Imidazo[1,2]hetarylglyoxylates: Synthesis and Reactivity toward Nucleophiles

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Received 3 February 2010

Abstract: A practical approach to imidazo[1,2]hetarylglyoxylates via Friedel–Crafts acylation of the parent fused imidazoles with ethyl oxalyl chloride is reported. The reaction is strongly influenced by the electron-donating properties of the starting heterocycle. The generated imidazo[1,2]hetarylglyoxylates undergo standard transformations typical of α-keto esters upon reaction with various nucleophiles. All the products contain an imidazoheterocyclic scaffold which is considered a privileged structure for drug discovery.

Key words: imidazoheterocycles, acylation, glyoxylates, privileged scaffolds

The concept of privileged scaffolds, introduced to drug discovery by Evans et al. in 1988,[1] has attracted significant attention.[2] Having the ability to bind to multiple receptors, these compounds represent very useful building blocks for the synthesis of potential lead compounds. Imidazoheterocycles can be considered as privileged structures for drug discovery. In particular, they are represented by several marketed drugs including the sedatives zolpidem (**1**), alpidem (**2**) and necopidem (**3**),[3] olprinone (**4**) for the treatment of heart failure,[4] and zolimidine (**5**)[5] which is used to treat peptic ulcers and gastroesophageal reflux disease (Figure 1). Furthermore, several other examples are undergoing biological testing and preclinical evaluation.

In order to expand the range of compounds comprising the imidazo[1,2]heterocyclic scaffold, we turned our attention to the preparation of glyoxylate derivatives of general formula **6**. Compounds of this type are highly reactive 1,2-bis-electrophiles toward various nucleophiles.[6] To the best of our knowledge, the only literature approach for the synthesis of hetarylglyoxylates **6** involves metalation of halides **7** followed by quenching the resulting carbanions with a dialkyl oxalate.[7] Herein, we report an alternative method for the synthesis of compounds **6** via Friedel–Crafts acylation of the parent imidazo[1,2]heterocycles **8** with ethyl oxalyl chloride (Scheme 1).[8]

It should be noted that Friedel–Crafts acylation of fused imidazoles of type **8** is not well documented in the literature.[9] The conditions used to achieve analogous transformations depend strongly on the electron-donating properties of the heterocyclic substrate. Taking this into consideration, we selected a range of imidazoles **8a–h** possessing different electronic properties as model compounds for this study (Figure 2).

The reactions of heterocyclic compounds **8** with ethyl oxalyl chloride were performed by heating the substrates in 1,4-dioxane or xylene. The following results were obtained: acylation of imidazo[1,2-*a*]pyridines **8a**,**b** occurred in 1,4-dioxane at reflux, however, due to their low basicity the products **6a**,**b** formed slowly as their free bases. The acylation of imidazo[1,2-*a*]pyrimidines **8c**,**d** was accomplished by prolonged heating of the substrates in xylene at reflux temperature to give compounds **6c**,**d** as the free bases. Acylation of imidazo[2,1-*b*][1,3]thiazoles

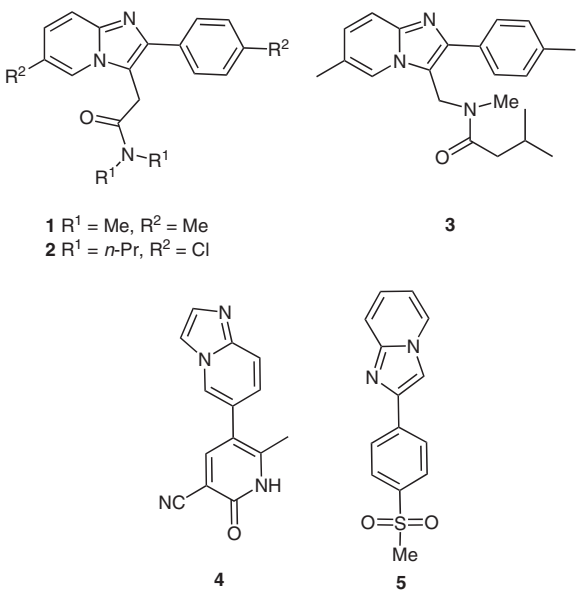
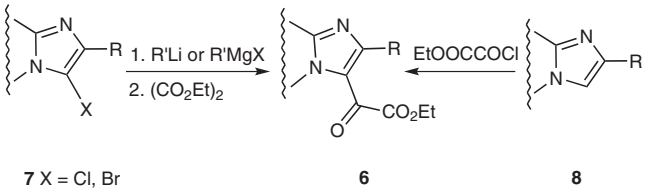


