Applications of Ethyl Carboethoxyformimidate to Heterocyclic Synthesis: Preparation of Condensed Pyrazinones and 1,4-Oxazinones

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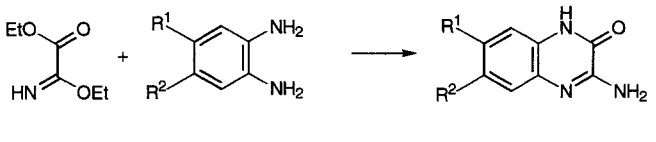
Aromatic and heteroaromatic 1,2-diamines, and *o*-aminophenols, condense smoothly with ethyl carboethoxyformimidate to give good yields of condensed pyrazinones and 1,4-oxazinones.

Imidates are valuable and versatile electrophilic reagents for organic synthesis. Ethyl carboethoxyformimidate **(1)**, which is readily available in bulk from ethyl cyanoformate and is easily handled either as such or as the hydrochloride salt, is a potentially very attractive 1,2-di-electrophile for heterocyclic synthesis whose utility has been developed only recently. Early work with **1** showed that dimerisation and trimerisation occurred readily, but that complex mixtures of products were often obtained in low yields from apparently straightforward reactions with nucleophiles.[1-3] We have been studying the chemistry of imidate **1** for some time, and have shown that the two distinctly different electrophilic carbon atoms can react with nucleophiles in three different ways (Scheme 1).[4,5] Many of these reactions are either highly chemoselective or chemospecific, the imidate carbon being the more electrophilic, and by appropriate choice of nucleophile and reaction conditions a wide variety of otherwise difficultly accessible heterocycles can be obtained easily in high yield. In the present report we describe the 2,3-cyclisation pathway with the imidate **1**, using aromatic and heteroaromatic 1,2-diamines and *o*-aminophenols as dinucleophiles.

Reaction of the hydrochloride salt of **1** with 1,2-phenylenediamine **(2a)** gave only polymeric material. When the free imidate was used, however, reaction proceeded smoothly but slowly at room temperature when ethanol was used as solvent. At reflux temperature reaction was complete after one hour, and 3-aminoquinoxalin-2(1*H*)-one **(3a)** was obtained in quantitative yield (Scheme 2). The structure of **3a** was established by analytical and spectroscopic means, and by its conversion into the known 1-methyl derivative by base-catalysed alkylation with dimethyl sulfate.[6] 4,5-Dimethyl- and 4,5-dichloro-1,2-phenylenediamine, **(2b)** and **(2c)**, reacted analogously to give the aminoquinoxalinones **3b** and **3c**. The 1,2-phenylenediamines **2d** and **2e** were then used to probe the chemoselectivity of the initial nucleophile-to-electrophile condensation. In the case of the methyldiamine **2d** the effect of the methyl group on the basicity of the amino group para to it is very small. An excellent yield of condensation product was obtained, but ^{13}C NMR spectroscopy clearly showed this to be essentially a 1:1 mixture of the 6- and 7-methylquinoxalinones **3d** (6-: $R^1 = H$, $R^2 = CH_3$; 7-: $R^1 = CH_3$, $R^2 = H$). By contrast, the electronic effect of the nitro group in **2e** is such that reaction with **1** gave only the 6-nitroquinoxalinone **3e**.

