The synthesis of aminoimidazo[1,2-*a*]azinecarboxylic acid esters from ethyl glyoxylate

V. G. Nenajdenko, A. L. Reznichenko, and E. S. Balenkova*

Department of Chemistry, M. V. Lomonosov Moscow State University,
1 Leninskie Gory, 119992 Moscow, Russian Federation.
Fax: +7 (495) 932 8846. E-mail: nen@acylium.chem.msu.ru

Three-component reactions of aminoazines, isonitriles, and ethyl glyoxylate gave mixtures of isomeric ethyl 2- and 3-aminoimidazo[1,2-*a*]azinecarboxylates in moderate yields.

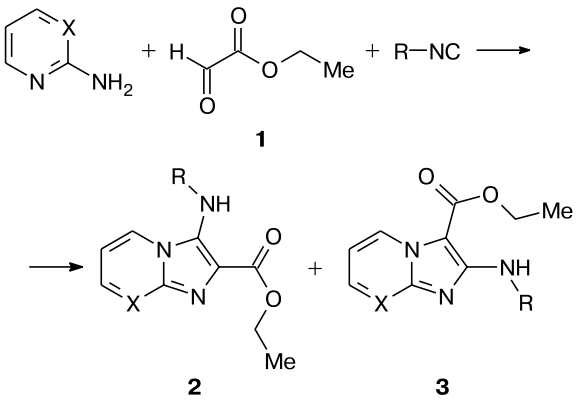
Key words: multicomponent reactions, ethyl glyoxylate, isonitriles, imidazo[1,2-*a*]azines.

Multicomponent reactions have acquired great importance in modern preparative organic chemistry because they are straightforward, significantly spare time, and make it possible to create complex molecular structures.[1,2] The Groebke reaction, which is a version of the Ugi reaction, was proposed in 1998.[3—5] Reactions of 2-aminoazines and -azoles with a carbonyl compound and isonitrile in the presence of Brønsted and Lewis acids give 3-aminoimidazo[1,2-*a*]azines and -azoles, which are valuable building blocks in medicinal chemistry.[6—8] In recent years,[9,10] convenient preparative versions of the Groebke reaction both in solution and on solid supports have been developed. A thorough study[11] showed that this reaction yields, along with the target 3-aminoheterocycles, alternative 2-isomers as by-products. In nonpolar solvents, the formation of the alternative isomer can be avoided in some cases.[12] It is worth noting that the use of glyoxylic acid as a carbonyl component of the Groebke reaction does not afford the target amino acids; instead, 2-unsubstituted 3-aminoimidazo[1,2-*a*]azines are obtained only.[13] We assumed that derivatives of the corresponding amino acids can be synthesized when glyoxylic acid is replaced by ethyl glyoxylate **1**.

First, we optimized the reaction conditions with 2-aminopyridine and benzyl isocyanide as model compounds. While varying the solvent (methanol, ethanol, toluene, acetonitrile, and chloroform) and the acid catalyst ($HClO_4$, HOAc, and NH_4Cl), we reached the best results in toluene in the presence of NH_4Cl. The target ester **2a** was obtained as a sole isomer in 35% yield. With the other solvents and catalysts, the yield of the target product **2a** was substantially lowered.

At the next step, we studied reactions of a number of aliphatic and aromatic isonitriles with 2-aminopyridine (Scheme 1, Table 1). It turned out that the reaction is of general character: in all cases, the target ethyl 3-aminoimidazo[1,2-*a*]pyridine-2-carboxylates **2** are obtained in moderate yields, with ethyl 2-aminoimidazo[1,2-*a*]pyridine-3-carboxylate **3** as a by-product (TLC data). It is known[11,12] that the 3-amino isomer is the major product of the Groebke reaction. Esters **2a,e,g** were isolated in the individual state; in other cases, we failed to separate a mixture of isomers. The nature of the isonitrile component only slightly influences the pathway of the Groebke reaction in the system under study: in all cases, the yields are 30—40%. Earlier, it has been reported that aminoazoles can also participate in the Groebke reaction to give the corresponding fused heterocycles. We tried to use 2-aminothiazole in a reaction with ethyl glyoxylate and isonitrile; however, no target products were obtained. Along with 2-aminopyridine, 2-aminopyrimidine can be employed in the reaction, producing the corresponding heterocycles in moderate yields. They can be isolated as mixtures of two regioisomers (see Table 1).

