Pergamon

Tetrahedron Letters 43 (2002) 1035–1038

TETRAHEDRON LETTERS

High-pressure-promoted condensation of isothiocyanates with aminopyridines: efficient synthesis of pyridine–thiourea conjugates as building blocks for hydrogen-bonding receptors†

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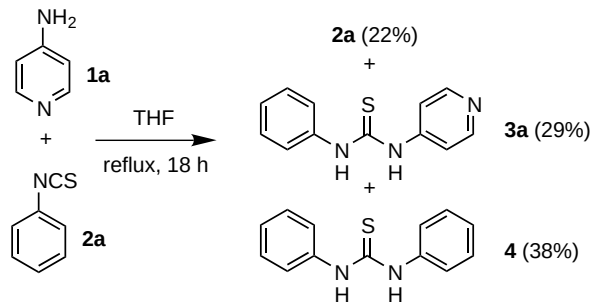
Received 2 November 2001; accepted 30 November 2001

Abstract—New *N*-pyridinothiourea derivatives have been prepared by the high-pressure-promoted condensation of isothiocyanates with aminopyridines under uncatalyzed conditions. Complexation of the prototype **3c** with diphenyl hydrogen phosphate was investigated by ^{1}H NMR, and the results suggest that it may be useful as a building block for hydrogen-bonding receptors.

Thiourea and its related molecules are important as structural components and as intermediates in agricultural and pharmaceutical chemistry.[2] Recently, these compounds have attracted considerable attention for their potential use as binding units for artificial receptors in supramolecular chemistry because of their characteristic behavior based on Lewis acids and strong hydrogen-bond donors.[3] Furthermore, in the field of advanced material chemistry, thioureas can serve as a useful scaffold by connecting them to electroluminescent organic dyes.[4] Their enormous potential has led to the development of several methods for preparing thiourea derivatives.[5] The most common of these methods involves the condensation of isothiocyanates with amino derivatives. However, despite its utility and simplicity, limitations are sometimes encountered, particularly with less reactive amine substrates.

For example, in contrast to the case of aniline derivatives,[6] we found that 4-aminopyridine (**1a**) reacted fairly slowly with phenylisothiocyanate (**2a**), even in refluxing THF, to produce a complex mixture of products from which, after 18 h, *N*-pyridinothiourea **3a** could be isolated in 29% yield along with unreacted **2a** (22%) and *N*,*N*′-diphenylthiourea (**4**, 38%) (Scheme 1). The latter compound **4** must be formed by the self-recombination of **2a** via decomposition to aniline. Considerable attempts to facilitate the desired condensation reaction under acid- or base-catalyzed conditions were unsuccessful. These results can be easily understood by invoking the weakly nucleophilic character of the amino group of **1a**. To overcome this difficulty and also to suppress undesired side-reactions, we decided to apply a high-pressure methodology, since our previous experience suggested that such a condensation reaction should be favorable at high pressure.[7] We report here the realization of this expectation. The results are summarized in Table 1.[8]

When the reaction of **1a** with 1.2 equiv. of **2a** in THF was conducted at 0.6 GPa and 40°C for 24 h,[9] the desired adduct **3a**, mp 142–143°C (from methanol), was obtained in a much better yield of 67%, contaminated

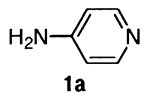
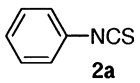
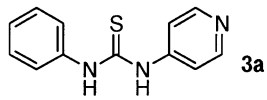
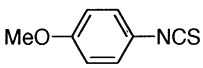
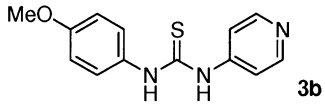
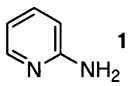
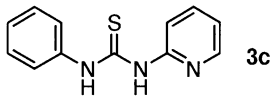
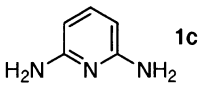
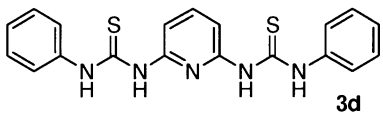
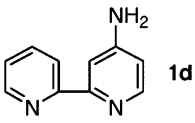
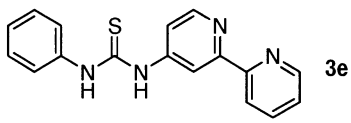
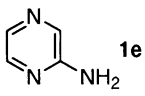
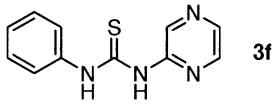
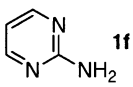
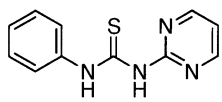
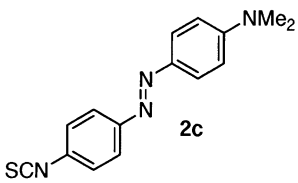
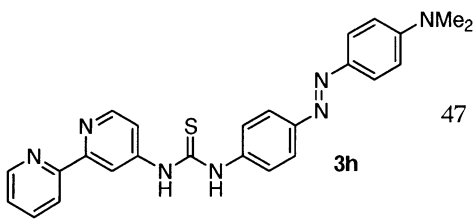
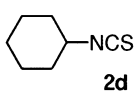
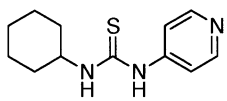
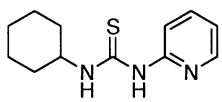


Scheme 1.

