. S. P. Rao and S. P. Senthilkumar, *Indian J. Chem.*, **43B**, 2426 (2004).
11. H. S. P. Rao, S. P Senthilkumar, and K. Jayalakshmi, *Heterocycl. Commun.*, **9**, 65 (2003).
12. H. S. P. Rao, S. Jothilingam, and H. W. Scheeren, *Tetrahedron*, **60**, 1625 (2004).
13. H. S. P. Rao and S. Jothilingam, *Tetrahedron Lett.*, **58**, 2189 (2002).
14. H. S. P. Rao and S. P. Senthilkumar, *J. Chem. Sci.*, **116**, 163 (2004).
15. A. A. H. Saeed, *Heterocycles*, **24**, 45 (1986).
16. M. Ueda, M. Yabuuchi, and Y. Imai, *J. Polym. Sci. Polym. Chem.*, **15**, 2641 (1977).
17. M. Soriano-Garcia, J. S. X. Serrano, J. G. Jimenez, and R. A. Toscano, *Acta Crystallogr.*, **C42**, 1828 (1986).
18. A. Husain, S. M. Hasan, S. Lal, and M. M. Alam, *Indian J. Heterocycl. Chem.*, **14**, 163 (2004).
19. L. F. Tietze and T. Eicher, *Reactions and Synthesis in the Organic Chemistry Laboratory*, University Science Books, Mill Valley, California, 1989, p. 137.