Figure 1 Marketed drugs containing the imidazo[1,2]heterocyclic scaffold



Scheme 1 Syntheses of imidazo[1,2]hetarylglyoxylates

SYNTHESIS 2010, No. 10, pp 1692–1696
Advanced online publication: 15.04.2010
DOI: 10.1055/s-0029-1218739; Art ID: P01310SS

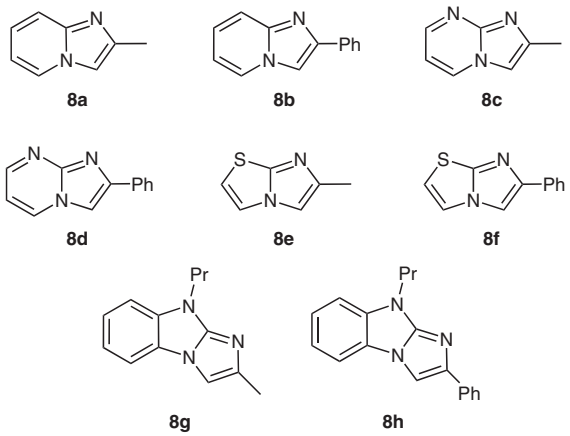
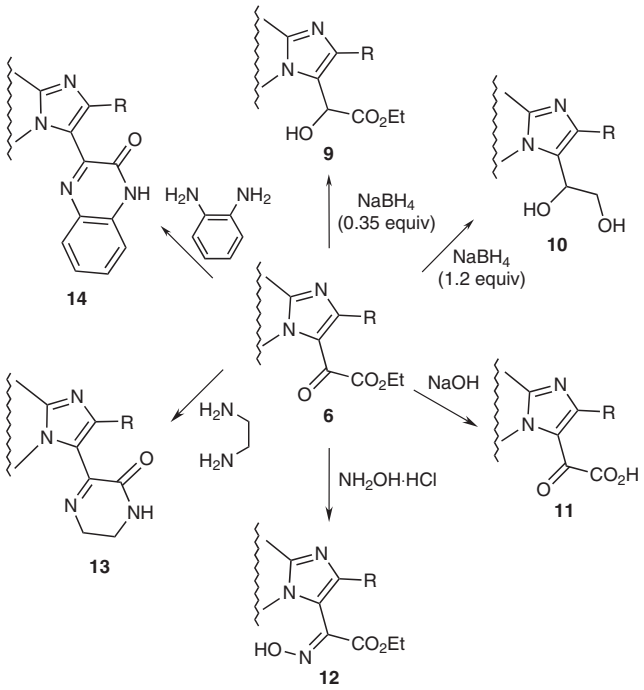


Figure 2 Structures of the imidazo[1,2]heterocycles **8a–h** used in this study

8e,**f** proceeded smoothly in 1,4-dioxane at reflux temperature to afford the corresponding products **6e**,**f** as their hydrochloride salts. Finally, the acylation of imidazo[1,2-*a*]benzimidazoles **8g**,**h** in 1,4-dioxane resulted in only 40–50% yields of the products **6g**,**h**. Higher yields of **6g**,**h** (75–85%) were obtained by performing the reaction in xylene at reflux temperature; the products were again formed as their hydrochloride salts (Table 1).

