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Convenient Preparation of a Novel Class of Imidazo[1,5-*a*]pyridines: Decisive Role by Ammonium Acetate in Chemoselectivity

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Received February 14, 2003

Abstract: A facile and one-pot straightforward methodology has been developed to prepare a novel class of imidazo-[1,5-*a*]pyridines. A key role played by ammonium acetate in chemoselectivity has been examined.

The chemistry of fused nitrogen heterocyclic imidazo-[1,5-*a*]pyridines and the closely related isomers has attracted increasing attention due to their medicinal significance.[1] Imidazo[1,5-*a*]pyridines possess thromboxane A_2 synthetase inhibiting property.[2] The isomers such as imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyridines possess antiviral,[3] antiulcer,[4] and D4 receptor antagonistic properties.[5] Many other structurally closely related molecules possessing fused imidazoles are also biologically active. For example, imidazo[1,5-*a*]pyrazines and imidazo[1,2-*a*]pyrimidones exhibit potent corticotropin releasing hormone (CRH) receptor and GnRH receptor antagonistic effects, respectively.[6]

The previous synthesis of imidazo[1,5-*a*]pyridines mainly involves the use of α-2-pyridylalkylamine, followed by subsequent functionalization to anchor various electrophilic reagents.[2,7−11] Other approaches include the use of imine derivatives,[12] 2-cyanopyridine,[13] and recently, benzotriazoles.[14] Most syntheses require strict reaction conditions because of the use of highly sensitive reagents such as LDA,[12] MeLi,[13] $TiCl_4$,[14] dicyclohexylcarbodiimide (DCC),[7] phosphoric oxychloride,[8,15] or PCl_5.[16] The formation of the fused ring framework usually takes two or more steps to complete. Additional steps would be required when functional motif groups are introduced.[1,2,9,11] We report here a new and straightforward one-pot approach; this simple methodology does not involve the use of highly sensitive reagents.

Treatment of benzaldehyde with 2,2′-pyridil in the presence of ammonium acetate in acetic acid gave 1-(2-pyridoyl)-3-phenylimidazo[1,5-*a*]pyridine **1a** and 4,5-bis-(2-pyridyl)-2-phenylimidazole **2a** (Scheme 1). Generally, **1** showed up as a yellow spot in TLC, which can be easily recognized and separated by chromatography in a silica column. Further purification was obtained by recrystallization from ethyl acetate/hexane. Compound **1** possessed good solubility in most polar organic solvents such as chloroform, THF, and ethyl acetate. Examination of the IR band showed that the C═O vibration of **1a** was at 1643 cm^{-1}. The chemical shift of C═O in the ^{13}C NMR spectrum was 186.6 ppm. The structure of **1a** by X-ray crystallographic determination revealed that two fused rings were perfectly coplanar (Figure S1). The phenyl group at the 3-position is twisted 36.07(5)° from the imidazole ring. The carbonyl group is twisted from the pyridyl ring by 46.20(4)°. This group is also not coplanar with the imidazole ring, and the deviation is 9.17(7)°. The twist between the imidazole ring and the pyridyl ring is 50.53(4)°.

Optimization of the reaction conditions was initiated on the preparation of **1a**, based on the fact that **2a** was a major product, and **1a** was obtained but in a very low yield. The initial reaction condition included a 1:1 molar ratio of 2,2′-pyridil and benzaldehyde, 118 °C reaction temperature, and 24 h reaction time. A lower reaction temperature (65 °C) was also used. In both cases, the yield was ca. 2%. Compounds **1b** (4.1%, yield), **1c** (2.3%), **1d** (2.4%), **1e** (3.9%), and **1f** (4.5%) were also obtained in low yields (118 °C, 24 h). Shortening the reaction time to 6 h did not affect the yields. Further investigation was carried out using different ratios of 2,2′-pyridil to benzaldehyde at 6 h and 118 °C. The use of 1.5:1 of 2,2′-pyridil to benzaldehyde gave **1a** in 8.2% yield. When a 2:1 ratio was used, the yield was further increased to 12.1%. This ratio seems to give the best yield because a 2.5:1 ratio gave **1a** in 11.9% yield. The need of excess 2,2′-bipyridil probably originates from its reactivity. In addition to **2** formed from these reactions, the formation of black and insoluble tar side products was also observed. Most likely,

