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Novel Synthesis of Hydrogenated Derivatives of Indole and Benzo[*b*]thiophene based on Thorpe–Ziegler Cyclization

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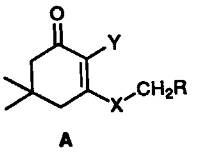
A new synthesis of 3-amino-4,5,6,7-tetrahydro-indole and -benzo[*b*]thiophene derivatives, based on Thorpe–Ziegler cyclization, is described.

Although heterocyclic syntheses based on 1,3-cyclohexanedione derivatives have been studied in detail,[1–2] preparative procedures for obtaining functionally-substituted 3-aminoindoles and -benzo[*b*]thiophenes are lacking.

In the present study an attempt is made to use for this synthesis intermediates **A**, where R is an electron-attracting substituent, X is a heteroatom and Y is a function susceptible to cyclization on the active methylene group. As a suitable starting material, the readily-available 1-ethoxy-2-cyano-5,5-dimethylcyclohex-l-enone **1**, which is known [3–5] to react smoothly with amines to yield the corresponding cyanoenamines, was employed. The latter are used for the synthesis of imidazole, oxazole and similar derivatives. As the first stage of this investigation, the possibility of obtaining substances similar to **A** was studied by treating **1** with the potassium salt of glycine, followed by esterification of enaminoacid **2a** to give ester **2b** , yield 96%, m.p. 144–46 °C (EtOH). However, the preparation of **2b** by the treatment of **1** with glycine ethyl ester hydrochloride in the presence of AcONa was more convenient. Under these conditions the yield of **2b** was 81%.[†,§] It is necessary to note that **2b** does not transform to indole derivatives, even in the presence of a large excess of AcONa, *i.e.* CH_2-protons are not sufficiently active. On the contrary, Thorpe–Ziegler cyclization[6] to 2-ethoxycarbonyl-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-2*H*-indole **3**, yield 80%, m.p.188–90 °C[‡] (EtOH), proceeds smoothly under the action of EtONa.

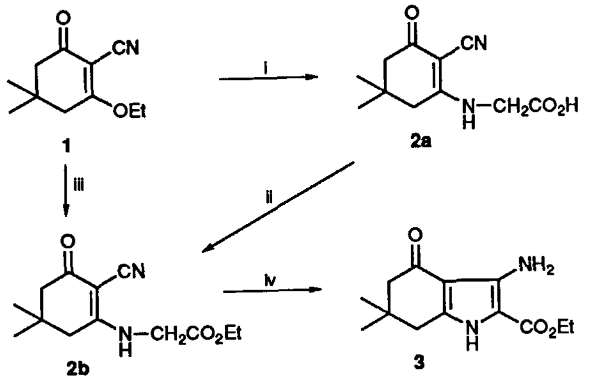


A

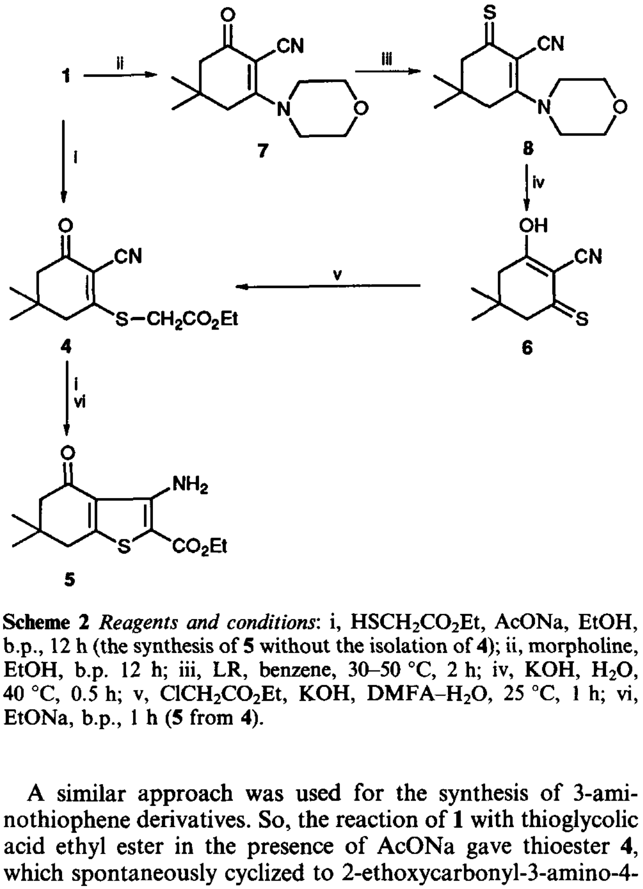
[†] Spectroscopic data for **2b** IR ν/cm^{-1} 3280, 2190, 1745, 1630; *m*/*z* 250 (M^+).