From the results listed in Table 1, the following order of reactivity was observed in the acylation reaction: imidazo[2,1-*b*]thiazoles > imidazo[1,2-*a*]benzimidazoles > imidazo[1,2-*a*]pyridines > imidazo[1,2-*a*]pyrimidines. Moreover, the reactivities of the heterocycles possessing an electron-withdrawing phenyl substituent (**8b**,**d**,**f**,**h**) were similar or lower than those of the corresponding methyl analogues (**8a**,**c**,**e**,**g**). These results correlate well



Scheme 2 Reactions of imidazo[1,2]hetarylglyoxylates **6** with various nucleophiles

Table 1 Acylation of Fused Imidazoles **8a–h**

Imidazole	Product	Solvent	Yield
8a	**6a**	1,4-dioxane	76
8b	**6b**	1,4-dioxane	71
8c	**6c**	xylene	73
8d	**6d**	xylene	68
8e	**6e**	1,4-dioxane	79
8f	**6f**	1,4-dioxane	82
8g	**6g**	xylene	85
8h	**6h**	xylene	75

with reported data on the electron-donating properties of the starting heterocycles.[10]

Next, various standard reactions of hetarylglyoxylates **6** (see experimental section for selected examples) with H-, O- and N-nucleophiles were explored (Scheme 2). Reduction of **6** with sodium borohydride resulted in the formation of hydroxy esters **9** or diols **10** depending on the number of equivalents of the reducing reagent used for the reaction. Alkaline hydrolysis of **6** afforded glyoxylic acids **11** whilst reaction of **6** with hydroxylamine hydrochloride yielded the corresponding oximes **12**. Finally, 5,6-dihydropyrazin-2-ones **13** and quinoxalin-2-ones **14** were obtained when glyoxylates **6** were reacted with ethylenediamine and *o*-phenylenediamine, respectively.

In conclusion, a simple and practical one-step procedure for the synthesis of imidazo[1,2]hetarylglyoxylates **6** has

been developed. The products were shown to undergo standard transformations characteristic of α-keto esters upon reaction with various H-, O- and N-nucleophiles.

Fused imidazoles **8a**,[11] **8b**,[12] **8c**,**d**,**g**,**h**,[9b] **8e**[13] and **8f**[14] were synthesized according to the literature. Solvents were purified using standard procedures. Starting materials were purchased from Acros, Merck and Fluka. Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer at 499.9 MHz (^{1}H) and 124.9 MHz (^{13}C), respectively, in DMSO-d_6 as solvent. Chemical shifts are reported in ppm downfield with respect to TMS as the internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument using atmospheric pressure chemical ionization (APCI). Elemental analysis (C, H, N and S) data was obtained using an Elementar Vario MICRO Cube CHNS/O analyzer.

Hetarylglyoxylates 6a–d; General Procedure

To a soln of **8a**–**d** (0.1 mol) in anhyd 1,4-dioxane or xylene (40 mL, see Table 1) was added ethyl oxalyl chloride (16.8 mL, 0.15 mol) dropwise. The mixture was heated at reflux for 7–8 h, then allowed to cool and evaporated. The residue was triturated with H_2O (80 mL) and the resulting precipitate was either removed by filtration and washed with H_2O (20 mL) (**6a**,**c**,**d**) or extracted with CH_2Cl_2 (3 × 60 mL) (**6b**). In the latter case, the combined organic extracts were dried over Na_2SO_4 and evaporated to afford the product.

Ethyl (2-Methylimidazo[1,2-*a*]pyridin-3-yl)(oxo)acetate (6a)

Colorless solid; yield: 76%; mp 74 °C.

^{1}H NMR (DMSO-d_6): δ = 9.42 (1 H, t, *J* = 6.8 Hz), 7.71 (2 H, m), 7.13 (1 H, t, *J* = 6.8 Hz), 4.47 (2 H, q, *J* = 7.0 Hz), 2.48 (3 H, s), 1.32 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 175.2, 164.8, 156.4, 148.4, 132.3, 129.2, 117.6, 117.1, 116.8, 62.9, 16.0, 14.2.

MS (APCI): *m*/*z* = 233 [M + H$^+$].

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.31; H, 4.98; N, 12.17.

Ethyl (2-Phenylimidazo[1,2-*a*]pyridin-3-yl)(oxo)acetate (6b)

Colourless oil; yield: 71%.

^{1}H NMR (DMSO-d_6): δ = 9.61 (1 H, d, *J* = 6.9 Hz), 7.95 (1 H, d, *J* = 8.8 Hz), 7.81 (1 H, dd, *J* = 8.8, 6.9 Hz), 7.54–7.60 (5 H, m), 7.41 (1 H, t, *J* = 6.9 Hz), 3.46 (2 H, d, *J* = 7.0 Hz), 0.92 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 176.5, 163.6, 158.1, 148.2, 133.8, 132.5, 130.1, 130.0, 129.2, 128.8, 117.8, 117.7, 117.2, 62.3, 13.6.