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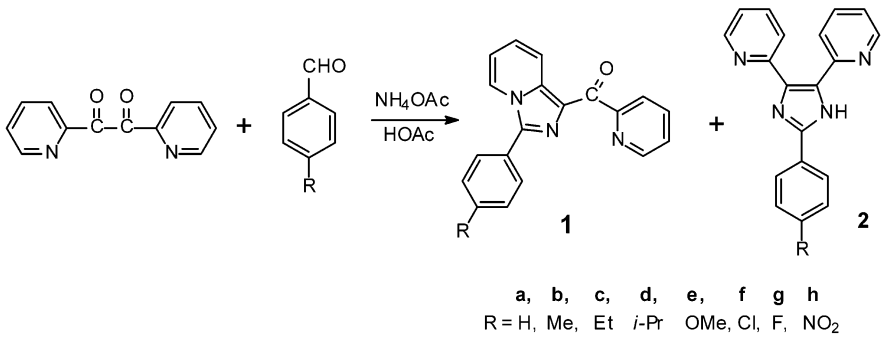
10.1021/jo0342020 CCC: $25.00
Published on Web 05/29/2003

SCHEME 1



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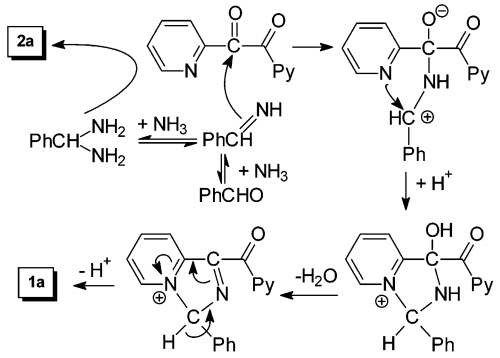

an excessive amount of 2,2′-pyridil compensates the consumption by side reactions. Ammonium acetate used in all of the reactions is 8 equiv to aldehyde.

Further optimization was based on the following rationales: (1) the reaction led to the formation of **2** as the major product; and (2) the formation of 1 mol of **2** would require 2 mol of ammonia, whereas the formation of 1 mol of **1** would require only 1 mol of ammonia (Scheme 2). Thus, we beg one innocent question: will ammonium acetate have a dramatic effect on the reaction? Ammonium acetate is a solid source of ammonia, which can be conveniently generated in situ through the dissociation of ammonium acetate. Usually, the amount of ammonium acetate used is loosely controlled. A large excess is often used for two reasons: one is that it is water-soluble and any leftover can be easily removed during a workup, and the other is that it is a neutral salt and not a significantly active species other than as an ammonia source. *We envision that the formation of **1** may depend on the amount of ammonium acetate.* That means that ammonium acetate is not merely used as ammonia source, and most importantly, the amount may hold the key to chemoselectivity. If all of the prior results obtained are due to the use of 8 equiv ammonium acetate, which favors the formation of **2** because the amount was far excessive, then a reduced amount of ammonia acetate would favor the formation of **1**. To prove this theory, a series of experiments have been focused on the use of a reduced amount of ammonium acetate. Table 1 lists the results obtained from varied equivalence of ammonium acetate to benzaldehyde. The reduced amount of ammonium acetate was applied to the previously established 2:1 ratio of 2,2′-pyridil to benzaldehyde (vide supra). When ammonium acetate was reduced to 6 equiv, the yield of **1a** was increased to 40.5% (run 8, Table 1), a significant jump compared to 12.1% from 8 equiv (run 9, Table 1). This revealed an important and critical role played by the *amount* of ammonium acetate. Further investigation showed that 2 equiv of ammonium acetate gave the highest yield (67.2%, run 5, Table 1). Equally significantly, the present reaction condition has to consider the reactivity of 2,2′-pyridil as discussed previously. It is clear that the optimal results can be achieved only when the ratio of 2,2′-pyridil to benzaldehyde is maintained at 2:1. A simple use of 2 equiv of ammonium acetate without the optimal ratio of 2,2′-pyridil to benzaldehyde will lead to a compromised result. The reaction from 2,2′-pyridil, benzaldehyde, and ammonium acetate in a 1:1:2 ratio reduced yield to 14.7% (run 2, Table 1), a significant decrease compared to 67.2% from a ratio of 2:1:2. Therefore, 2,2′-pyridil, benzaldehyde, and ammonium acetate at a molar ratio of 2:1:2 is an optimal combination for the requisite imidazo[1,5-*a*]pyridines. Table 2 lists results using various benzaldehyde analogues. In all of these cases, **1** was obtained as the major products in good yields. The formation of **2** was also observed, but the yield was significantly low. The isolated

