Multicomponent one-pot synthesis of pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines as a novel approach to condensed pyridines

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10.1070/MC2003v013n06ABEH001851

Multicomponent one-pot reactions of aromatic aldehydes, cyanothioacetamide, ethyl benzoylacetate, acetone and malononitrile in the presence of *N*-methylmorpholine or similar reactions of pyridinethiones or -thiolates with malononitrile and acetone afford the title compounds, which were unknown before.

Fused pyridines and, in particular, thienopyridines are well known as biologically active compounds. Thus, in the series of thienopyridines and related condensed analogues, antithrombotic,[1] antihistamine (antianaphylactic,[2] antibacterial[3] and antiallergic[4]) and neuroprotective[5] agents were found. Polysubstituted and partially hydrogenated pyridothienopyridines are new heterocycles with potential biological activity.[6] Their syntheses are based on a multi-step approach and often require inaccessible reagents.

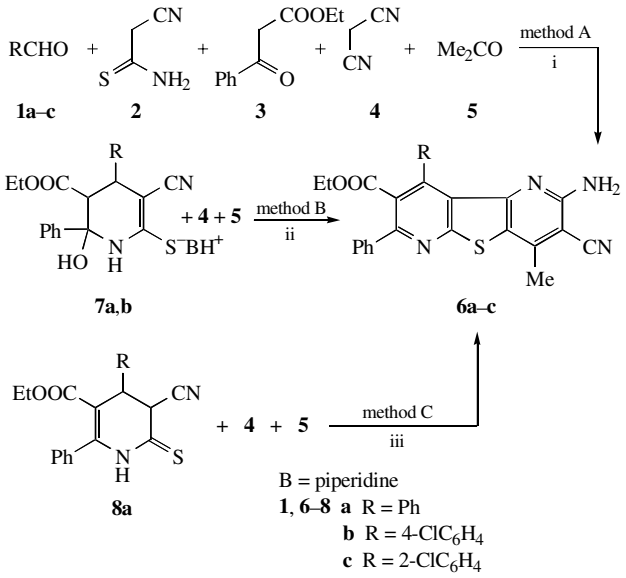
Recently, we described a simple one-pot route to tetrahydrodipyridothiophenes *via* the multicomponent condensation of tetrahydropyrid-2-one-6-thiolates, malononitrile and acetone.[7] This new promising strategy for building three-ring systems from 3-cyanopyridine-2-thiolates can be improved using acyclic precursors of the above thiolates. In this context, we report novel one-pot approach to dipyridothiophenes, which were unknown before. All of the initial compounds are commercially available. In spite of the low yields, the proposed method is of importance due to its simplicity and accessibility. Moreover, this approach is the only way to pyrido[3′,2′:4,5]thieno[3,2-*b*]-pyridines using a multicomponent condensation reaction.

Thus, the consequent interaction of aldehydes **1**, cyanothioacetamide **2**, ethyl benzoylacetate **3**, malononitrile **4** and acetone **5** in refluxing EtOH in the presence of *N*-methylmorpholine gave condensed pyridines **6**† (Scheme 1, method A).

On the other hand, thiolates **7** or thiones **8**, which can be easily obtained by the condensation of aldehydes **1**, amide **2** and ester **3** in the presence of a base,[8] were also good precursors to form compounds **6** in a similar way (heating in EtOH containing a base) (Scheme 1, methods B and C, respectively).‡

Comparing these three independent routes to fused pyridines **6**, note that proposed methods A–C gave comparable results (Table 1). Evidently, path A is most preferable in this case because of its facility. None of the intermediates of these reactions was isolated. Therefore, neither the consequence of steps nor the overall reaction mechanism can be postulated unambiguously. We suggest that corresponding bis(pyrid-2-yl)-disulfides could be formed from **7** or **8** in the course of the reaction. The further nucleophilic cleavage of the S–S bond under an attack of the isopropylidene malononitrile anion, which was formed *in situ* from malononitrile **4** and acetone **5**, followed by double cascade cyclization affords target compounds **6**. The mechanisms of these and related transformations[7] are under study.

The structural charactersation of fused pyridines **6** was based on spectroscopic and analytical data. The ^{1}H NMR spectra



Scheme 1 *Reagents and conditions*: i, method A: EtOH, *N*-methylmorpholine, reflux, 15–25 h; ii, method B: EtOH, reflux, 25–30 h; iii, method C: EtOH, piperidine, reflux, 12 h.

† *General procedure for the preparation of compounds* **6** (method A). Ethyl benzoylacetate **3** (2.5 ml, 15 mmol) and *N*-methylmorpholine (2.5 ml, 22.5 mmol) were added to a stirred mixture of aldehyde **1** (15 mmol), cyanothioacetamide **2** (1.5 g, 15 mmol) and two drops of *N*-methylmorpholine in EtOH (25 ml). The reaction mixture was stirred vigorously for 1 h; then, malononitrile **4** (1.98 g, 30 mmol) and acetone **5** (11 ml, 0.15 mol) were added. The mixture was heated under reflux for 15 h (25 h for **6a**) and then allowed to cool at room temperature. The resulting precipitate was filtered and crystallised to give **6**.