MS (APCI): *m*/*z* = 295 [M + H$^+$].

Ethyl (2-Methylimidazo[1,2-*a*]pyrimidin-3-yl)(oxo)acetate (6c)

Colorless solid; yield: 73%; mp 108 °C.

^{1}H NMR (DMSO-d_6): δ = 9.72 (1 H, d, *J* = 6.8 Hz), 8.88 (1 H, d, *J* = 4.2 Hz), 7.45 (1 H, dd, *J* = 6.8, 4.2 Hz), 4.42 (2 H, q, *J* = 7.0 Hz), 2.51 (3 H, s), 1.35 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 175.7, 164.4, 157.9, 155.9, 151.1, 137.6, 116.3, 112.9, 63.2, 16.7, 14.2.

MS (APCI): *m*/*z* = 234 [M + H$^+$].

Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.29; H, 4.70; N, 17.73.

Ethyl (2-Phenylimidazo[1,2-*a*]pyrimidin-3-yl)(oxo)acetate (6d)

Colorless solid; yield: 68%; mp 124–126 °C.

^{1}H NMR (DMSO-d_6): δ = 9.78 (1 H, d, *J* = 6.8 Hz), 8.93 (1 H, d, *J* = 4.2 Hz), 7.49 (1 H, dd, *J* = 6.8, 4.2 Hz), 7.60–7.50 (5 H, m), 3.62 (2 H, q, *J* = 7.0 Hz), 0.88 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 176.9, 163.2, 159.0, 156.4, 150.8, 137.8, 130.5, 130.0, 129.0, 116.2, 113.2, 62.5, 13.6.

MS (APCI): *m*/*z* = 266 [M + H$^+$].

Hetarylglyoxylates 6e–h; General Procedure

To a soln of **8e**–**f** (0.1 mol) in anhyd 1,4-dioxane or xylene (40 mL, see Table 1) was added ethyl oxalyl chloride (16.8 mL, 0.15 mol) dropwise. The resulting mixture was heated at reflux for 7–8 h, then allowed to cool and evaporated. The residue was treated with H_2O (100 mL) and neutralized with 20% aq Na_2CO_3 (100 mL) soln. The product was either filtered and washed with H_2O (20 mL) (**6f**,**h**) or extracted with CH_2Cl_2 (3 × 60 mL) (**6e**,**g**). In the latter case, the combined organic extracts were dried over Na_2SO_4 and evaporated.

Ethyl (6-Methylimidazo[2,1-*b*][1,3]thiazol-5-yl)(oxo)acetate (6e)

Colorless solid; yield: 79%; mp 63–65 °C.

^{1}H NMR (DMSO-d_6): δ = 8.30 (1 H, d, *J* = 4.5 Hz), 7.58 (1 H, d, *J* = 4.5 Hz), 4.41 (2 H, q, *J* = 7.0 Hz), 2.40 (3 H, s), 1.32 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 173.8, 164.5, 156.5, 156.4, 122.0, 121.2, 117.4, 61.6, 16.1, 14.2.

MS (APCI): *m*/*z* = 239 [M + H$^+$].

Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.08; H, 3.99; N, 11.62; S, 13.31.

Ethyl (6-Phenylimidazo[2,1-*b*][1,3]thiazol-5-yl)(oxo)acetate (6f)

Colorless solid; yield: 82%; mp 90–92 °C.

^{1}H NMR (DMSO-d_6): δ = 8.50 (1 H, d, *J* = 4.5 Hz), 8.15 (2 H, d, *J* = 7.3 Hz), 7.87 (1 H, d, *J* = 4.5 Hz), 7.68 (2 H, t, *J* = 7.3 Hz), 7.45 (1 H, t, *J* = 7.3 Hz), 4.52 (2 H, q, *J* = 7.0 Hz), 0.92 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 173.2, 153.9, 159.2, 147.9, 133.5, 128.7, 127.3, 121.2, 122.6, 117.4, 61.7, 15.8.