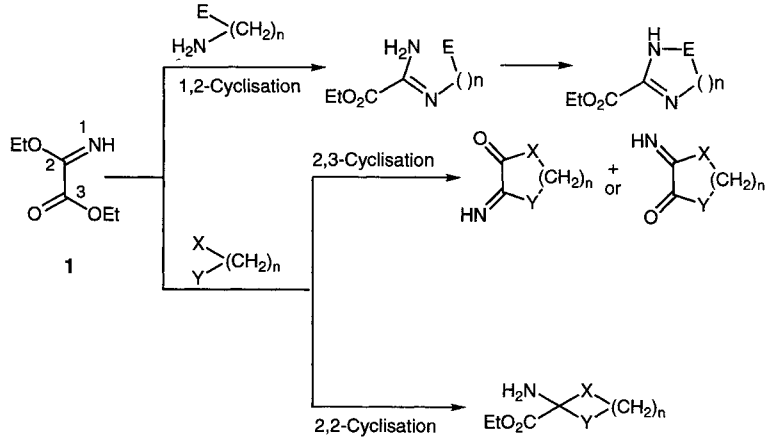


1 **2** **3**

	R^1	R^2	3, %
a	H	H	99
b	CH_3	CH_3	80
c	Cl	Cl	58[a]
d	H	CH_3	89[a,b]
e	H	NO_2	92

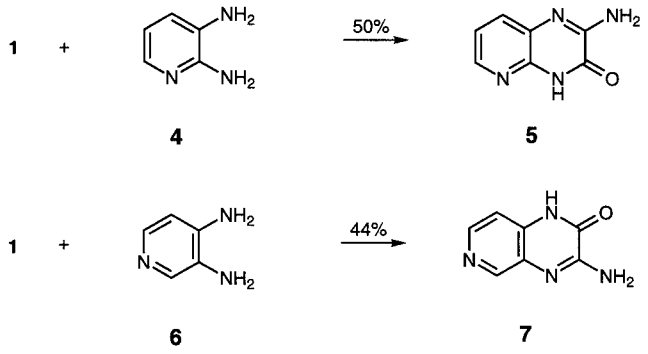
[a] Based on recovered diamine.
[b] As a 1:1 mixture of $R^1 = H$, $R^2 = CH_3$ and $R^1 = CH_3$, $R^2 = H$ (^{13}C NMR).

Scheme 2



Scheme 1

Application of the above methodology to the construction of heterofused pyrazinones was straightforward. Condensation of 2,3- and 3,4-diaminopyridine, **4** and **6**, with **1**, for example, gave the pyridopyrazinones **5** and **7**, although in modest yield. Rather better results were obtained for the very important conversion of 4,5-diaminopyrimidines into aminopteridinones.