Scheme 1



Thus, we studied a new version of the three-component Groebke reaction with ethyl glyoxylate, which affords ethyl 2- and 3-aminoimidazo[1,2-*a*]azinecarboxy-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 539—541, March, 2007.

Table 1. Synthesis of aminoimidazo[1,2-*a*]azinecarboxylic acid esters

Compound	R	X	**2** : **3**	Yield (%)
2a	Bn	CH	1 : 0	35
2b	Bn	N	5 : 1	32
2c	*cyclo*-C_6H_{11}	CH	6 : 1	30
2d	*cyclo*-C_6H_{11}	N	4 : 1	34
2e	Bu^t	CH	1 : 0	35
2f	Bu^t	N	4 : 1	32
2g	4-BrC_6H_4	CH	1 : 0	30
2h	4-BrC_6H_4	N	4 : 1	34

lates in moderate yields. The reaction was found to be regioselective.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. Merck 60 F_{254} plates were used for TLC. Column chromatography was carried out on Merck silica gel (63—200 mesh).

Ethyl glyoxylate (as a hydrate) was prepared according to a described procedure.[14]

Synthesis of ethyl 3-aminoimidazo[1,2-*a*]azine-2-carboxylates (2). A solution of an aminoazine (1.0 mmol) and ethyl glyoxylate hydrate (1.0 mmol) in toluene (15 mL) was kept at 40 °C for 30 min. Then NH_4Cl (2.0 mmol) and isonitrile (1.0 mmol) were added in one portion and the reaction mixture was refluxed for 6 to 8 h. After cooling, the mixture was washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography with CH_2Cl_2—MeOH as an eluent (gradient from 1 : 1 to 20 : 1).

Ethyl 3-(benzylamino)imidazo[1,2-*a*]pyridine-2-carboxylate (2a), a yellow oil, R_f 0.21 (CH_2Cl_2—MeOH (20 : 1)). Found (%): C, 69.01; H, 5.69. $C_{17}H_{17}N_3O_2$. Calculated (%): C, 69.14; H, 5.80. ^1H NMR, δ: 9.36—9.34 (m, 1 H); 7.51—7.39 (m, 7 H); 6.83 (t, 1 H, J = 4.8 Hz); 4.80 (s, 2 H); 4.38 (q, 2 H, J = 7.7 Hz); 1.37 (t, 3 H, CH_3, J = 7.7 Hz). ^{13}C NMR, δ: 167.2, 144.2, 143.9, 140.0, 128.2, 127.5, 126.92, 126.90, 124.1, 119.8, 113.0, 103.0, 102.5, 60.1, 51.2, 14.2.

Ethyl 3-(benzylamino)imidazo[1,2-*a*]pyrimidine-2-carboxylate (2b), a mixture with isomer **3b** (5 : 1), a yellow oil, R_f 0.22 (CH_2Cl_2—MeOH (20 : 1)). Found (%): C, 64.71; H, 5.50. $C_{16}H_{16}N_4O_2$. Calculated (%): C, 64.85; H, 5.44. ^1H NMR, δ, major isomer: 9.78—9.70, 8.87 (both m, 1 H each); 7.56—7.32 (m, 5 H); 6.72 (t, 1 H, J = 4.8 Hz); 4.85 (s, 2 H); 4.36 (q, 2 H, J = 7.7 Hz); 1.35 (t, 3 H, Me, J = 7.7 Hz); isomer **3b**: 9.78—9.70, 8.87 (both m, 1 H each); 7.56—7.32 (m, 5 H); 6.72 (t, 1 H, J = 4.8 Hz); 4.85 (s, 2 H); 4.36 (q, 2 H, J = 7.7 Hz); 1.35 (t, 3 H, Me, J = 7.7 Hz); the other signals overlap with the signals for the major isomer. Compound **2b**, ^{13}C NMR, δ: 166.4, 151.3, 149.9, 142.4, 140.1, 135.4, 128.2, 128.1, 126.9, 110.4, 100.1, 59.4, 50.6, 14.3.