MS (APCI): *m*/*z* = 301 [M + H$^+$].

Ethyl (2-Methyl-9-propyl-9*H*-imidazo[1,2-*a*]benzimidazol-3-yl)(oxo)acetate (6g)

Colorless solid; yield: 85%; mp 121 °C.

^{1}H NMR (DMSO-d_6): δ = 8.44 (1 H, d, *J* = 7.8 Hz), 7.70 (1 H, d, *J* = 8.0 Hz), 7.41 (1 H, dd, *J* = 8.0, 7.0 Hz), 7.28 (1 H, dd, *J* = 8.0, 7.0 Hz), 4.22 (4 H, m), 2.40 (3 H, s), 1.84 (2 H, m), 1.32 (3 H, t, *J* = 7.0 Hz), 0.85 (3 H, t, *J* = 7.8 Hz).

^{13}C NMR (DMSO-d_6): δ = 172.7, 165.8, 157.8, 151.0, 135.1, 125.2, 124.7, 121.7, 119.7, 115.6, 111.6, 62.8, 44.9, 21.9, 16.5, 14.2, 11.4.

MS (APCI): *m*/*z* = 314 [M + H$^+$].

Ethyl (2-Phenyl-9-propyl-9*H*-imidazo[1,2-*a*]benzimidazol-3-yl)(oxo)acetate (6h)

Colorless solid; yield: 75%; mp 142–144 °C.

^{1}H NMR (DMSO-d_6): δ = 8.55 (1 H, d, *J* = 7.5 Hz), 7.80 (1 H, d, *J* = 7.5 Hz), 7.6–7.5 (5 H, m), 7.49 (1 H, t, *J* = 7.5 Hz), 7.35 (1 H, t, *J* = 7.5 Hz), 4.30 (2 H, t, *J* = 7.0 Hz), 3.65 (2 H, q, *J* = 7.4 Hz), 1.94 (2 H, m), 0.90 (6 H, 2 × t, *J* = 7.2 Hz).

^{13}C NMR (DMSO-d_6): δ = 173.5, 164.6, 159.2, 159.1, 150.9, 135.3, 134.3, 130.0, 129.9, 128.7, 125.0, 121.8, 119.6, 115.8, 111.6, 62.1, 45.0, 22.0, 13.7, 11.5.

MS (APCI): *m*/*z* = 376 [M + H$^+$].

Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.07; H, 5.63; N, 11.03.

Hydroxy Esters 9; General Procedure

Hetarylglyoxylate **6** (0.01 mol) was dissolved in anhyd THF (25 mL), cooled to –78 °C, and $NaBH_4$ (0.13 g, 0.0035 mol) was added with stirring. The cooling bath was removed and the mixture was stirred for 2–3 h and then quenched with H_2O (25 mL). The mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and evaporated. The residue was dissolved in acetone (2–3 mL) and allowed to stand at –4 °C for 10–12 h. The precipitate that formed was removed by filtration and washed with acetone (1 mL).

Ethyl hydroxy(2-methylimidazo[1,2-*a*]pyridin-3-yl)acetate (9a)

Colorless solid; yield: 52%; mp 132 °C (acetone).

^{1}H NMR (DMSO-d_6): δ = 8.42 (1 H, d, *J* = 6.9 Hz), 7.45 (1 H, d, *J* = 8.8 Hz), 7.22 (1 H, dd, *J* = 8.8, 6.9 Hz), 6.87 (1 H, t, *J* = 6.9 Hz), 6.21 (1 H, d, *J* = 5.2 Hz), 5.15 (1 H, d, *J* = 5.2 Hz), 4.17–4.02 (2 H, m), 2.31 (3 H, s), 1.08 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 171.5, 144.2, 141.4, 126.0, 124.9, 118.0, 116.6, 112.1, 64.6, 61.4, 14.5, 13.7.

MS (APCI): *m*/*z* = 235 [M + H$^+$].

Ethyl Hydroxy(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)acetate (9e)

Colorless solid; yield: 53%; mp 134 °C (acetone).

