JOC Notes

Green Chemistry Approaches to the Synthesis of 5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones by a Three-Component Coupling of One-Pot Condensation Reaction: Comparison of Ethanol, Water, and Solvent-free Conditions

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Received August 6, 2002

Abstract: A general and practical green chemistry route to the Biginelli cyclocondensation reaction using cerium(III) chloride as the catalyst (25% mol) is described under three different sets of reaction conditions. This method provides an efficient and much improved modification of original Biginelli reaction reported in 1893, in terms of high yields, short reaction times, and simple work-up procedure, and it has the ability to tolerate a wide variety of substitutions in all three components, which is lacking in existing procedures.

At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials.[1] Green chemistry approaches hold out significant potential not only for reduction of byproducts, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies.[2] Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/product ratio, are perhaps the most ripe for greening.[3]

In recent years, dihydropyrimidinones and their derivatives occupy an important place in the realm of natural and synthetic organic chemistry because of their therapeutic and pharmacological properties.[4] They have emerged as integral backbones of several calcium channel blockers, antihypertensive agents, α-1a-antagonists, and neuropeptide Y (NPY) antagonists.[5] Moreover, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties.[6] Most notably among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors.[7] Thus, synthesis of this heterocyclic nucleus is of much current importance. The most simple and straightforward procedure, first reported by Biginelli in 1893, involves three-component, one-pot condensation of a β-ketoester with an aldehyde and urea under strongly acidic conditions.[4] One major drawback of this so-called Biginelli reaction, however, is the low to moderate yields (20−60%) that are frequently encountered when using substituted aromatic or aliphatic aldehydes.[8] This has led to the development of more complex multistep strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot Biginelli protocol.[8,9]

The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amounts of solvents, and expensive purification techniques represents a fundamental target of the modern organic synthesis.[10] Thus, Biginelli's reaction for the synthesis of dihydropyrimidinone has received renewed interest, and several improved procedures have recently been reported,[4b,11] although some of these methods involve strong Lewis acids such as $BF_3{\cdot}OEt_2$,[11d] protic acids such as HCl,[11g] AcOH,[11d] and additives.[11d] Consequently, there is scope for further renovation toward mild reaction conditions, increased variation of the substituents in all three components, and better yields.

Over recent years, lanthanide salt mediated Lewis acid reactions have attracted tremendous interest throughout scientific communities due to their low toxicity, ease of handling, low cost, stability, and recoverability of the reagent from water.[12] In this paper, we describe a general

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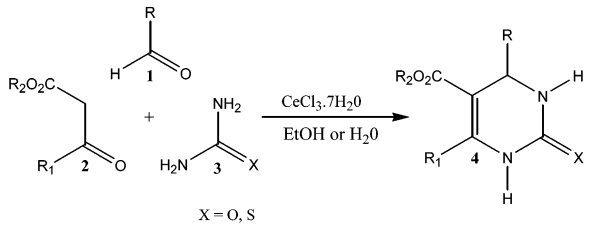
10.1021/jo0205199 CCC: $25.00
Published on Web 12/19/2002

TABLE 1. $CeCl_3$-Catalyzed Synthesis of Dihydropyrimidinones

entry	R	R1	R2	X	time (h)	product (**4**)[a]	yield[b] (%) EtOH reflux	H_2O	solvent-free	ref
1	Ph	CH_3	CH_3	O	3	**4a**	90	88	70	11f
2	4-(OCH_3)-C_6H_4	CH_3	C_2H_5	O	2.5	**4b**	95	90 (3 h)	80 (10 h)	11d
3	4-$(NCH_3)_2$-C_6H_4	CH_3	CH_3	O	4	**4c**	88	82	68	
4	4-$(NCH_3)_2$-C_6H_4	CH_3	CH_3	S	4	**4d**	86	84	69	
5	2,4-$(OCH_3)_2$-C_6H_3	CH_3	CH_3	O	2.5	**4e**	95	90	75	
6	2,4-$(Cl)_2$-C_6H_3	CH_3	CH_3	O	4.0	**4f**	90	84	70	
7	3,4-$(OCH_3)_2$-C_2H_3	C_2H_5	C_2H_5	O	3.0	**4g**	91	89	73	
8	3,4-$(OCH_3)_2$-C_2H_3	CH_3	$C(CH_3)_3$	S	3.0	**4h**	95	86	71	
9	C_6H_5-CH=CH	CH_3	C_2H_5	O	4.5	**4i**	88	83	77	13
10	$CH_3CH_2CH_2$	CH_3	C_2H_5	O	4.0	**4j**	83	76	73	14
11	$(CH_3)_2CH$	CH_3	C_2H_5	O	5.0	**4k**	80	73	65	14
12	3,4,5-$(OCH_3)_3$-C_6H_2	CH_3	$C(CH_3)_3$	O	2.5	**4l**	95	90	80	
13		CH_3	$C(CH_3)_3$	O	3.0	**4m**	93	85	70	
14	2-(NO_2)-C_6H_4	CH_3	C_2H_5	O	5.0	**4n**	82	78	65	11e