Ethyl 3-(cyclohexylamino)imidazo[1,2-*a*]pyridine-2-carboxylate (2c), a yellow oil, R_f 0.22 (CH_2Cl_2—MeOH (20 : 1)). Found (%): C, 66.95; H, 7.49. $C_{16}H_{21}N_3O_2$. Calculated (%): C, 66.88; H, 7.37. ^1H NMR, δ: 9.82—9.76 (m, 1 H); 7.75—7.74 (m, 2 H, J = 8.9 Hz); 6.83 (t, 1 H, J = 4.8 Hz); 4.38 (q, 2 H, J = 7.7 Hz); 3.92—3.87 (m, 1 H); 2.03—1.85 (m, 4 H); 1.41—1.35 (m, 7 H); 1.25—1.20 (m, 2 H). ^{13}C NMR, δ: 166.3, 145.4, 144.2, 124.2, 121.2, 110.4, 105.0, 102.0, 60.1, 55.7, 33.5, 25.5, 25.3, 14.5.

Ethyl 3-(cyclohexylamino)imidazo[1,2-*a*]pyrimidine-2-carboxylate (2d), a mixture with isomer **3d** (4 : 1), a yellow oil, R_f 0.22 (CH_2Cl_2—MeOH (20 : 1)). Found (%): C, 62.14; H, 6.82. $C_{15}H_{20}N_4O_2$. Calculated (%): C, 62.48; H, 6.99. ^1H NMR, δ, major isomer: 9.80—9.63 (m, 1 H); 7.72—7.74 (d, 1 H, J = 8.8 Hz); 6.83 (t, 1 H, J = 4.8 Hz); 4.35 (q, 2 H, J = 7.7 Hz); 3.92—3.87 (m, 1 H); 2.07—1.89 (m, 4 H); 1.42—1.34 (m, 7 H); 1.26—1.19 (m, 2 H); isomer **3d**: 9.92—9.79 (m, 1 H); 7.87—7.69 (d, 1 H, J = 8.9 Hz); 6.78 (t, 1 H, J = 4.8 Hz); the other signals overlap with the signals for the major isomer. Compound **2d**, ^{13}C NMR, δ: 166.4, 151.3, 149.9, 142.4, 140.1, 135.4, 128.2, 128.1, 126.9, 110.4, 100.1, 59.4, 50.6, 14.3.

Ethyl 3-(*tert*-butylamino)imidazo[1,2-*a*]pyridine-2-carboxylate (2e), yellow crystals, m.p. 49 °C, R_f 0.16 (CH_2Cl_2—MeOH (20 : 1)). Found (%): C, 64.05; H, 7.40. $C_{14}H_{19}N_3O_2$. Calculated (%): C, 64.35; H, 7.33. ^1H NMR, δ: 9.82—9.64 (m, 1 H); 7.32—7.20 (m, 2 H, J = 9.8 Hz); 6.83 (t, 1 H, J = 4.8 Hz); 4.32 (q, 2 H, J = 7.7 Hz); 1.37 (t, 3 H, Me, J = 7.7 Hz); 1.21 (s, 9 H, Bu^t). ^{13}C NMR, δ: 166.3, 145.5, 142.2, 124.9, 119.3, 111.1, 105.0, 101.5, 60.0, 54.2, 31.1, 14.4.

Ethyl 3-(*tert*-butylamino)imidazo[1,2-*a*]pyrimidine-2-carboxylate (2f), a mixture with isomer **3f** (4 : 1), a yellow oil, R_f 0.21 (CH_2Cl_2—MeOH (20 : 1)). Found (%): C, 59.01; H, 6.69. $C_{13}H_{18}N_4O_2$. Calculated (%): C, 59.53; H, 6.92. ^1H NMR, δ, major isomer: 9.87—9.69 (m, 1 H); 8.85 (d, 1 H, J = 9.8 Hz); 6.78 (t, 1 H, J = 4.8 Hz); 4.29 (q, 2 H, J = 7.7 Hz); 1.35 (t, 3 H, Me, J = 7.7 Hz); 1.21 (s, 9 H, Bu^t); minor isomer: 8.78 (d, 1 H, J = 9.8 Hz); 6.85 (t, 1 H, J = 4.8 Hz); 1.17 (s, 9 H, Bu^t); the other signals overlap with the signals for the major isomer. Compound **2f**, ^{13}C NMR, δ: 166.2, 151.2, 150.9, 140.0, 136.1, 110.0, 100.5, 60.3, 54.3, 31.2, 14.3.