^{1}H NMR (DMSO-d_6): δ = 7.70 (1 H, d, *J* = 4.5 Hz), 7.18 (1 H, d, *J* = 4.5 Hz), 6.25 (1 H, s), 5.45 (1 H, s), 4.16–4.02 (2 H, m), 2.20 (3 H, s), 1.11 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 171.4, 148.2, 141.6, 120.3, 120.0, 112.4, 64.9, 61.3, 14.4, 13.8.

MS (APCI): *m*/*z* = 241 [M + H$^+$].

Anal. Calcd for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66; S, 13.34. Found: C, 50.31; H, 5.07; N, 11.81; S, 13.69.

Diols 10; General Procedure

Hetarylglyoxylate **6** (0.01 mol) was dissolved in anhyd THF (25 mL), cooled to 5–10 °C, and $NaBH_4$ (0.45 g, 0.012 mol) was added with stirring. The mixture was stirred for 2–3 h, quenched with H_2O (25 mL) and stirred for 1 h. The product was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phase dried over Na_2SO_4 and evaporated.

1-(2-Phenylimidazo[1,2-*a*]pyrimidin-3-yl)ethane-1,2-diol (10d)

Colorless oil; yield: 63%.

^{1}H NMR (DMSO-d_6): δ = 9.10 (1 H, dd, *J* = 6.8, 2.0 Hz), 8.53 (1 H, dd, *J* = 4.3, 2.0 Hz), 7.82 (2 H, d, *J* = 7.2 Hz), 7.48 (2 H, t, *J* = 7.2 Hz), 7.41 (1 H, t, *J* = 7.2 Hz), 7.02 (1 H, dd, *J* = 6.8, 4.3 Hz), 5.83 (1 H, d, *J* = 6.3 Hz), 5.22 (1 H, q, *J* = 6.3 Hz), 5.11 (1 H, t, *J* = 6.1 Hz), 3.98–3.82 (2 H, m).

^{13}C NMR (DMSO-d_6): δ = 150.4, 147.8, 144.0, 136.3, 134.6, 129.3, 128.9, 128.4, 120.3, 108.3, 66.9, 64.3.

MS (APCI): *m*/*z* = 256 [M + H$^+$].

1-(2-Methyl-9-propyl-9*H*-imidazo[1,2-*a*]benzimidazol-3-yl)ethane-1,2-diol (10g)

Colorless oil; yield: 58%.

^{1}H NMR (DMSO-d_6): δ = 8.07 (1 H, d, *J* = 8.1 Hz), 7.70 (1 H, d, *J* = 8.1 Hz), 7.42 (1 H, dd, *J* = 8.1, 7.0 Hz), 7.30 (1 H, dd, *J* = 8.1, 7.0 Hz), 5.95 (1 H, d, *J* = 6.1 Hz), 4.97 (1 H, m), 4.87 (1 H, m), 4.63 (1 H, m), 3.75 (1 H, m), 3.45–3.35 (2 H, m), 2.33 (3 H, s), 1.9–1.75 (2 H, m), 0.87 (3 H, t, *J* = 7.8 Hz).

^{13}C NMR (DMSO-d_6): δ = 149.1, 140.9, 136.0, 128.6, 125.0, 123.4, 120.2, 114.7, 110.1, 66.4, 64.7, 44.5, 21.8, 14.9, 11.7.

MS (APCI): *m*/*z* = 274 [M + H$^+$].

Glyoxylic Acids 11; General Procedure

Hetarylglyoxylate **6** (0.1 mol) was dissolved in 30% aq NaOH (50 mL) soln and the resulting mixture was stirred at ambient temperature for 30 h, and then at 70–75 °C for 30–50 min. After cooling, the mixture was neutralized with 6 M HCl until pH 7. The precipitate formed (if any) was filtered and washed with cold H_2O (10 mL). If the precipitate did not form, the solution was evaporated to 80–100 mL and left at 4 °C for 10–12 h, then worked up as described above.

(2-Methylimidazo[1,2-*a*]pyridin-3-yl)(oxo)acetic Acid (11a)

Colorless solid; yield: 82%; mp >220 °C.

^{1}H NMR (DMSO-d_6): δ = 9.54 (1 H, d, *J* = 6.8 Hz), 7.82 (1 H, d, *J* = 8.7 Hz), 7.70 (1 H, dd, *J* = 8.7, 6.8 Hz), 7.35 (1 H, t, *J* = 6.8 Hz), 2.55 (3 H, s). COOH proton is exchangeable with deuterium protium oxide (HDO).