[a] All products were characterized by ^1H NMR, IR, and mass spectroscopy. [b] Isolated and unoptimized yields.

SCHEME 1



and practical route for the Biginelli cyclocondensation reaction using cerium(III) chloride heptahydrate as the catalyst. Three different sets of reaction conditions were examined: (i) traditional ethanol reflux; (ii) water reflux; and (iii) solvent-free conditions. This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the dihydropyrimidine-2(1*H*)-ones (Scheme 1).

In a typical general experimental procedure by using traditional conditions, a solution of β-dicarbonyl compound, an aldehyde, and urea in ethanol was heated under reflux in the presence of a catalytic amount of $CeCl_3 \cdot 7H_2O$ (25 mol %) for a certain period of time required to complete the reaction (TLC), resulting in the formation of dihydropyrimidinone. The reaction mixture was then poured into crushed ice, and the solid product separated was filtered and recrystallized.

To study the generality of this process, several examples illustrating this novel and general method for the synthesis of dihydropyrimidinones were studied and are summarized in Table 1. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes carrying either electron-donating or -withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked well without the formation of any side products. Thiourea has been used with similar success to provide the corresponding dihydropyrimidine-(2*H*)-thiones, which are also of much interest with regard to biological activity.[4b] Thus, variations in all three components have been accommodated very comfortably. However, under the present reaction conditions β-ketoaldehydes do not produce the corresponding dihydropyrimidinones; instead they lead to multiple products whose identities are yet to be established.

Use of just 25 mol % $CeCl_3 \cdot 7H_2O$ in refluxing EtOH is sufficient to push the reaction forward. Higher amounts of $CeCl_3$ did not improve the result to a greater extent. No additive or protic/Lewis acid is necessary in this procedure. The yields are, in general, very high regardless of the structural variations in dicarbonyl compound, aldehyde, or urea. The crude products obtained are of high purity (>95% by ^1H NMR). Another important aspect of this procedure is survival of a variety of functional groups such as NO_2, Cl, OH, OCH_3, and conjugated C=C double bond under the reaction conditions. Presumably, the reaction may proceed through the acid-catalyzed formation of an acyl imine intermediate or *N*-alkylidene urea formed by reaction of the aldehyde with urea, the key rate-determining step. Interception of the iminium ion by ethyl acetoactate produces an open-chain ureide **6** which subsequently cyclizes to the dihydropyrimidinones **4**. Because of the 4f empty orbital in the cerium ion, a complex **5** can be formed through a coordinative bond and stabilized by cerium. So we propose a mechanism similar to that of Kappe[11e] for the cerium promoted Biginelli reaction as in Scheme 2.

To reduce the employment of ecologically suspected solvents, we have chosen to carry out the reactions in water. Indeed water is recognized as an attractive medium for many organic reactions. Biginelli reaction using water as a solvent showed a significant improvement upon the isolated product yields ranging from 73 to 90% in the presence of $CeCl_3 \cdot 7H_2O$ (1 mmol). Additionally, difficulties were still encountered in the use of $-NO_2$-substituted benzaldehydes. However, these

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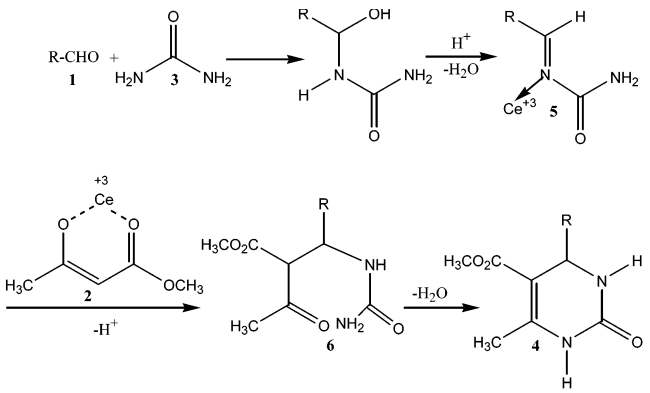
SCHEME 2



reactions were confounded from the green perspectives, by the requirements for extractive isolation followed by recrystallization to afford material of a suitable quality.