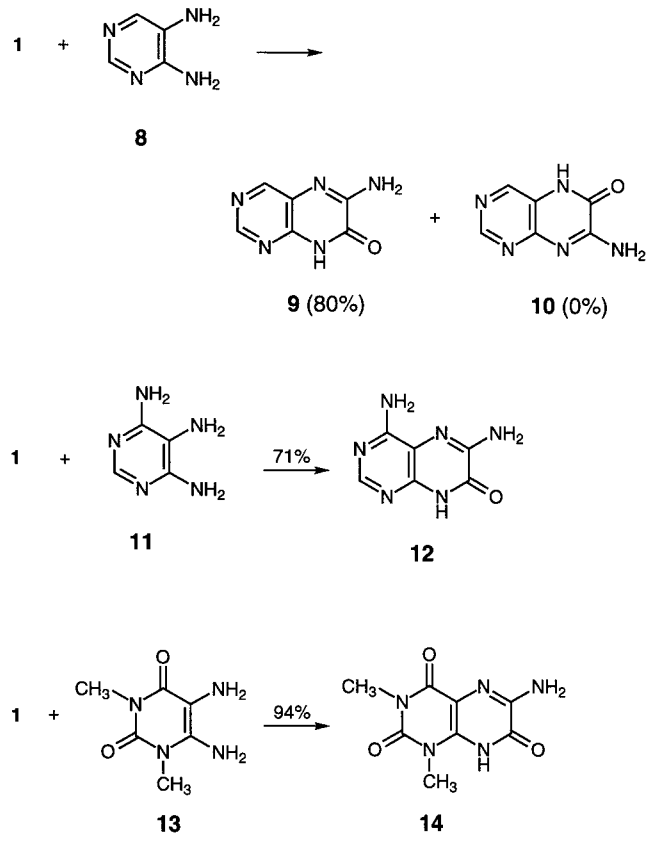


It has been recorded that over 90 % of all pteridines have been prepared by condensation of a 4,5-diaminopyrimidine with a 1,2-dicarbonyl compound (or equivalent),[7] but that use of unsymmetrical 1,2-dicarbonyl compounds almost always gives mixtures.[8,9] Clearly, condensation of **1** with 4,5-diaminopyrimidine **(8)** could in principle give either 6-aminopteridin-7-one **(9)** or 7-aminopteridin-6-one **(10)**, or some mixture of the two. In practice, a single pure product was obtained in 80 % yield, the spectral data for which were compatible with either of the pteridinone structures **9** or **10**. That the product was the 6-amino isomer **9**, arising by chemospecific attack of the more nucleophilic 5-amino group of **8** at the imidate carbon of **1**, was established by independent synthesis of both **9** and **10**[10] and comparison of physical and spectroscopic properties. Treatment of 4,5,6-triaminopyrimidine **(11)** with **1** failed to result in any condensation, but use of the sulfate salt of **11** led to smooth formation of 4,6-diaminopteridin-7-one **(12)** in 71 % yield. 5,6-Diamino-1,3-dimethyluracil **(13)** reacted cleanly with **1** to give an almost quantitative yield of **14**.

From the above results it was expected that *o*-aminophenols would react chemospecifically with **1** to give 3-aminobenzoxazin-2-ones and this proved to be the case (Scheme 3). As before, all reactions proceeded smoothly in ethanol at reflux.

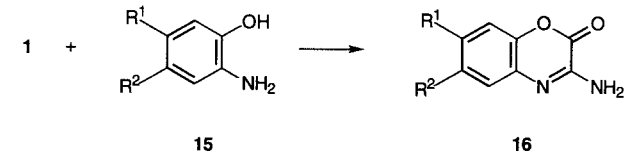
These results demonstrate the utility of ethyl carboethoxyformimidate as a 1,2-dielectrophile for the synthesis of condensed six-membered heterocyclic systems. The imidate carbon is the more electrophilic of the two centres in **1**, and when 1,2-dinucleophiles are used the reactions are highly or completely chemospecific provided the two electron-rich centres differ sufficiently in nucleophilicity.

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on Nujol mulls between salt plates in a Perkin-Elmer 457 instrument. ^{1}H NMR spectra (δ_H)



and ^{13}C NMR spectra (δ_C) were recorded on a Jeol FX-90Q spectrometer operating at 90 and 22.2 MHz, respectively. Mass spectra were recorded on a Kratos MS 25 instrument. Microanalyses were performed by Mr A. W. R. Saunders at the University of East Anglia, using a Carlo Erba elemental analyser, model 1102.

Ethyl Carboethoxyformimidate (1):
Anhyd HCl gas was bubbled slowly through a solution of ethyl cyanoformate (16.5 g, 0.166 mol) in a mixture of absolute EtOH (9.6 mL, 0.166 mol) and anhyd petroleum ether (bp 40–60 °C; 30 mL) previously cooled to and maintained at −15 °C until the weight of the flask had increased by 6.5–7.0 g. The resulting solution was stirred for 4 h, during which time the temperature was allowed to rise to 5 °C. The solution was then kept for two days in the refrigerator at 0–2 °C. The hydrochloride salt which had separated was collected by filtration, washed with ice-cold absolute EtOH (4 × 10 mL) and ice-cold anhyd Et_2O (4 × 10 mL). This gave 28.5 g



	R^1	R^2	16, %
a	H	H	83
b	H	CH_3	67
c	CH_3	H	65
d	H	Cl	76
e	H	NO_2	65

Scheme 3

(95%) of the imidate hydrochloride of **1** as colourless plates, mp 73–76°C (dec.) (Lit.[1] mp 73°C). A solution of K_2CO_3 (23.5 g, 0.18 mol) in ice-water (50 mL) and Et_2O (20 mL) was added to the hydrochloride salt, the mixture was stirred and the organic layer was separated. The aqueous layer was then extracted with a further portion of Et_2O (5 mL) and the combined organic layers were dried (K_2CO_3) at 0–2°C. The organic solution was then filtered and the solvent was removed by evaporation in vacuo. Distillation under reduced pressure gave pure **1** (19 g, 79.5%) as a colourless liquid, bp 73°C/16 Torr (Lit.[1] bp 73°C/16 Torr).

Aminoquinoxalinones 3a–e and Aminobenzoxazinones 16a–e; General Procedure:

A solution or suspension of the diamine or the aminophenol (0.010 mol) and ethyl carboethoxyformimidate (1.60 g, 0.011 mol) in absolute EtOH (25 mL) was heated under reflux for 1 h and then stirred at r.t. for 3 h. The solid which separated was collected by filtration, washed with EtOH (2 × 10 mL) and then Et_2O (2 × 10 mL) and dried. The crude material was purified as indicated for individual compounds.