TABLE 1. Yields of 1a Obtained from Use of Different Molar Ratios of Reactants

run	molar ratio[a]	yield of **1a** (%)
1	1:1:1	16.7
2	1:1:2	14.7
3	2:1:1	28.9
4	2:1:1.5	29.4
5	**2:1:2**	**67.2**
6	2:1:2.5	52.1
7	2:1:4	41.7
8	2:1:6	40.5
9	2:1:8	12.1

[a] 2,2′-pyridil/benzaldehyde/ammonium acetate.

TABLE 2. Yields of 1 and 2 Obtained in Different Conditions

entry	R	yield[a] of **1** (%)	yield[b] of **2** (%)
1	H	**1a**: 67.2	**2a**: 37.5
2	CH_3	**1b**: 51.3	**2b**: 41.7
3	CH_2CH_3	**1c**: 57.1	**2c**: 33.9
4	$CH(CH_3)_2$	**1d**: 42.4	**2d**: 25.6
5	OCH_3	**1e**: 68.1	**2e**: 31.7
6	Cl	**1f**: 55.7	**2f**: 34.4
7	F	**1g**: 65.2	**2g**: 41.7
8	NO_2	**1h**: 52.2	**2f**: nd[c]

[a] Obtained from 2:1:2 ratio of pyridil, aldehyde, and ammonium acetate. [b] Obtained from 1:1:8 ratio of pyridil, aldehyde, and ammonium acetate. [c] Not determined.

yield of **2a** was less than 4%. Table 2 also lists yields of **2** obtained from the 1:1:8 ratio (pyridil, aldehyde, and ammonium acetate) for comparison. The dramatically different results from the two reaction conditions highlight the importance of the amount of ammonium acetate in controlling chemoselectivity and thus the outcome of the reactions.

Theoretically, the formation of **1** only needs 1 equiv of ammonia, but practically 2 equiv of ammonium acetate is utilized. This seeming contradiction likely comes from the fact that not all ammonia generated in situ from dissociation of ammonium acetate participates in the requisite reaction. Free ammonia is a gas, and some of it may escape in gaseous state during the reaction.

In summary, a novel class of imidazo[1,5-*a*]pyridines with a pyridoyl unit has been obtained. The condensation of 2,2′-pyridil, aldehydes, and ammonium acetate was found to be dictated by the amount of ammonium acetate. A 2:1:2 ratio of 2,2′-pyridil, aldehydes, and ammonium acetate offers the desirable chemoselectivity for the synthesis of the requisite imidazo[1,5-*a*]pyridines. The present method provides one-step direct condensation using commercially available and inexpensive starting materials to achieve structurally rather complex imidazo-[1,5-*a*]pyridines.

Experimental Section

General Procedure for Preparation of 1. A mixture consisting of 2,2′-pyridil (1.06 g, 5.00 mmol), 4-substituted benzaldehyde (2.50 mmol), and NH_4OAc (0.385 g, 5.00 mmol) in 25 mL of glacial acetic acid was stirred at 110 °C under N_2. The reaction was monitored by the TLC. After 6 h, the reaction mixture was cooled to room temperature, poured into 100 mL of water, and then neutralized with a 20% NaOH aqueous solution to pH 11−12. The solid was filtered, redissolved in CH_2Cl_2, and washed with water and brine. The organic layer was separated and dried over Na_2SO_4. Upon removal of solvent, the brown residue was purified using flash chromatography on a silica column with an eluent of 2:1:0.1 CH_2Cl_2/ethyl acetate/MeOH (v/v/v) to give **1**, which was further purified by crystallization from solvents to afford analytically pure compounds. Yields of **1** are listed in Table 2.

1-(2-Pyridoyl)-3-phenyl-imidazo[1,5-*a*]pyridine (1a). Recrystallized from ethyl acetate/hexanes 3/1 (v/v); yellow crystal, mp 128−130 °C; IR (KBr) ν_{max} 1643 (C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 4.5 Hz, 1H), 8.48 (d, J = 9.0 Hz, 1H), 8.31 (d, J = 7.4 Hz, 2H), 7.79 (m, 1H), 7.74 (d, J = 7.0 Hz, 2H), 7.50−7.43 (m, 3H), 7.38 (m, 1H), 7.21 (m, 1H), 6.83 (t, J = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 186.6, 155.9, 149.3, 139.1, 137.2, 136.3, 129.5, 129.0, 128.7, 126.1, 125.5, 125.3, 122.5, 121.1, 115.3; MS (EI) 299 (M^+). Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 76.33; H, 4.42; N, 14.11.