In our final series of experiments we set out to examine the solvent-free reaction. β-Ketoester, aldehyde, urea, and $CeCl_3 \cdot 7H_2O$ (30 mol %) were mixed together, and the heterogeneous mixture was stirred rapidly and refluxed for 10 h. The corresponding dihydropyrimidinones were afforded in a typically good yield (65−80%) with the notable exception of the reaction with 2-nitrobenzaldehyde. The solvent-free approach afforded good yields of most of the other nitrobenzaldehydes examined during the course of this study. In the majority of instances, our solvent-free approaches generated dihydropyrimidinones of good purity.

In conclusion, the present procedure of the synthesis of dihydropyrimidin-2(1*H*)-ones by cerium(III) chloride catalyzed, three-component condensation provides an efficient and much improved modification of Biginelli's reaction. In addition, it is possible to apply the tenets of green chemistry to the generation of biologically interesting Biginelli products using aqueous medium approaches, which are less expensive and less toxic than those with organic solvents. Moreover, this method offers several advantages including high yields, short reaction times, and a simple work-up procedure, and it also has the ability to tolerate a wide variety of substitutions in all three components, which is lacking in existing procedures. Furthermore, the present procedure is readily amenable to parallel synthesis and the generation of combinatorial dihydropyrimidinone libraries.

Experimental Section

General Methods. All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on Silica Gel 60 F254 precoated plates. Melting points are uncorrected. Infrared spectra were recorded as thin films on KBr plates with ν_{max} in inverse centimeters. ^{1}H NMR spectra were taken in commercial deuterated solvents on a multinuclear spectrometer with all chemical shifts being reported in parts per million (δ) relative to internal tetramethylsilane (TMS, δ 0.0) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), broad (br), and multiplet (m)], coupling constants [Hz], integration). ^{13}C NMR spectra were taken on a multinuclear spectrometer (200 MHz), using diluted solutions of each compound in DMSO-d_6 as the solvent, and the chemical shifts are reported in ppm (δ unit) downfield from tetramethylsilane as the internal standard ($CDCl_3$, δ 77.0). Mass spectra were obtained utilizing electron impact (EI) at an ionizing potential of 70 eV.

Representative Procedure for 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 2). A solution of methyl acetoacetate (1.16 g, 10 mmol), 4-methoxybenzaldehyde (1.36 g, 10 mmol), and urea (1.8 g, 30 mmol) in ethanol (5 mL) was heated under reflux in the presence of $CeCl_3 \cdot 7H_2O$ (931 mg, 25 mol %) for 2.5 h (monitored by TLC). The reaction mixture (after being cooled to room temperature) was poured onto crushed ice (30 g) and stirred for 5−10 min. The solid separated was filtered under suction (water aspirator), washed with ice-cold water (50 mL), and then recrystallized from hot ethanol to afford pure product (2.62 g, 95%), mp 198−200 °C (lit.[11d] mp 201−203 °C). IR (KBr): 3225, 3098, 2928, 2835, 1710, 1651, 1613, 1583, 1513 cm^{-1}. ^{1}H NMR δ 8.95 (br s, N1-*H*), 7.24 (br s, N3-H), 7.18 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 5.09 (d, J = 3.2 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 2.24 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 165.0, 158.2, 152.0, 147.4, 136.9, 127.1, 113.2, 99.5, 58.6, 54.6, 53.3, 17.5, 13.8. EIMS: *m*/*z* (%) 290 (M$^+$, 23), 261 (100), 217 (80), 155 (60), 77 (35), 42 (98). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83; N, 10.14. Found: C, 60.69; H, 5.76; N, 10.02.

This procedure was followed for the preparation of all the dihydropyrimidinones and thiones listed in Table 1. The known compounds have been identified by comparison of spectral data and mp with those reported. The mp, spectral, and analytical data of the new compounds have been presented below in order of their entries.