^{13}C NMR (DMSO-d_6): δ = 178.1, 167.1, 155.6, 147.9, 131.9, 129.1, 117.5, 117.0, 116.6, 15.8.

MS (APCI): *m*/*z* = 205 [M + H$^+$].

(6-Methylimidazo[2,1-*b*][1,3]thiazol-5-yl)(oxo)acetic Acid (11e)

Colorless solid; yield: 89%; mp >220 °C.

^{1}H NMR (DMSO-d_6): δ = 8.63 (1 H, d, *J* = 4.4 Hz), 7.62 (1 H, d, *J* = 4.4 Hz), 2.41 (3 H, s). COOH proton is exchangeable with HDO.

^{13}C NMR (DMSO-d_6): δ = 176.1, 166.8, 155.8, 153.1, 121.9, 121.0, 117.2, 15.9.

MS (APCI): *m*/*z* = 211 [M + H$^+$].

Oximes 12; General Procedure

To a soln of hetarylglyoxylate **6** (0.0125 mol) in EtOH (50 mL) was added a soln of hydroxylamine hydrochloride (6.3 g, 0.09 mol) and sodium acetate trihydrate (13 g, 0.09 mol) in H_2O (50 mL). The resulting mixture was heated at reflux for 2 d, then cooled, evaporated to 20–30 mL of the original volume, and diluted with H_2O (80 mL). The obtained precipitate was filtered and washed with H_2O (20 mL).

Ethyl (2*E*/*Z*)-(Hydroxyimino)(2-methylimidazo[1,2-*a*]pyridin-3-yl)acetate (12a)

Colorless solid; yield: 91%; mp 176 °C.

^{1}H NMR (DMSO-d_6): δ (1:1 mixture of *E*/*Z* isomers) = 12.72 (0.5 H, s), 11.69 (0.5 H, s), 9.09 (0.5 H, d, *J* = 6.9 Hz), 7.77 (0.5 H, d, *J* = 6.9 Hz), 7.64 (0.5 H, d, *J* = 8.7 Hz), 7.53 (0.5 H, d, *J* = 8.7 Hz), 7.42 (0.5 H, dd, *J* = 8.7, 6.9 Hz), 7.30 (0.5 H, dd, *J* = 8.7, 6.9 Hz), 7.12 (0.5 H, t, *J* = 6.9 Hz), 6.93 (0.5 H, t, *J* = 6.9 Hz), 4.36 (2 × 0.5 H, q, *J* = 7.1 Hz), 4.25 (2 × 0.5 H, q, *J* = 7.1 Hz), 2.30 (3 × 0.5 H, s), 2.18 (3 × 0.5 H, s), 1.30 (3 × 0.5 H, t, *J* = 7.1 Hz), 1.32 (3 × 0.5 H, t, *J* = 7.1 Hz).

^{13}C NMR (DMSO-d_6): δ (1:1 mixture of *E*/*Z* isomers) = 163.2, 163.1, 145.8, 145.7, 145.1, 144.5, 144.2, 140.0, 128.0, 127.3, 127.2, 125.7, 116.9, 116.4, 114.2, 112.3, 112.2, 111.9, 62.3, 62.0, 15.0, 14.8, 14.5, 14.3.

MS (APCI): *m*/*z* = 248 [M + H$^+$].

Ethyl (2*E*/*Z*)-(Hydroxyimino)(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)acetate (12e)

Colorless solid; yield: 94%; mp 180 °C.

^{1}H NMR (DMSO-d_6): δ (1:1 mixture of *E*/*Z* isomers) = 13.08 (0.5 H, s), 11.77 (0.5 H, s), 7.98 (0.5 H, d, *J* = 4.5 Hz), 7.61 (0.5 H, d,

J = 4.5 Hz), 7.38 (0.5 H, d, J = 4.5 Hz), 7.20 (0.5 H, d, J = 4.5 Hz), 4.35 (2 × 0.5 H, q, J = 7.0 Hz), 4.26 (2 × 0.5 H, q, J = 7.0 Hz), 2.23 (3 × 0.5 H, s), 2.12 (3 × 0.5 H, s), 1.30 (3 × 0.5 H, t, J = 7.0 Hz), 1.21 (3 × 0.5 H, t, J = 7.0 Hz).

