Three-Component One-Pot Synthesis of 4-Aryl-2,3-dihydropyrimido[1,2-*a*]benzimidazol-2-ones Catalyzed by L-Proline

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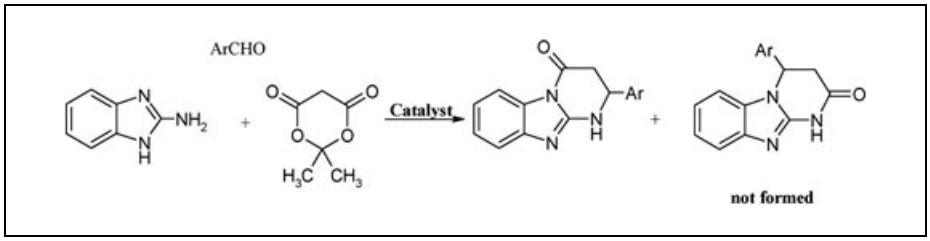
Received March 29, 2011
DOI 10.1002/jhet.1030
View this article online at wileyonlinelibrary.com.



An efficient chemoselective synthesis of 4-aryl-2,3-dihydropyrimido[1,2-*a*]benzimidazol-2-one derivatives from three-component reactions of 2-aminobenzimidazole, Meldrum's acid, and aldehydes *via* [3+3] atom combination is described. The reaction occurs in different conditions such as in DMF as solvent at reflux and in the presence of L-proline as base catalyst.

J. Heterocyclic Chem., **49**, 1386 (2012).

INTRODUCTION

2-Aminobenzo-1,3-diazoles are a biologically important class of molecules and are versatile reagents, which have been utilized in synthesis of pharmaceutical productions as 1, 3-dinucleophiles [1,2]. 2-Aminobenzimidazole has three nitrogen atoms as electron-rich sites. Nucleophilic reactions on this compound can take place on either the exocyclic or the endocyclic nitrogen center, depending on the reaction conditions and the nature of the electrophile [3,4]. The preparation of fused three-hetero-cyclic compounds has been reported *via* reactions of 2-aminobenzimidazole or 2-aminobenzothiazole, with several 1,3-dielectrophiles [5–7]. Recently, we have reported several reactions of 2-aminobenzimidazole or 2-amino-benzothiazole with 1,3-dielectrophiles such as ethyl-α-cyanocinnamoates, α-cyanocinnamonitrile, 3-benzylidene-2,4-pentanedione, and (chlorocarbonyl)phenylketene [8,9], which afforded dihydropyrimido[1,2-*a*]benzimidazole derivatives (**I**, **II**, **III**, **IV**, and **V**). In these reactions, 2-amino-benzo-1,3-diazoles act as regioselective compounds (Scheme 1).

Dihydropyrimido[1,2-*a*]benzimidazoles and their oxo derivatives deserve interest for their biological and pharmacological activities and have stimulated new methods and reagents for the preparation of these heterocyclic compounds [10]. Condensed pyrimidine and pyrimidinone compounds with five-membered aromatic ring such as 2-aminobenzo-1,3-diazoles have been shown to exhibit interesting pharmacological properties [11], and several synthetic methods have been reported for their preparation [12].