[‡] For **3** IR ν/cm^{-1} 3480, 3360, 3210, 1660, 1615; ^{1}H NMR ($CDCl_3 + CD_3OD$) δ 1.09 (6H, s, CMe_2), 1.31 (3H, t, CH_2CH_3), 2.18 (2H, s, 6–CH_2), 2.28 (2H, s, 4–CH_2), 4.28 (2H, quar., CH_2CH_3); *m*/*z* 250 (M^+).

[§] All new compounds gave the expected IR, ^{1}NMR and mass spectroscopic data and satisfactory elemental analyses.



Scheme 1 *Reagents and conditions*: i, $NH_2CH_2CO_2H$, KOH, EtOH, b.p., 3 h; ii, passage of gaseous HCl, EtOH, b.p., 2, h; iii, $NH_2CH_2CO_2Et$ HCl, AcONa, EtOH, b.p., 4 h; iv, EtONa, EtOH, b.p., 1 h.



Scheme 2 *Reagents and conditions*: i, $HSCH_2CO_2Et$, AcONa, EtOH, b.p., 12 h (the synthesis of **5** without the isolation of **4**); ii, morpholine, EtOH, b.p. 12 h; iii, LR, benzene, 30–50 °C, 2 h; iv, KOH, H_2O, 40 °C, 0.5 h; v, $ClCH_2CO_2Et$, KOH, DMFA-H_2O, 25 °C, 1 h; vi, EtONa, b.p., 1 h (**5** from **4**).

A similar approach was used for the synthesis of 3-aminothiophene derivatives. So, the reaction of **1** with thioglycolic acid ethyl ester in the presence of AcONa gave thioester **4**, which spontaneously cyclized to 2-ethoxycarbonyl-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene **5**, yield 66%, m.p. 129–131 °C[¶] (EtOH), *i.e.* the activity of the CH_2-group of **4** is higher than that in **2b**. Further preparative possibilities are opened up by using an alternative method of synthesis for **5**, based on the previously-unknown 2-cyanothiodimedone **6**.[*] This was prepared from **1** in three steps: first, **1** was treated with morpholine to give cyanoenaminoketone **7**, yield 72%, m.p.181–183 °C (H_2O). The latter was treated with Lawesson's reagent (LR) with formation of enaminothione **8**,[†] yield 100%, m.p. 225–228 °C (CH_3CN). Finally **8** was hydrolysed under the action of alkali to give **6**, yield 70%, m.p. 60 °C (hexene). Alkylation of **6** by ethyl chloroacetate gave the intermediate **4**, yield 97%, m.p. 97–98 °C (EtOH/H_2O), which was easily transformed to bicycle **5** under the action of EtONa (Thorpe–Ziegler cyclization). Although this synthesis has more stages than the synthesis from thioglycolic acid esters, it has a number of advantages, *i.e.* the isolation of the new synthon **6** and greater accessibility of halogenonitriles, halogenoketones, *etc.* compared with the corresponding thiols. This method therefore provides considerable possibilities for the synthesis of various 2-substituted 4,5,6,7-benzohydro-3-aminobenzo[*b*]thiophenes. Compounds **3** and **5** represent new synthons for polycyclic systems which are of interest for biological investigation.

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[¶] Spectroscopic data for **5** IR ν/cm^{-1} 3440, 3225, 1670, 1640; ^1H NMR ($CDCl_3$) δ 1.10 (6H, s, CMe_2), 1.33 (3H, t, CH_2CH_3), 2.39 (2H, s, 6–CH_2), 2.79 (2H, s, 4-CH_2), 4.26 (2H, quar., CH_2CH_3), 6.89 (2H, br.s. NH); *m/z* 267 (M^+).

[*] Spectroscopic data for **6** ^1H NMR ($CDCl_3$) δ 1.09 (6H, s, CMe_2), 2.34 (2H, s, 6–CH_2), 2.61 (2H, s, 4–CH_2), 4.72 (1H,br. s, SH); *m/z* 181 (M^+).

[†] For **8** IR ν/cm^{-1} 2190, 1525; ^1H NMR ($CDCl_3$), δ 1.06 (6H, s, CMe_2), 1.44 (2H, s, 6–CH_2), 2.79 (2H, s, 4–CH_2), 3.87 (8H, s, CH_2-morpholine); *m/z* 250 (M^+).