Water Reflux. 4-Methoxybenzaldehyde (1.36 g, 10 mmol) was suspended in water (15 mL) along with urea (1.8 g, 30 mmol), methyl acetoacetate (1.16 g, 10 mmol) and $CeCl_3 \cdot 7H_2O$ (3.72 g, 10 mmol), and the heterogeneous mixture was stirred rapidly and refluxed for 3 h (monitored by TLC). The reaction mixture after being cooled to room temperature was poured onto crushed ice (40 g) and stirred for 5−10 min. The solid separated was filtered under suction (water aspirator), washed with ice-cold water (20 mL), and then recrystallized from hot ethanol to afford pure product (2.48 g, 90%).

Solvent Free. To a mixture of 4-methoxybenzaldehyde (1.36 g, 10 mmol), urea (1.8 g, 30 mmol), and methyl acetoacetate (1.16 g, 10 mmol) (15 mL) was added $CeCl_3 \cdot 7H_2O$ (1.11 g, 30 mol %) at room temperature. After it was stirred for 5 min, the resulting mixture was heated at 90 °C in a preheated oil bath for 10 h (monitored by TLC). The reaction mixture (after being cooled to room temperature) was poured onto crushed ice (40 g) and stirred for 5−10 min. The solid separated was filtered under suction (water aspirator), washed with ice-cold water (40 mL), and then recrystallized from hot ethanol to afford pure product (2.20 g, 80%).

5-Methoxycarbonyl-4-(4-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 3). mp 213-215 °C. IR (KBr): 3250, 3120, 2928, 2835, 1700, 1651, 1613, 1583, 1230 cm^{-1}. ^{1}H NMR δ 8.98 (br s, N1-*H*), 7.31 (br s, N3-H), 7.18 (d, J = 9.1 Hz, 2H), 6.63 (d, J = 9.1 Hz, 2H), 5.18 (s, 1H), 3.62 (s, 3H), 2.91 (s, 6H), 2.30 (s, 3H). EIMS: *m*/*z* (%) 289 (M$^+$, 33), 274 (66), 260 (37), 216 (65), 183 (25), 169 (36), 121 (80), 120 (100), 69 (43), 43 (68). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.61; N, 14.52. Found: C, 62.01; H, 6.54; N, 14.06.

5-Methoxycarbonyl-4-(4-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (Entry 4). mp 152−155 °C. IR (KBr): 3280, 3185, 2928, 1710, 1651, 1613, 1583 cm^{-1}. ^{1}H NMR δ 9.98 (br s, N1-*H*), 9.31 (br s, N3-H), 7.16 (d, J = 9.1 Hz, 2H), 6.62 (d, J = 9.1 Hz, 2H), 5.13 (s, 1H), 3.60 (s, 3H), 2.92 (s, 6H), 2.30 (s, 3H). ^{13}C NMR δ 174.1, 166.2, 150.3, 144.9, 131.2, 127.4, 112.6, 101.3, 53.7, 51.3, 17.4. EIMS: *m*/*z* (%) 305 (M$^+$, 21), 246 (25), 231 (8), 185 (22), 171 (18), 141(37), 120 (32), 78-(100), 43 (87). Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76. Found: C, 58.78; H, 6.18; N, 13.68.

5-Methoxycarbonyl-4-(2,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 5). mp 225−227 °C. IR (KBr): 3400, 3220, 3110, 2958, 1710, 1650, 1613, 1583, 1450,

1320, 1220 cm^{-1}. ^{1}H NMR δ 9.10 (br s, N1-*H*), 6.93 (d, J = 8.7 Hz, 2H), 6.80 (br s, N3-H), 6.49 (s, 1H), 6.38 (d, J = 8.7 Hz, 2H), 5.44 (s, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.55 (s, 3H), 2.32 (s, 3H). ^{13}C NMR δ 159.0, 158.2, 137.3, 128.2, 125.1, 115.7, 104.0, 98.6, 96.3, 55.2, 55.0, 39.0, 37.2. EIMS: *m*/*z* (%) 306 (M$^+$, 62), 291 (76), 274 (51), 247 (100), 228 (32), 192 (12), 169 (71), 138 (40), 110 (25), 77 (9), 42 (19). Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.81; H, 5.92; N, 9.14. Found: C, 58.64; H, 5.82; N, 9.05.