3-Aminoquinoxalin-2(1H)-one **(3a)**:

Colourless microcrystals (1.6 g, 99%) from HOAc/EtOH; mp > 320°C (Lit.[11] > 350°C).

IR (Nujol): ν = 3410, 3150, 1670 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): δ = 7.23 (m).

^{13}C NMR (22.2 MHz, D_2O/NaOD): δ = 162.05, 154.85, 141.80, 138.10, 127.10, 126.85, 126.67.

MS (EI): *m/z* = 161 (M^+).

3-Amino-6,7-dimethylquinoxalin-2(1H)-one **(3b)**:

Yellow microcrystals (1.51 g, 80%) from HOAc; mp > 320°C. An analytical sample was prepared by vacuum sublimation at 200°C/0.05 Torr.

Anal. ($C_{10}H_{11}N_3O$): Calc. C, 63.49; H, 5.82; N, 22.12. Found: C, 63.62; H, 5.80; N, 22.12.

IR (Nujol): ν = 3410, 3200, 1670 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): δ = 2.05 (s, 6H), 7.09 (s, 2H).

^{13}C NMR (22.2 MHz, D_2O/NaOD): δ = 161.01, 154.51, 140.56, 136.30, 134.70, 127.76, 127.01, 22.30, 22.10.

MS (EI): *m/z* = 189 (M^+).

3-Amino-6,7-dichloroquinoxalin-2(1H)-one **(3c)**:

Colourless microcrystals (1.20 g, 58% based on recovered diamine starting material) from HOAc; mp > 320°C. An analytical sample was prepared by vacuum sublimation at 220°C/0.05 Torr.

Anal. ($C_8H_5Cl_2N_3O$): Calc. C, 41.77; H, 2.17; Cl, 30.81; N, 18.27. Found C, 41.19; H, 2.46; Cl, 30.11, N, 17.76.

IR (Nujol): ν = 3410, 3200, 1670 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): δ = 7.20 (s).

^{13}C NMR (22.2 MHz, D_2O/NaOD): δ = 162.87, 156.45, 142.52, 138.79, 130.26, 128.80, 127.90, 127.63.

MS (EI): *m/z* = 234 (M^+).

3-Amino-7-methylquinoxalin-2(1H)-one and 3-Amino-6-methylquinoxalin-2(1H)-one **(3d)**:

Colourless microcrystals (1.07 g, 89% based on recovered diamine starting material) from HOAc; mp > 320°C. An analytical sample was prepared by vacuum sublimation at 200°C/0.05 Torr.

Anal. ($C_9H_9N_3O$). Calc. C, 61.71; H, 5.14; N, 24.00. Found C, 61.27; H, 5.12, 23.59.

IR (Nujol): ν = 3420, 3100, 1670 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): δ = 2.10 (s, 3H), 7.05 (m, 3H).

^{13}C NMR (22.2 MHz, TFA-*d*): δ = 153.24, 150.08, 142.28, 131.47, 130.35, 126.76, 125.91, 121.95, 120.84, 118.99, 118.80, 21.31, 20.25.

MS (EI): *m/z* = 175 (M^+).

3-Amino-6-nitroquinoxalin-2(1H)-one **(3e)**:

The crude product was dissolved in aqueous K_2CO_3 solution, and the solution was treated with charcoal and filtered. Acidification with HOAc gave a pale orange-coloured solid which was recrystallised from HOAc. This gave 1.65 g (92%, based on recovered diamine starting material) of pale orange microcrystals; mp > 320°C.

Anal. ($C_{12}H_9N_3O \cdot \frac{1}{2}H_2O$): Calc. C, 65.45; H, 4.55; N, 19.09. Found C, 65.86; H, 4.36; N, 18.54.

IR (Nujol): ν = 3410, 3150, 1675 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): δ = 7.35 (m).

^{13}C NMR (22.2 MHz, TFA-*d*): δ = 153.58, 151.73, 146.85, 123.56, 131.02, 124.68, 119.76, 115.86.

MS (EI): *m/z* = 211 (M^+).