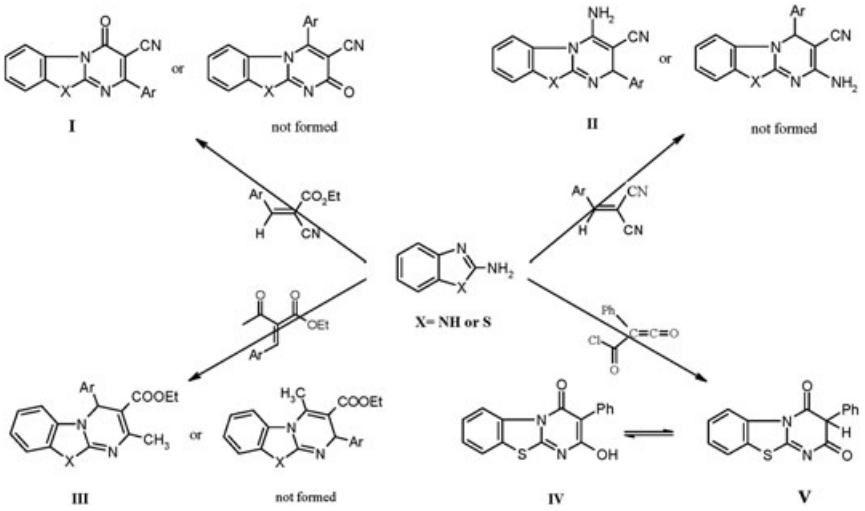
Lipson *et al.* have reported the synthesis of substituted and unsubstituted 1,2,3,4-tetrahydripyrimido[1,2-*a*] benzimidazol-2-and-5-ones from the conjugate addition of 2-aminobenzimidazole **1** with esters of substituted cinnamic acids or the acetylenic acids [13]. In this article, we describe the chemoselective reaction of 2-aminobenzimidazole with arylidene Meldrum's acid derivatives to prepare 4-aryl-2,3-dihydropyrimido[1,2-*a*]benzimidazol-2-one derivatives in the presence of base catalyst such as L-proline. Arylidene Meldrum's acid derivatives were satisfactorily prepared by condensation of commercially available Meldrum's acid **2** with aldehydes in different conditions, and these compounds generally used for the generation of the C═C double bonds [14].

RESULTS AND DISCUSSION

In this study, as exhibited in Scheme 2, we studied the regioselectivity of three-component reaction of 2-aminobenzimidazole **1**, Meldrum's acid **2**, and aldehydes **3** under thermal conditions and microwave heating. We found that when equimolar amounts of 2-aminobenzimidazole are refluxed with both Meldrum's acid and aldehydes (**3a**–**f**) in DMF, the compounds 4-aryl-2,3-dihydropyrimido[1,2-*a*]benzimidazol-2-one derivatives **4a**–**f** are formed. The same products are obtained when these reactions are carried out in the presence of L-proline as a base catalyst in ethanol.

So, we have investigated the regioselectivity of the 2-aminobenzothiazole **1** with Meldrum's acid **2** and

Scheme 1



aldehydes **3** in ethanol under microwave irradiation, which afforded same products with thermal conditions.

As it is shown in Table 1, yield of the reaction is markedly affected by the reaction conditions, and optimum results were obtained, when reactions were run in ethanol and in the presence of L-proline as a base catalyst. The reactions were carried out in alcoholic solution with high yields, and enhanced reactivity and selectivity were observed because of the solubility of all the reagents in alcohol solvent.

As the three-component reaction of 2-aminobenzimidazole **1**, Meldrum's acid **2**, and aldehydes **3a**–**f** involve, first, Knoevenagel condensation to produce arylidene Meldrum's acid derivatives followed by Michael addition, we have investigated the regioselectivity of Michael addition of 2-aminobenzimidazole with arylidene Meldrum's acid derivatives **5a**,**b** in various conditions which afforded products **4a**,**b** (Scheme 3).

2-Aminobenzimidazole **1a** acts as a binucleophile toward the deficient centers at C_β and carbonyl group of arylidene Meldrum's acid derivatives to release 4-aryl-2,3-dihydropyrimidopyrimido[1,2-*a*]benzimidazol-2-ones as the only product. These products are due to chemoselective addition of the exocyclic nitrogen center on C_β and endocyclic nitrogen center on carbonyl groups.

The structures of compounds **4a**–**f** were established on the basis of spectral data and shown distinctive, expected features. The IR spectra of these compounds measured in potassium bromide pellets show bands at 3400–3100 cm^{-1} and 1728–1689 cm^{-1} related to elongation of the NH and C═O groups, respectively. In the ^1H NMR spectra of compounds **4a**–**f**, five kinds of proton signals along with one signal quite down field (δ = 11.70 ppm), arising from the NH group, and the aromatic proton signals at δ = 7.82–6.98 ppm (m, 9H) were observed. The ABX system of protons of the moiety ─CH─CH_2─ of the pyrimidine ring appeared at chemical shifts δ 5.93 (1H, dd, CH), 3.50 (1H, dd, $^2J_{BA}$ = 16.2, $^3J_{BX}$ = 7.2 Hz, H_B) and 2.88 (1H, dd, CH_2 (H_A). The ^{13}C NMR of these compounds showed 16 distinct resonances in agreement with the proposed structure.