5-Methoxycarbonyl-4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 6). mp 242−244 °C. IR (KBr): 3380, 3230, 3104, 2960, 1700, 1641, 1613 cm^{-1}. ^{1}H NMR δ 9.13 (br s, N1-*H*), 7.31 (s, 1H), 7.12−7.24 (m, 2H), 6.98 (br s, N3-H), 5.63 (s, 1H), 3.55 (s, 3H), 2.33 (s, 3H). EIMS: *m*/*z* (%) 314 (M$^+$, 26), 299 (85), 279 (100), 255 (98), 219 (8), 183 (66), 170 (100), 137 (93), 110 (32), 67 (11), 42 (50). Anal. Calcd for $C_{13}H_{12}N_2O_3Cl_2$: C, 49.54; H, 3.83; N, 8.89. Found: C, 49.51; H, 3.76; N, 8.78.

5-Ethoxycarbonyl-4-(3,4-dimethoxyphenyl)-6-ethyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 7). mp 163−165 °C. IR (KBr): 3340, 3230, 3106, 2980, 1700, 1651, 1613 cm^{-1}. ^{1}H NMR δ 8.90 (br s, N1-*H*), 7.11 (br s, N3-*H*), 6.72−6.89 (m, 3H), 5.23 (s, 1H), 4.02−4.18 (m, 2H), 3.85 (s, 6H), 2.73−2.78 (m, 2H), 1.15−1.35 (m, 6H). ^{13}C NMR δ 164.4, 152.6, 152.0, 147.6, 147.1, 136.3, 117.5, 110.2, 109.2, 98.4, 58.4, 54.7, 54.6, 53.2, 23.7, 13.0, 11.8. EIMS: *m*/*z* (%) 334 (M$^+$, 67), 305 (100), 261 (45), 260 (22), 197 (37), 169 (7). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.37. Found: C, 60.83; H, 6.51; N, 8.18.

5-*tert*-Butoxycarbonyl-4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (Entry 8). mp 193−195 °C. IR (KBr): 3157, 3122, 2980, 1710, 1651, 1596 cm^{-1}. ^{1}H NMR δ 8.10 (br s, N1-*H*), 7.58 (br s, N3-*H*), 6.80 (s, 3H), 5.33 (s, 1H), 3.88 (s, 6H), 2.38 (s, 3H), 1.85 (s, 9H). ^{13}C NMR δ 173.9, 164.5, 149.0, 148.9, 141.6, 135.1, 118.9, 111.3, 110.1, 104.2, 81.0, 55.9, 28.0, 17.9. EIMS: *m*/*z* (%) 364 (M$^+$), 307 (100, −57, *t-But*), 263 (52), 248 (9), 171 (46), 138 (29), 57 (35). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.3; H, 6.63; N, 7.67. Found: C, 59.15; H, 6.61; N, 7.63.

5-*tert*-Butoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 12). mp 196−198 °C. IR (KBr): 3260, 3140, 2920, 1710, 1651, 1613, 1265, 1130 cm^{-1}. ^{1}H NMR δ 8.75 (br s, N1-*H*), 7.09 (br s, N3-*H*), 6.55 (s, 2H), 5.22 (s, 1H), 3.88 (s, 6H), 3.75 (s, 3H), 2.28 (s, 3H), 1.38 (s, 9H). ^{13}C NMR δ 163.7, 151.6, 151.3, 145.4, 138.9, 135.4, 102.1, 99.5, 58.7, 57.9, 54.3, 53.1, 26.5, 16.4. EIMS: *m*/*z* (%) 378 (M$^+$, 19), 322 (100), 292 (12), 278 (20), 156 (75), 141 (27). Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.37; H, 6.92; N, 7.40. Found: C, 60.22; H, 6.89; N, 7.32.

5-*tert*-Butoxycarbonyl-4-(3-furfuryl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 13). mp 169−171 °C. IR (KBr): 3278, 3140, 2920, 1716, 1655, 1585, 1265, 1130 cm^{-1}. ^{1}H NMR δ 8.82 (br s, N1-*H*), 7.31 (s, 1H), 7.18 (s, 1H), 6.51 (br s, N3-*H*), 6.40 (s, 1H), 5.26 (s, 2H), 2.23 (s, 3H), 2.45 (s, 9H). EIMS: *m*/*z* (%) 278 (M$^+$), 222 (100, −56, *t-But*), 205 (33), 178 (100), 155 (40), 122 (10), 94 (7), 44 (52). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.19; H, 6.50; N, 9.95.

JO0205199