2-Aminopyrido[2,3-*b*]pyrazin-3(4*H*)-one (5):

A solution of **1** (0.60 g, 4.15 mmol) and 2,3-diaminopyridine (0.45 g, 4.10 mmol) in EtOH (15 mL) was heated under reflux for 5 h. The mixture was cooled and the solid which separated was collected by filtration and washed with EtOH. Recrystallisation from HOAc gave the pure product (0.332 g, 50%) as grey microcrystals; mp > 320°C.

Anal. ($C_7H_6N_4O$): Calc. C, 51.85; H, 3.70; N, 34.52. Found C, 51.55; H, 3.90; N, 33.85.

IR (Nujol): ν = 3400, 3110, 1680 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): δ = 8.56 (m, 1H), 8.40 (m, 1H), 7.60 (m, 1H).

^{13}C NMR (22.2 MHz, TFA-*d*): δ = 152.69, 152.22, 142.22, 141.37, 130.87, 128.88, 119.46.

MS (EI): *m/z* = 162 (M^+).

3-Aminopyrido[3,4-b]pyrazin-2(1H)-one **(7)**:

Exactly the same procedure was used as is described for **5**. Recrystallisation of the crude product from HOAc gave 0.298 g (44%) of pure yellow microcrystals; mp > 320°C.

Anal. ($C_7H_6N_4O$): Calc. C, 51.85; H, 3.70; N, 34.52. Found C, 51.62; H, 3.57; N, 34.50.

IR (Nujol): ν = 3310, 3100, 1690, 1640 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): δ = 9.20 (s, 1H), 8.60 (d, 1H, *J* = 10), 7.86 (d, 1H, *J* = 9.5).

^{13}C NMR (22.2 MHz, TFA-*d*): δ = 152.87, 151.93, 145.73, 143.15, 134.09, 130.02, 109.19.

MS (EI): *m/z* = 162 (M^+).

6-Aminopteridin-7(8*H*)-one (9):

A suspension of 4,5-diaminopyrimidine (1.10 g, 0.01 mol) and **1** (1.60 g, 0.011 mol) in absolute EtOH (25 mL) was heated under reflux for 2 h and then stirred at r.t. for a further 2 h. The solid which separated was collected by filtration and washed with EtOH. The crude product was dissolved in dilute K_2CO_3 solution and the solution was treated with charcoal and filtered. The filtrate was acidified with HOAc and the product was collected by filtration, washed with H_2O and EtOH, and dried in vacuo to give a cream coloured solid. Yield 1.30 g (80%); mp > 320°C.

Anal. ($C_6H_5N_5O \cdot \frac{1}{2}H_2O$): Calc. C, 41.86; H, 3.51; N, 40.68. Found C, 41.89; H, 3.05; N, 40.27.

IR (Nujol): ν = 3300, 3100, 1660 cm^{-1}.

^1H NMR (90 MHz, D_2O/NaOD): δ = 8.90 (s, 1H), 8.60 (s, 1H).

^{13}C NMR (22.2 MHz, TFA-*d*): δ = 154.12, 153.31, 152.31, 148.90, 140.03, 124.25.

MS (EI): *m/z* = 163 (M^+).

4,6-Diaminopteridin-7(8*H*)-one (12):

A solution of **1** (0.60 g, 4.15 mmol) and 4,5,6-triaminopyrimidine sulfate monohydrate (1.00 g, 4.15 mmol) in EtOH (15 mL) was heated under reflux for 2 h. The solid which separated was collected by filtration and washed with EtOH. The pale yellow solid thus obtained was dissolved in dilute NaOH solution and the mixture was treated with charcoal and filtered. Acidification with HOAc gave a solid which was collected by filtration, washed with H_2O and dried in vacuo. This gave 0.524 g (71%) of pure product as a light yellow coloured solid; mp 250°C (dec).

Anal. ($C_6H_6N_6O \cdot 1.5\,H_2O$): Calc. C, 35.12; H, 4.39; N, 40.97. Found C, 35.35; H, 4.42; N, 40.74.

IR (Nujol): ν = 3470, 3280, 3100, 1710 cm^{-1}.

^1H NMR (90 MHz, TFA-*d*): gave a broad line spectrum.

MS (EI): m/z = 178 (M^+).