1-(2-Pyridoyl)-3-(4-methylphenyl)imidazo[1,5-*a*]pyridine (1b). Recrystallized from benzene/hexanes 5/1 (v/v); yellow crystal, mp 140−141°C; IR(KBr) ν_{max} 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.72 (d, J = 4.5 Hz, 1H), 8.43 (d, J = 9.1 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 7.1 Hz, 1H), 7.77 (t, J = 8.6 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.33 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.16 (m, 1H), 6.78 (t, J = 6.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 186.4, 155.9, 149.4, 139.7, 139.2, 137.1, 136.2, 129.3, 128.6, 126.1, 125.4, 125.2, 122.6, 120.9, 115.2, 21.3; MS 313 (M^+). Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.45; H, 4.79; N, 13.40.

1-(2-Pyridoyl)-3-(4-ethylphenyl)imidazo[1,5-*a*]pyridine (1c). Recrystallized from benzene/hexanes 5/1 (v/v); yellow crystal, mp 136−138 °C; IR(KBr) ν_{max} 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.72 (d, J = 4.4 Hz, 1H), 8.44 (d, J = 9.1 Hz, 1H), 8.31 (d, J = 7.9 Hz, 1H), 8.26 (d, J = 7.1 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.62 (d, J = 7.9 Hz, 2H), 7.32 (m, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.14 (m, 1H), 6.76 (t, J = 6.8 Hz, 1H), 2.60 (q, J = 7.7 Hz, 2H), 1.19 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 186.4, 155.9, 149.4, 146.0, 139.2, 137.1, 136.2, 129.3, 128.7, 128.5, 128.2, 126.3, 126.0, 125.6, 125.2, 122.6, 120.9, 115.2, 28.7, 15.4; MS 327 (M^+). Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.17; H, 5.28; N, 12.75.

1-(2-Pyridoyl)-3-(4-isopropylphenyl)imidazo[1,5-*a*]pyridine (1d). Recrystallized from benzene/hexanes 5/1 (v/v); yellow crystal, mp 154−155 °C; IR(KBr) ν_{max} 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.71 (d, J = 4.2 Hz, 1H), 8.44 (d, J = 9.0 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.27 (d, J = 7.0 Hz, 1H), 7.75 (m, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.32 (m, 3H), 7.14 (m, 1H), 6.75 (m, 1H), 2.87, (m, 1H), 1.22 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ186.5, 162.3, 155.9, 150.6, 149.4, 139.2, 136.2, 135.4, 128.7, 127.9, 127.1, 126.6, 126.5, 126.0, 125.5, 125.2, 123.8, 120.9, 115.2, 34.0, 23.8; MS 341 (M^+). Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.58; H, 5.67; N, 12.30.

1-(2-Pyridoyl)-3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine (1e). Recrystallized from benzene/hexanes 5/1 (v/v); yellow crystal, mp 132−134 °C; IR(KBr) ν_{max} 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.71 (d, J = 4.1 Hz, 1H), 8.39 (d, J = 8.9 Hz, 1H), 8.27 (d, J = 7.9 Hz, 1H), 8.20 (d, J = 7.0 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.32 (m, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.75 (t, J = 6.8 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 186.2, 160.5, 155.7, 149.2, 139.1, 137.0, 136.3, 130.5, 130.1, 129.1, 126.0, 125.6, 125.2, 121.3, 122.6, 120.9, 115.2, 114.4, 55.7; MS 329 (M^+). Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 73.09; H, 4.66; N, 12.67.

1-(2-Pyridoyl)-3-(4-chlorophenyl)imidazo[1,5-*a*]pyridine (1f). Recrystallized from ethyl acetate/hexanes 3/1 (v/v); yellow crystal, mp 158−159 °C; IR(KBr) ν_{max} 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.73 (d, J = 4.4 Hz, 1H), 8.44 (d, J = 9.1 Hz, 1H), 8.25 (d, J = 7.1 Hz, 2H), 7.78 (m, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.36 (m, 1H), 7.20 (m, 1H), 6.84 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 186.5, 155.8, 149.3, 137.8, 137.2, 136.3, 135.5, 129.9, 129.3, 127.5, 126.2, 125.3, 122.3, 121.1, 115.6; MS 333 (M^+). Anal. Calcd for $C_{19}H_{12}ClN_3O$: C, 68.37; H, 3.62; N, 12.59. Found: C, 68.32; H, 3.63; N, 12.49.