Although the detailed mechanism of the above reactions in the diferent reaction conditions not to be fully clarified, the formation of compounds **4a**–**f** in the presence of L-proline as a base catalyst could be explained by a reaction sequence that

Scheme 2

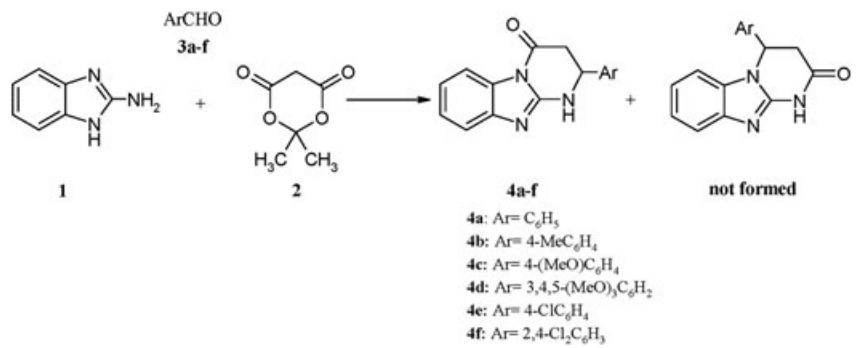


Table 1

Synthesis of **4a–f** under different reaction conditions.

		Without catalyst (DMF as solvent)		L-Proline (ethanol as solvent)	
Compd No.	Ar	Time (min)	Yield (%)	Time (min)	Yield (%)
4a	C_6H_5	60	80	10	90
4b	4-MeC_6H_4	62	77	10	90
4c	4-$MeOC_6H_4$	70	74	12	85
4d	3,4,5-$(MeO)_3C_6H_2$	60	70	12	75
4e	4-ClC_6H_4	30	90	5	92
4f	2,4-$Cl_2C_6H_3$	30	85	5	90

presented in Scheme 4. In principle, these reactions can proceed *via* a reaction sequence of condensation, addition, cyclization, and elimination. L-Proline catalyzed the formation of iminium ion **I**, and the higher reactivity of iminum ion compared to the carbonyl group could facilitate Knoevenagel condensation of aldehydes with Meldrum's acid, *via* intermediate **II**, and after the elimination of L-proline, arylidine Meldrum's acid **III** might be produced as an intermediate. 2-Aminobenzimidazole will attack arylidine Meldrum's acid derivatives *via* chemoselective Michael addition to give the intermediate **IV**, which followed by the cycloaddition and losing one molecule of acetone and CO_2 to form the final products **4**.

In summary, we have described chemoselective synthesis of 4-aryl-2,3-dihydropyrimido[1,2-*a*]benzimida-zol-2-one derivatives from three-component reactions of 2-aminobenzimidazole, Meldrum's acid, and aldehydes *via* [3+3] atom combination in different reaction conditions such as in DMF as solvent at reflux and in the presence of L-proline as a base catalyst under reflux condition. The advantage of these procedures reported here are high conversions and selectivity, high purity of products, and easy workup.

EXPERIMENTAL

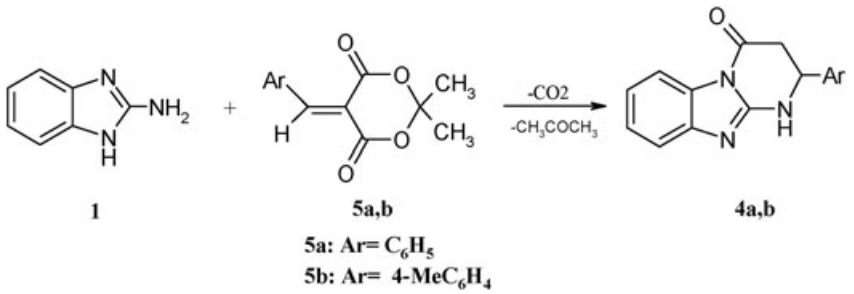
General procedures. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FTIR spectrometer. The proton and carbon NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General procedure for the preparation of 4-aryl-2,3-dihydropyrimido[1,2-*a*][1,3]benzimidazol-2-one derivatives (4a–f). ***Method I.*** A mixture of 2-aminobenzimidazole (2 mmol), aldehyde (2 mmol), and Meldrum's acid (2 mmol) was refluxed in DMF (2 mL) for the time reported in Table 1 (the progress of the reaction being monitored by TLC and using *n*-hexane/ethyl acetate as an eluent). The product was precipitated from the reaction mixture after cooling, and then 2-propanol (10 mL) was added. The precipitate was filtered and recrystallized from ethanol.