6-Amino-1,3-dimethylpteridine-2(1H),4(3H),7(8H)-trione **(14)**:

This compound was prepared in an identical manner, and on the same scale, as described for compound **12**. The crude product was recrystallised from aqueous HOAc, which gave yellow microcrystals (94%); mp >320 °C.

IR (Nujol): ν = 3250, 3080, 1660 cm^{-1}.

Anal. ($C_8H_9N_5O_3 \cdot H_2O$): Calc. C, 39.83; H, 4.56; N, 29.04. Found C, 39.22; H, 4.49; N, 28.68.

^1H NMR (90 MHz, TFA-*d*): δ = 3.15 (s, 3 H), 3.35 (s, 3 H).

MS (EI): m/z = 223 (M^+).

3-Amino-1,4-benzoxazin-2-one **(16a)**:

Rose coloured plates (83%) from EtOH; mp 211–3 °C.

Anal. ($C_8H_6N_2O_2$): Calc. C, 59.62; H, 3.70; N, 17.28. Found C, 59.09; H, 3.84; N, 17.27.

IR (Nujol): ν = 3420, 3100, 1793 cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 7.20 (m).

^{13}C NMR (22.2 MHz, DMSO-d_6): δ = 151.26, 147.75, 143.83, 132.74, 125.08, 123.67, 115.54.

MS (EI): m/z = 162 (M^+).

3-Amino-6-methyl-1,4-benzoxazin-2-one **(16b)**:

Pink microcrystals (67%) from HOAc; mp 284–6 °C.

Anal. ($C_9H_8N_2O_2$): Calc. C, 61.37; H, 4.55; N, 15.92. Found C, 61.52; H, 4.78; N, 15.68.

IR (Nujol): ν = 3420, 3100, 1730 cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 2.30 (s, 3 H), 3.35 (br s, 2 H), 6.90–8.80 (m, 3 H).

^{13}C NMR (22.2 MHz, DMSO-d_6): δ = 151.30, 147.10, 143.55, 133.56, 130.26, 125.88, 123.51, 115.66, 20.47.

MS (EI): m/z = 176 (M^+).

3-Amino-7-methyl-1,4-benzoxazin-2-one **(16c)**:

Pale grey amorphous powder (65%) from EtOH/acetone; mp 236 °C.

Anal. ($C_9H_8N_2O_2$): Calc. C, 61.36; H, 4.54; N, 15.91. Found C, 61.12; H, 4.70; N, 15.59.

IR (Nujol): ν = 3415, 3100, 1740 cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 2.37 (s, 3 H), 2.53 (br s, 2 H), 7.10–7.35 (m, 3 H).

^{13}C NMR (22.2 MHz, DMSO-d_6): δ = 151.32, 147.13, 143.59, 133.59, 130.28, 125.89, 123.96, 115.68, 20.48.

MS (EI): m/z = 176 (M^+).

3-Amino-6-chloro-1,4-benzoxazin-2-one **(16d)**:

Pink-purple coloured crystals (76%) from EtOH/HOAc; mp 253 °C.

Anal. ($C_8H_5ClN_2O_2$): Calc. C, 48.80; H, 2.55; Cl, 18.06; N, 14.25. Found C, 48.48; H, 2.77; Cl, 17.93; N, 14.53.

IR (Nujol): ν = 3410, 3100, 1730 cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 3.27 (br s, 2 H), 7.17–7.30, (m, 2 H), 7.60–7.75 (m, 1 H).

^{13}C NMR (22.2 MHz, TFA-*d*): δ = 172.46, 170.03, 164.30, 155.79, 150.18, 144.49, 136.61.

MS (EI): m/z = 196 (M^+).

3-Amino-6-nitro-1,4-benzoxazin-2-one **(16e)**:

Brown coloured crystals (65%) from EtOH/HOAc; mp 260 °C.

Anal. ($C_8H_5N_3O_4$): Calc. C, 46.37, H, 2.41, N, 20.28. Found C, 45.71, H, 2.83, N, 20.67.

IR (Nujol): ν = 3410, 3150, 1745 cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 7.49 (d, 1 H, J = 9), 7.80–8.10 (m, 2 H).

^{13}C NMR (22.2 MHz, DMSO-d_6): δ = 150.44, 149.03, 148.39, 144.27, 133.65, 118.64, 118.20, 116.59.

MS (EI): m/z = 207 (M^+).

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