1-(2-Pyridoyl)-3-(4-fluorophenyl)imidazo[1,5-*a*]pyridine (1g). Recrystallized from ethyl acetate/hexanes 3/1 (v/v); yellow crystal; mp 143−145 °C; IR (KBr) ν_{max} 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (d, J = 4.4 Hz, 1H), 8.39 (d, J = 9.0 Hz, 1H), 8.20 (t, J = 8.0 Hz, 2H), 7.75 (t, J = 7.7 Hz, 1H), 7.69 (m, 2H), 7.32 (m, 1H), 7.13 (m, 3H), 6.79 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 186.5, 164.4, 162.0, 155.8, 149.2, 138.1, 137.1, 136.3, 130.8, 129.3, 126.2, 125.3, 122.3, 120.9, 116.3, 116.0, 115.5; MS 317 (M^+). Anal. Calcd for $C_{19}H_{12}FN_3O$: C, 71.92; H, 3.81; N, 13.24. Found: C, 71.87; H, 3.97; N, 13.13.

1-(2-Pyridoyl)-3-(4-nitrophenyl)imidazo[1,5-*a*]pyridine (1h). Recrystallized from ethanol; yellow solid, mp 229−230 °C; IR(KBr) ν_{max} 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.73 (d, J = 4.3 Hz, 1H), 8.48 (d, J = 9.1 Hz, 1H), 8.38 (d, J = 7.1 Hz, 1H), 8.30 (d, J = 8.6 Hz, 2H), 8.24 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.82 (t, J = 7.7 Hz, 1H), 7.39 (m, 1H), 7.28 (m, 1H), 6.95 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 186.6, 155.5, 149.3, 147.7, 137.6, 136.4, 135.2, 130.3, 129.0, 126.8, 125.8, 125.3, 124.2, 122.3, 121.3, 116.4; MS 344 (M^+). Anal. Calcd for $C_{19}H_{12}N_4O_3$: C, 66.28; H, 3.51; N, 16.27. Found: C, 66.13; H, 3.59; N, 16.15.

General Procedure for Preparation of 2. To a 100-mL round-bottom flask were added 20 mL of glacial acetic acid and 2,2-pyridil (1.00 g, 4.71 mmol). The mixture was allowed to stir at room temperature until all of the solid was dissolved. Aldehyde (4.71 mmol) was then added, followed by the addition of ammonium acetate (2.90 g, 37.68 mmol). The reaction mixture was magnetically stirred at 118 °C for 6 h and then cooled to room temperature. The mixture was poured into 200 mL of ice water and neutralized with a 10% sodium carbonate solution to a pH of 6.5−7.0. The formed precipitate was collected and redissolved in methylene chloride. The organic phase was washed with water (100 mL and then 2 × 75 mL) and then dried over sodium sulfate. Upon removal of solvent under reduced pressure, the residue was run on a silica column using an eluent of CH_2Cl_2/EtOAc (1:10, v/v) to remove other undesirable components first and then using (CH_2Cl_2/EtOAc, 3:1, v/v) to obtain

1. After **1** was eluted out, EtOAc/CH_2Cl_2 (3:1,v/v) was used to obtain **2**. Both **1** and **2** were further purified by recrystallization. Conditions used for the purification of **1** were the same as that described above. Yields of **1** have been discussed in the text, and yields of **2** are listed in Table 2. Compounds **2a**, **2b**, **2e**, and **2g** obtained in this way have been compared to the reported values in the literature.[17,18]

Acknowledgment. Financial support in part by the U.S. Army (DAAD19-01-0746), NASA (NCC3-552 and NCC3-910), and DOE (DE-FC02-02EW15254) is gratefully acknowledged.

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Supporting Information Available: X-ray crystal structure of **1a** and complete sets of structural parameters including coordinates, bonding distances, and angles; general experimental procedures and full characterization of **2c**, **2d**, and **2f** including data from ^{1}H NMR, ^{13}C NMR, MS, IR, elemental analysis, and melting points; and recrystallization conditions for the purification of each of these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0342020