Method II. A mixture of 2-aminobenzimidazole (2 mmol), aldehyde (2 mmol), Meldrum's acid (2 mmol), and L-proline (0.2 mmol) was refluxed in ethanol (2 mL) for the time reported in Table 1 (monitored by TLC), and then 30 mL of H_2O was added. The precipitate was filtered off and recrystallized from ethanol.

2-Phenyl-2,3-dihydropyrimido[1,2-a]benzimidazole-2-one (4a). Pale yellow crystals. mp 281–284°C. IR (KBr, ν_{max}/cm^{-1}): 3125 (NH), 1728 (C=O), 1649 (C=N), 1589 (C=C). ^1H NMR (500 MHz, DMSO-d_6): 11.70 (1H, s, NH), 7.82 (1H, d, $^3J_{HH}$ = 7.7 Hz Ar), 7.43–6.98 (8H, m, Ar), 5.93 (1H, dd, $^3J_{XB}$ = 7.1, $^3J_{XA}$ = 3.0 Hz, CH), 3.50 (1H, dd, $^2J_{BA}$ = 16.2, $^3J_{BX}$ = 7.2 Hz, CH_2 (H_B)), 2.88 (1H, dd, $^2J_{AB}$ = 16.2, $^3J_{AX}$ = 3.1 Hz, CH_2 (H_A)). ^{13}C NMR (125 MHz, DMSO-d_6): 165.7 (C=O), 153.7, 143.5, 129.0, 128.6, 127.9, 126.3, 125.6, 124.6, 120.5, 115.8, 113.2, 52.8 (C_2), 38.5 (C_3). EI-MS, *m/z* (%): 263 (M^+, 94), 220(76), 167(15), 149(54), 133(100), 103(47), 77(59), 57(64), 43(90). Anal. Calcd. For $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96 %. Found: C, 72.68; H, 4.75; N, 15.59.