Ethyl 3-(4-bromophenylamino)imidazo[1,2-*a*]pyridine-2-carboxylate (2g), yellow crystals, m.p. 62 °C, R_f 0.19 (CH_2Cl_2—MeOH (20 : 1)). Found (%): C, 53.28; H, 3.69. $C_{14}H_{16}BrN_3O_2$. Calculated (%): C, 53.35; H, 3.92. ^1H NMR, δ: 9.60—9.41 (m, 1 H); 8.77—8.65 (m, 2 H); 7.69 (d, 2 H, J = 8.1 Hz); 7.31 (d, 2 H, J = 8.1 Hz); 6.80 (t, 1 H, J = 4.8 Hz); 4.16 (q, 2 H, J = 7.7 Hz); 1.34 (t, 3 H, J = 7.7 Hz). ^{13}C NMR, δ: 166.4, 144.2, 143.6, 140.2, 131.8, 129.02, 124.0, 121.9, 114.3, 111.2, 106.0, 60.2, 14.3.

Ethyl 3-(4-bromophenylamino)imidazo[1,2-*a*]pyrimidine-2-carboxylate (2h), a mixture with isomer **3h** (4 : 1), yellow crystals, m.p. 62—65 °C, R_f 0.17 (CH_2Cl_2—MeOH, 20 : 1). Found (%): C, 50.01; H, 3.69. $C_{13}H_{15}BrN_4O_2$. Calculated (%): C, 49.88; H, 3.63. ^1H NMR, δ, major isomer: 9.60—9.41 (m, 1 H); 8.77 (d, 1 H, J = 9.8 Hz); 7.62, 7.26 (both d, 2 H each, J = 8.0 Hz); 6.85 (t, 1 H, J = 4.8 Hz); 4.15 (q, 2 H, J = 7.7 Hz); 1.36 (t, 3 H, J = 7.7 Hz); minor isomer: 9.62—9.45 (m, 1 H); 8.68 (d, 1 H, J = 9.7 Hz); 7.57 (d, 2 H, J = 8.0 Hz); 7.19 (d, 2 H, J = 8.0 Hz); the other signals overlap with the signals for the major isomer. Compound **2h**, ^{13}C NMR, δ: 166.3, 151.3, 148.5, 150.0, 140.2, 135.1, 131.2, 122.0, 110.9, 106.3, 103.2, 60.0, 50.6, 14.2.

References

1. *Multicomponent Reactions*, Eds J. Zhu and H. Bienaymé, Wiley-VCH Verlag, Weinheim, 2005.
2. A. Dömling, *Chem. Rev.*, 2006, **106**, 17.
3. C. Blackburn, *Tetrahedron Lett.*, 1998, **39**, 9127.
4. H. Bienaymé and K. Bouzid, *Angew. Chem., Int. Ed.*, 1998, **37**, 2234.
5. K. Groebke, L. Weber, and F. Mehlin, *Synlett*, 1998, 661.
6. C. Sablarolles, G. H. Cros, J. C. Mivalet, E. Recheng, J. P. Chapat, M. Boucard, J. J. Serrano, and J. McNeil, *J. Med. Chem.*, 1984, **27**, 206.
7. Y. Maryma, K. Arami, M. Teresawa, K. Goto, T. Imayoshi, Y. Kadobe, and Y. Mizushima, *Arzneimittel-Forsh.*, 1981, **31**, 1111.
8. C. Hamdochi, J. Ezquerra, J. A. Vega, J. J. Vanquero, J. Alvarez-Builla, and B. A. Heinz, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1391.
9. J. J. Chen, A. Golebiowski, J. McClenaghan, S. R. Klopfenstein, and L. West, *Tetrahedron Lett.*, 2001, **42**, 2269.
10. R. S. Varma and D. Kumar, *Tetrahedron Lett.*, 1999, **40**, 7665.
11. G. S. Mandair, M. Light, A. Russel, M. Hursthouse, and M. Bradley, *Tetrahedron Lett.*, 2002, **43**, 4267.
12. V. Z. Parchinsky, O. Shuvalova, O. Ushakova, D. V. Kravchenko, and M. Krasavin, *Tetrahedron Lett.*, 2006, **47**, 947.
13. M. A. Lyon and T. S. Kercher, *Org. Lett.*, 2004, **6**, 4989.
14. P. D. Bailey, P. D. Smith, F. Pederson, W. Cregg, G. M. Rosair, and S. J. Teat, *Tetrahedron Lett.*, 2002, **43**, 1067.

Received November 10, 2006;
in revised form February 19, 2007