Efficient synthesis of polyfunctionalised pyridines by conjugate addition of 2-thienylcarbonyl (thioacetanilides) to αβ-unsaturated nitriles

J. Chem. Research (S), 2002, 149–150
J. Chem. Research (M), 2002, 0419–0430

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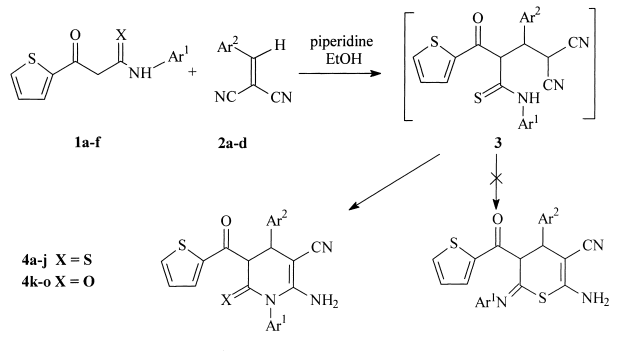
Conjugate addition of 2-thienylcarbonyl(thioacetanilides) (**1**) to arylmethylenemalononitriles (**2**) yielded 2-amino-1,4-diaryl-5-(2-thienylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitriles (**4**), which when oxidised with HgO gave functionalised 2,6-dioxopiperidines (**6**), whereas with MCPBA they afforded pyrido[2,1-*b*]benzothiazole-2-carbonitrile derivatives (**7**).

Keywords: thioamides, thiophenes, aβ-unsaturated nitriles, pyridines, fused benzothiazoles

Recently, we have shown that polyfunctionalised pyridines can be synthesised by conjugate addition of CH-acids to αβ-unsaturated nitriles such as arylmethylenemalononitriles, ethyl α-cyanocinnamates[6] and cyclohexylidenemalononitrile.[7] Benzoyl(thioacetanilides)[6] and cyclic β-keto-thioanilides[8,9] were used as the CH-acids. The efficiency of this method prompted us to apply this procedure to the synthesis of β-enaminonitriles of pyridine possessing heterocyclic substituents namely the 2-thienyl group. Since various thienylpyridine derivatives show fluorescence, they are studied intensively due to the potential of these compounds in the construction of molecular electronics and chemical sensor devices.[10]

To realise the synthesis of target molecules we used thienylcarbonyl-(thioacetanilides) (**1**) and arylmethylemalononitriles (**2**) as CH-acids. The reactions of **1a–c** with **2a–c** carried out in ethanolic solution in the presence of piperidine yielded **4a–j** in good yield (Scheme 1). The IR spectrum of **4a** reveals a carbonyl band at 1635 cm^{-1}, the band at 2187 cm^{-1} for the cyano group and four bands in the range of 3365–3537 cm^{-1} for the amino group. The observed band pattern in the spectrum of **4a** was typical for β-enaminonitriles. In the ^1H NMR spectrum of **4a** two doublets at δ = 4.12 ppm (^3J = 2.1 Hz) and 5.38 ppm (^3J = 2.1 Hz) corresponding to two adjacent protons were observed. The protons of the amino group appeared as the singlet at δ = 4.44 ppm and aromatic protons of phenyl and thienyl groups resonated as two multiplets in the range of 7.22–7.59 and 7.79–7.88 ppm. The above reaction is assumed to proceed, as conjugate addition of the anion of the thioanilide **1**, generated in basic medium, to **2**, involving the Michael adduct **3**, which underwent spontaneous cyclisation to pyridine skeleton (**4**). The alternative cyclisation of the intermediate **3** to form a thiopyran ring (**5**) was rejected on the basis of the ^{13}C NMR spectrum of product **4a**, because it revealed two signals at δ = 198 and 186 ppm attributed carbon atoms of C = S and C = O groups respectively. The reaction of thienylcarbonyl(acetanilides) **1d–f** with **2d–f** carried out under similar conditions afforded compounds **4k–o** in good yields (56–76%). Their spectral features were similar to those of compounds **4a–j**.



1	2	4	X	Ar^1	Ar^2	1	2	4	X	Ar^1	Ar^2
a	a	a	S	C_6H_5-	C_6H_5-	a	d	i	S	C_6H_5-	2-Thienyl
b	a	b	S	4-Cl-C_6H_4-	C_6H_5-	c	d	j	S	4-CH_3-C_6H_4-	2-Thienyl
c	a	c	S	4-CH_3-C_6H_4-	C_6H_5-						
a	b	d	S	C_6H_5-	4-Cl-C_6H_4-	d	a	k	O	C_6H_5-	C_6H_5-
b	b	e	S	4-Cl-C_6H_4-	4-Cl-C_6H_4-	e	a	l	O	4-Cl-C_6H_4-	C_6H_5-
c	b	f	S	4-CH_3-C_6H_4-	4-Cl-C_6H_4-	f	a	m	O	4-CH_3-C_6H_4-	C_6H_5-
a	c	g	S	C_6H_5-	4-CH_3-C_6H_4-	d	b	n	O	C_6H_5-	4-Cl-C_6H_4-
c	c	h	S	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	d	c	o	O	C_6H_5-	4-CH_3-C_6H_4-