Scheme 3

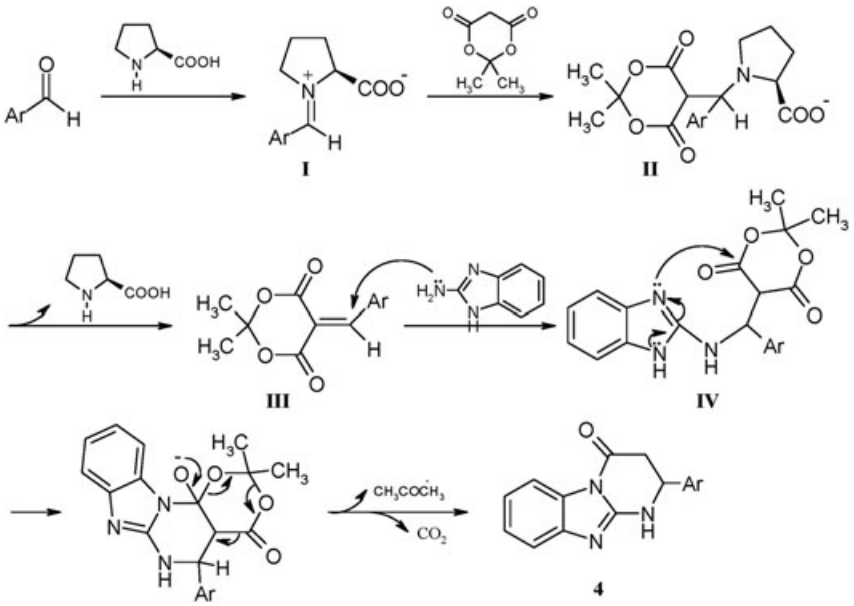


1 **5a,b** **4a,b**

5a: Ar= C_6H_5

5b: Ar= 4-MeC_6H_4

Scheme 4



2-(4-Methylphenyl)-2,3-dihydropyrimido[1,2-a]benzimidazole-2-one (4b). Orange crystals. mp 281–285°C. IR (KBr, ν_{max}/cm^{-1}): 3321 (NH), 1689 (C═O), 1636 (C═N), 1582 (C═C). ^1H NMR (500 MHz, DMSO-d_6): 11.72 (1H, s, NH), 7.44–6.94 (8H, m, Ar), 5.88 (1H, dd, $^3J_{XB}$ = 7.8, $^3J_{XA}$ = 2.9 Hz, CH), 3.46 (1H, dd, $^2J_{BA}$ = 16.3, $^3J_{BX}$ = 7.5 Hz, $CH_2(H_B)$), 2.87 (1H, dd, $^2J_{AB}$ = 16.4, $^3J_{AX}$ = 3.1 Hz, CH_2 (H_A)), 2.23 (3H, s, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): 167.3 (C═O), 147.9, 141.9, 137.5, 136.3, 132.3, 129.5, 129.1, 126.2, 125.6, 121.6, 120.8, 117.4, 109.5, 51.8 (C_2), 38.5 (C_3), 20.5 (CH_3). EI-MS, *m/z* (%): 277 (M^+, 7), 199(48), 175 (79), 170(79), 160(12), 144(5), 133(100), 118(5), 105(39), 90(12), 78(16), 63(10), 57(3), 51(14), 43(27). Anal. Calcd. For $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15%. Found: C, 73.38; H. 5.33; N; 14.91.

2-(4-Methoxyphenyl-2,3-dihydropyrimido[1,2-a]benzimidazole-2-one (4c). Pale yellow crystals. mp 285–288°C. IR (KBr, ν_{max}/cm^{-1}): 3431 (NH), 1728 (C═O), 1648 (C═N), 1589 (C═C). ^1H NMR (500 MHz, DMSO-d_6): 11.66 (1H, s, NH), 7.83–6.72 (8H, m, Ar), 5.84 (1H, dd, $^3J_{XB}$ = 7.5, $^3J_{XA}$ = 3.2 Hz, CH), CH), 3.68 (3H, s, CH_3), 3.42 (1H, dd, $^2J_{BA}$ = 16.1, $^3J_{BX}$ = 7.5 Hz, CH_2 (H_A)), 2.88 (1H, dd, $^2J_{AB}$ = 16.5, $^3J_{AX}$ = 3.3 Hz, $CH_2(H_B)$). ^{13}C NMR (125 MHz, DMSO-d_6): 167.4 (C═O), 159.0, 147.9, 147.9, 132.3, 131.0, 127.0, 124.7, 121.5, 120.7, 117.4, 115.6, 114.4, 109.5, 55.1 (CH_3), 51.8 (C_2), 38.6 (C_3). EI-MS, *m/z* (%): 293 (M^+, 41), 250 (10), 161 (100), 133(16), 91(10), 77(10), 43(6). Anal. Calcd. For $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33 %. Found: C, 69.35; H, 5.04; N, 14.49.

2-(3,4,5-Trimethoxyphenyl)-2,3-dihydropyrimido[1,2-a] benzimidazole-2-one (4d). Pale yellow crystals. mp 290–295°C. IR (KBr, ν_{max}/cm^{-1}): 3409 (NH), 1713 (C═O), 1665 (C═N), 1591 (C═C). ^1H NMR (500 MHz, DMSO-d_6): 8.51 (1H, s, NH), 7.85 (1H, d, $^3J_{HH}$ = 7.8 Hz, Ar), 7.24 (1H, d, $^3J_{HH}$ = 7.8 Hz, Ar), 7.17 (1H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 7.03 (1H, t, $^3J_{HH}$ = 7.6 Hz, Ar), 6.79 (2H, s, Ar), 4.95 (1H, dd, $^3J_{XB}$ = 10.2, $^3J_{XA}$ = 4.5 Hz, CH), 3.77 (6H, s, OCH_3), 3.65 (3H, S, OCH_3), 3.19 (1H, dd, $^2J_{BA}$ = 16.6, $^3J_{BX}$ = 10.4 Hz, $CH_2(H_B)$), 3.03 (1H, dd, $^2J_{AB}$ = 16.6, $^3J_{AX}$ = 4.4 Hz, CH_2 (H_A)). ^{13}C NMR (125 MHz, DMSO-d_6): 166.7 (C═O), 154.7, 153.8, 144.4, 137.9, 136.8, 130.5, 125.5, 121.4, 116.8, 114.1, 104.8, 60.8 (C_2), 59.8 ($2OCH_3$), 54.1 (OCH_3), 40.9 (C_3). EI-MS, *m/z* (%): 353 (M^+, 6.5), 279(8.5), 221(15), 196(10.5), 167 (20), 149(91.2), 133(45), 105(25), 69(56), 57(81), 43(100). Anal. Calcd. For $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89 %. Found: C, 64.22; H, 5.36; N, 11.51.