*2-Amino-3-cyano-8-ethoxycarbonyl-4-methyl-7,9-diphenylpyrido[3′,2′:4,5]thieno[3,2-*b*]pyridine* **6a**. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.66–7.29 (m, 10H, 2Ph), 5.72 (br. s, 2H, NH$_2$), 3.78 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 2.64 (s, 3H, Me), 0.78 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). IR (ν/cm^{-1}): 3440, 3350 (NH$_2$), 2112 (CN), 1722 (CO). Found (%): C, 69.01; H, 4.33; N, 12.10. Calc. for C$_{27}$H$_{20}$N$_4$O$_2$S (%): C, 69.81; H, 4.34; N, 12.06.

*2-Amino-9-(4-chlorophenyl)-3-cyano-8-ethoxycarbonyl-4-methyl-7-phenylpyrido[3′,2′:4,5]thieno[3,2-*b*]pyridine* **6b**. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.68–7.31 (m, 9H$_{arom}$), 6.09 (br. s, 2H, NH$_2$), 3.84 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 2.63 (s, 3H, Me), 0.81 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). IR (ν/cm^{-1}): 3445, 3350 (NH$_2$), 2108 (CN), 1720 (CO). Found (%): C, 65.14; H, 3.86; N, 11.26. Calc. for C$_{27}$H$_{19}$ClN$_4$O$_2$S (%): C, 64.99; H, 3.84; N, 11.23.

*2-Amino-9-(2-chlorophenyl)-3-cyano-8-ethoxycarbonyl-4-methyl-7-phenylpyrido[3′,2′:4,5]thieno[3,2-*b*]pyridine* **6c**. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.69–7.22 (m, 9H$_{arom}$), 5.99 (br. s, 2H, NH$_2$), 3.83 (q, 2H, OC*H*$_2$Me, *J* 7.1 Hz), 2.61 (s, 3H, Me), 0.76 (t, 3H, OCH$_2$*Me*, *J* 7.1 Hz). Found (%): C, 65.11; H, 3.87; N, 11.27. Calc. for C$_{27}$H$_{19}$ClN$_4$O$_2$S (%): C, 64.99; H, 3.84; N, 11.23.

‡ Piperidinium thiolates **7a**,**b** and thione **8a** were prepared according to the published procedure.[8]

*2-Amino-3-cyano-8-ethoxycarbonyl-4-methyl-7-phenyl-9-R-pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines* **6** (method B). A mixture of salt **7** (8 mmol), malononitrile **4** (1.06 g, 16 mmol) and acetone **5** (5.9 ml, 80 mmol) in EtOH (25 ml) was refluxed for 25–30 h and then allowed to cool at room temperature. The resulting precipitate was filtered and crystallised to give **6**.

*2-Amino-3-cyano-8-ethoxycarbonyl-4-methyl-7,9-diphenylpyrido[3′,2′:4,5]thieno[3,2-*b*]pyridine* **6a** (method C). A mixture of thione **8a** (2 g, 5.5 mmol), piperidine (0.55 ml, 5.5 mmol), malononitrile **4** (0.73 g, 11 mmol) and acetone **5** (5 ml, 68 mmol) in EtOH (15 ml) was refluxed for 12 h and then allowed to cool at room temperature. The resulting precipitate was filtered and crystallised to give **6a**.

Table 1 Yields and melting points of the compounds.

Product	Yield (%) (methods A–C)	mp/°C (solvent)
6a	17 (A), 13 (B), 14 (C)	305–306 (AcOH–DMF)
6b	25.5 (A), 16 (B)	330–332 (DMF)
6c	15(A)	317–319 (AcOH–DMF)

(200 MHz, [$^2H_6$]DMSO–TMS) contain usual signals of Ph and COOEt fragments. The presence of a broad singlet at δ 5.77–6.09 ppm, which is attributable to NH_2, and singlet due to the Me group (δ 2.61–2.64 ppm), by analogy with related dipyridothiophenes, whose structures were unambiguously determined by X-ray analysis,[7] provide support for the proposed structure. The absence of typical signals of partially hydrogenated pyridine ring protons[8] shows that aromatisation took place.

In conclusion, we found a new route to the synthesis of functionally substituted thienodipyridines derived from pyridinethiolates and pyridinethiones or their acyclic precursors *via* a multicomponent one-pot reaction.

This work was supported by the Russian Foundation for Basic Research (project no. 02-03-32063).

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Received: 1st September 2003; Com. 03/2177