Scheme 1

In the following experiments our effort was directed to the dehydrogenation of pyridine skeleton. Since reaction with H_2O_2 in acetic acid gave a complex mixture difficult to separate, HgO and MCPBA were used as oxidants. Reaction of **4a–c** with HgO carried out in acetic acid proceeded smoothly, yielding compounds **6a–c** in fair yields (52–65%). On the basis of our previous finding[6] we expected the dehydrogenation of the pyridine ring as well as the replacement of the sulfur atom of C = S group by an oxygen. To our surprise, analytical and spectral data of **6a-c** were not consistent with those expected for the products of dehydrogenation. The IR spectrum of **6a** showed bands of carbonyl (1651, 1692, 1731 cm^{-1}) and cyano (2208 cm^{-1}) groups. The ^1H NMR spectrum of **6a** revealed three multiplet signals at δ = 4.59, 5.17 and 5.56 ppm. The spectral pattern of these signals suggested the presence in **6a** of three adjacent hydrogen atoms. The ^{13}C NMR spectrum revealed three signals at 164.7, 168.7 and 186.5 ppm of carbonyl carbon atoms. The analytical data of **6a** and its molecular weight determined by MS showed that the molecule of **6a** contains two nitrogen atoms. These results indicated that the reaction of **4a** with HgO in acetic acid occurred with the replacement of the sulfur atom in C=S group by an oxygen, and the elimination of ammonia (Scheme 2). The corresponding data for **6b,c** were similar to those of **6a**.

Oxidation of **4a–c** with MCPBA in CH_2Cl_2 afforded compounds **7a–c** in good yields (47–64%). In contrast to the expected dehydrogenation of the 4,5-dihydropyridine ring, the obtained products were formed by the abstraction of two hydrogen atoms, one, formally, from the tautomeric SH form of the C = S group at C-6 and the second one from an *o*-position of the

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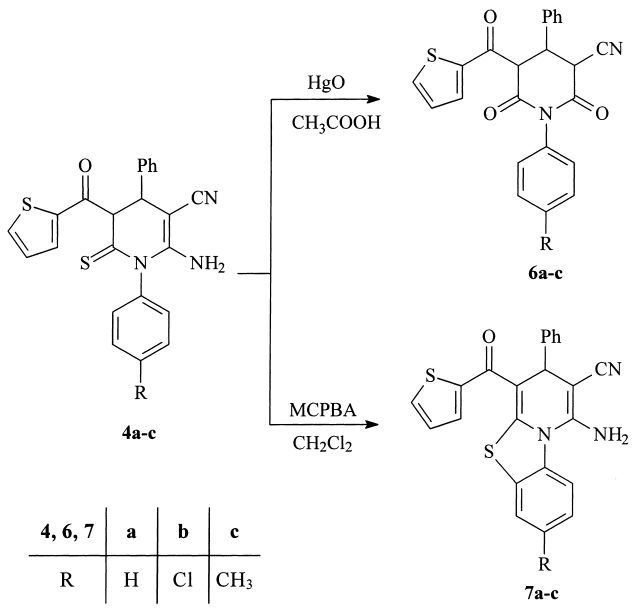

4, 6, 7	a	b	c
R	H	Cl	CH_3

Scheme 2

aryl group attached to pyridine nitrogen. The abstraction of these protons results in cyclisation and the formation of a thiazole ring

The structure of **7** was consistent with analytical and spectral data. The IR spectrum of **7a** revealed the bands of amino (3400 cm^{-1}), cyano (2188 cm^{-1}) and carbonyl (1647 cm^{-1}) groups. The ^1H NMR spectrum of **7a** showed two singlets at $\delta = 5.19$ ppm (C-4, 1H) and 6.55 ppm (NH_2, 2H). Aromatic protons resonated in the range of 7.84–7.89 and 7.09–7.40 ppm. However the ^{13}C NMR spectrum revealed only one signal at lower field at 179 ppm of carbonyl carbon. Molecular weights of **7a–c** were two mass units lower than those of compounds **4a–c** respectively. The alternative cyclisation of **4a–c** to thiopyran ring by abstraction of hydrogens from tautomeric SH group and from thienyl group at C-3 was rejected on the basis of MS data. The MS revealed intensive peaks at *m/z* 111 which corresponded to the thienylcarbonyl ion, for **7a**: 62%; **7b**: 100%; **7c**: 67%).

All compounds **7a–c** showed strong fluorescence evoked by UV light. The strongest yellow-green fluorescence was emitted by their ethanolic or acetonitrile solutions. The electronic spectra of **7a** obtained for acetonitrile solutions exhibited absorption at $\lambda_{max} = 258$ nm ($\varepsilon = 77500$ $dm^3/mol/cm$) and emission $\lambda_{max} = 325$ and 339 nm.

In conclusion, we have shown that 2-thienylcarbonyl(thioacetanilides) and 2-thienylcarbonyl- acetanilides are active CH acids for conjugate addition to α,β-unsaturated nitriles affording β-enaminonitriles of pyridine. Other advantages of these reactions are the accessibility of starting materials, mild conditions, simplicity of procedure and good yields of products. It was found that the obtained products can be converted into pyrido[2,1-*b*]benzothiazole derivatives which exhibited fluorescence properties.

Techniques used: IR, UV/fluorescence spectroscopy, ^1H, ^{13}C NMR, MS

References: 11

Schemes: 2

Received 1 October 2001; accepted 25 January 2002
Paper 01/1068

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