^{13}C NMR (DMSO-d_6): δ (1:1 mixture of *E*/*Z* isomers) = 163.3, 163.2, 151.2, 149.2, 145.2, 145.0, 143.1, 143.0, 121.7, 121.4, 114.6, 114.5, 112.1, 112.1, 62.3, 61.8, 15.5, 14.6, 14.4, 14.2.

MS (APCI): m/z = 254 [M + H$^+$].

5,6-Dihydropyrazin-2-ones 13 and Quinoxalin-2-ones 14; General Procedure

A soln of 1,2-ethylenediamine (0.85 mL, 0.013 mol) or *o*-phenylenediamine (1.38 g, 0.013 mol) was added to a soln of hetarylglyoxylate **6** (0.0125 mol) in anhyd MeCN (25 mL). The reaction mixture was heated at reflux for 2 d, then allowed to cool and left to stand at –4 °C for 10–12 h. The resulting precipitate was filtered and washed with MeCN (5–10 mL).

3-(6-Methylimidazo[2,1-*b*][1,3]thiazol-5-yl)-5,6-dihydropyrazin-2(1*H*)-one (13e)

Colorless solid; yield: 67%; mp >220 °C (MeCN).

^{1}H NMR (DMSO-d_6): δ = 8.65 (1 H, s), 7.96 (1 H, d, J = 4.5 Hz), 7.23 (1 H, d, J = 4.5 Hz), 3.82 (2 H, t, J = 6.1 Hz), 3.31 (2 H, t, J = 6.1 Hz), 2.32 (3 H, s).

^{13}C NMR (DMSO-d_6): δ = 155.9, 155.6, 150.4, 148.6, 122.1, 120.6, 112.6, 48.6, 38.4, 16.8.

MS (APCI): m/z = 235 [M + H$^+$].

Anal. Calcd for $C_{10}H_{10}N_4OS$: C, 51.27; H, 4.30; N, 23.91; S, 13.69. Found: C, 51.02; H, 4.68; N, 23.90; S, 14.02.

3-(2-Methylimidazo[1,2-*a*]pyridin-3-yl)quinoxalin-2(1*H*)-one (14a)

Colorless solid; yield: 84%; mp >220 °C (MeCN).

^{1}H NMR (DMSO-d_6): δ = 12.63 (1 H, s), 8.73 (1 H, d, J = 6.7 Hz), 7.82 (1 H, d, J = 8.8 Hz), 7.62–7.52 (2 H, m), 7.37 (1 H, d, J = 8.1 Hz), 7.41–7.33 (2 H, m), 6.97 (1 H, d, J = 8.4 Hz), 2.50 (3 H, s).

^{13}C NMR (DMSO-d_6): δ = 154.4, 149.6, 147.2, 145.6, 132.6, 132.2, 130.6, 128.9, 128.0, 126.4, 123.9, 118.2, 116.4, 115.7, 112.5, 16.2.

MS (APCI): m/z = 277 [M + H$^+$].

Anal. Calcd for $C_{16}H_{12}N_4$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.31; H, 4.25; N 20.33.

3-(6-Methylimidazo[2,1-*b*][1,3]thiazol-5-yl)quinoxalin-2(1*H*)-one (14e)

Colorless solid; yield: 81%; mp >220 °C (MeCN).

^{1}H NMR (DMSO-d_6): δ = 8.13 (1 H, d, J = 4.5 Hz), 7.80 (1 H, d, J = 4.5 Hz), 7.54 (1 H, t, J = 8.3 Hz), 7.37–7.28 (2 H, m), 7.27 (1 H, d, J = 8.1 Hz), 2.42 (3 H, s). NH proton is exchangeable with HDO.

^{13}C NMR (DMSO-d_6): δ = 154.2, 150.7, 149.0, 148.8, 132.6, 131.9, 130.1, 128.7, 123.9, 123.0, 120.9, 115.6, 112.3, 17.1.

MS (APCI): m/z = 283 [M + H$^+$].

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