2-(4-Chlorophenyl)-2,3dihydropyrimido[1,2-a]benzimidazole-2-one (4e). White crystals. Mp = 280–283°C. IR (KBr, ν_{max}/cm^{-1}): 3126 (NH), 1728 (C═O), 1646 (C═N), 1590 (C═C). ^1H NMR (500 MHz, DMSO-d_6): 11.92 (1H, s, NH), 7.91–6.86 (8H, m, Ar), 5.93 (1H, dd, $^3J_{XB}$ = 7.5, $^3J_{XA}$ = 2.9 Hz, CH), 3.50 (1H, dd, $^2J_{BA}$ = 16.6, $^3J_{BX}$ = 7.7 Hz, $CH_2(H_B)$), 2.84 (1H, dd, $^2J_{AB}$ = 16.6, $^3J_{AX}$ = 3.0 Hz, CH_2 (H_A)). ^{13}C NMR (125 MHz, DMSO-d_6): 165.5 (C═O), 153.60, 143.5, 139.5, 139.0, 138.2, 132.5, 131.5, 129.7, 129.7, 129.0, 129.0, 128.9, 128.8, 128.2, 128.0, 127.6, 124.64, 116.0, 113.2, 52.3 (C_2), 38.2 (C_3). EI-MS, *m/z* (%): 299 (M+2, 13), 297 (M^+, 39), 254(17), 220(15), 196(15), 161(96), 133(74), 118(15), 105(23), 97 (22), 90(27), 83(25), 77(49), 57(61), 43(100). Anal. Calcd. For $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11%. Found: C, 64.38; H, 3.91; N, 13.79.

2-(2,4-Dicholorophenyl)-2,3-dihydropyrimido[1,2-a] benzimidazole-2-one (4f). Yellow crystals. mp 291–293°C. IR (KBr, ν_{max}/cm^{-1}): 3383 (broad peak, NH), 1695 (C═O), 1636 (C═N), 1586 (C═C). ^1H NMR (500 MHz, DMSO-d_6): 11.86 (1H, s, NH), 7.8 5–6.50 (7H, m, Ar), 6.13 (1H, dd, $^3J_{XB}$ = 7.6, $^3J_{XA}$ = 2.8 Hz, CH), 3.58 (1H, dd, $^2J_{BA}$ = 16.6, $^3J_{BX}$ = 7.7 Hz, $CH_2(H_B)$), 2.85 (1H, dd, $^2J_{AB}$ = 16.4, $^3J_{AX}$ = 2.9 Hz, CH_2 (H_A)). ^{13}C NMR (125 MHz, DMSO-d_6): 179.9 (C═O), 166.34, 153.0, 148.1, 141.9, 135.1, 133.9, 132.3, 131.8, 129.9, 128.3, 127.6, 122.1, 121.2, 117.6, 109.1, 49.4 (C_2), 36.2 (C_3). EI-MS, *m/z* (%): 333 (M+2, 59), 331 (M^+, 91), 268(17), 254(14), 199(77), 171 (32), 133(100), 105(17), 90 (47), 75(26), 75(26), 57(24), 43(31). Anal. Calcd. For $C_{16}H_{11}Cl_2N_3O$: C, 57.85; H, 3.34; N, 12.65%. Found: C, 57.32; H, 3.21; N, 12.34.

Acknowledgment. The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Committee for its support of this investigation.

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