Keywords: high-pressure condensation; isothiocyanates; aminopyridines; *N*-pyridinothioureas; hydrogen-bonding receptors.
* Corresponding authors. Fax: +81-88-844-8359; e-mail: yuji@apc.saitama-u.ac.jp; kotsuki@cc.kochi-u.ac.jp
† High-Pressure Organic Chemistry. Part 25. For Part 24, see: Ref. 1.

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02295-X

Table 1. Synthesis of *N*-pyridinothioureas[a]

entry	amine	isothiocyanate	conditions	product	yield (%)[b]
1	 **1a**	 **2a**	0.6 GPa 40°C, 24 h	 **3a**	67
2	**1a**	 **2b**	0.6 GPa 40°C, 44 h	 **3b**	68
3	 **1b**	**2a**	0.6 GPa 40°C, 18 h	 **3c**	95
4[c]	 **1c**	**2a**	0.6 GPa 40°C, 44 h	 **3d**	75
5	 **1d**	**2a**	0.6 GPa 40°C, 44 h	 **3e**	68
6	 **1e**	**2a**	0.6 GPa 40°C, 24 h	 **3f**	84
7	 **1f**	**2a**	0.6 GPa 40°C, 44 h	 **3g**	80
8	**1d**	 **2c**	0.6 GPa 40°C, 72 h	 **3h**	47
9	**1a**	 **2d**	0.6 GPa 80°C, 48 h	 **3i**	71
10	**1b**	**2d**	0.6 GPa 60°C, 36 h	 **3j**	78

[a] Unless otherwise noted, all reactions were conducted in THF using 1.2 equiv of isothiocyanates **2**. [b] Isolated yield after purification. [c] 2.4 equiv of **2a** was used.

by only a trace amount of **4** (entry 1). Based on this general scheme, **3b**–**3g** were prepared in good yields as highly crystalline materials, but in some cases a longer reaction period was needed to increase the product yields (entries 2–7). Adduct **3h**, mp 181–183°C (from methanol), could be obtained by condensing aminobipyridine **1d** with azo-derived isothiocyanate **2c** (entry 8). This result implies that this procedure may be useful for devising a new type of azo-chromophore-based colorimetric receptor. The high-pressure technique was also effective for aliphatic homologs such as cyclohexylisothiocyanate (**2d**): the corresponding aminopyridine adducts **3i** and **3j** were produced in respective yields of 71 and 78% under slightly harsher conditions (entries 9 and 10).[10]

Another issue was whether the pyridine–thiourea conjugates obtained above could serve as potent building blocks for artificial receptors in supramolecular chemistry. Each molecule contains both a hydrogen-bonding acceptor (pyridine unit) and a hydrogen-bonding donor (thiourea unit), and this prompted us to evaluate their ability to bind to a phosphoric acid diester as a biologically important species.[11] The prototype **3c** was used for this purpose; binding was assessed by ^{1}H NMR data. Fig. 1 shows the results of titrations in which the chemical shifts of two types of thiourea NH protons (NH_a and NH_b, see Fig. 2) could be monitored as a function of the amount of diphenyl hydrogen phosphate (**5**) in CD_3CN at 23°C. In the absence of **5**, the resonances of NH_a (13.80 ppm) and NH_b (8.92 ppm) are distinguishable from each other; the extreme low-field signal of NH_a can be ascribed to favorable intramolecular hydrogen bonding between NH_a and pyridine-N.[12] Adding **5** to a solution of **3c** produced an up-field shift for NH_a and a down-field shift for NH_b. The former observation is attributable to the disruption of hydrogen bonding by a **5**-induced competitive binding event. We carefully analyzed the binding curve of NH_b based on a nonlinear curve-fitting procedure,[13] which suggested two complexation steps, as follows: H+G ⇄ HG (K_{a1}), HG+G ⇄ HGG (K_{a2}), $[H]_0=[H]+[HG]+[HGG]$, where [H] and [G] refer to **3c** and **5**, respectively. As a result, the analysis could fully reproduce the experimental data to estimate each association constant ($K_{a1}=51\pm14$ M^{-1} and $K_{a2}=1{,}100\pm220$ M^{-1}).[14] The results ($K_{a1} \ll K_{a2}$) could be explained on the basis of a K_{a1} binding mode accompanied by the competitive disruption of intramolecular hydrogen bonding (vide supra), as well as a **5**-assisted strong association (K_{a2}) of a second **5**.[15] The plausible complex motifs are shown in Fig. 2, where intermolecular hydrogen bonding between pyridine-N and **5**-OH has taken place, as inferred from a ^{1}H NMR dilution experiment[16] of a 1:1 mixture of **3c** and **5** in CD_3CN, which showed a concentration-dependent shift of the resonances due to the spherical pyridine *ortho*- and *para*-positioned protons (H_o and H_p, see Fig. 2). In a control experiment, when *N*-methyl-*N*-phenylthiourea, which lacks a pyridine moiety, was used for complexation, such binding behavior of **5** was not observed. Taken together, these preliminary results suggest a new approach to the development of new hydrogen-bonding molecular receptors and carriers based on pyridine–thiourea conjugates.

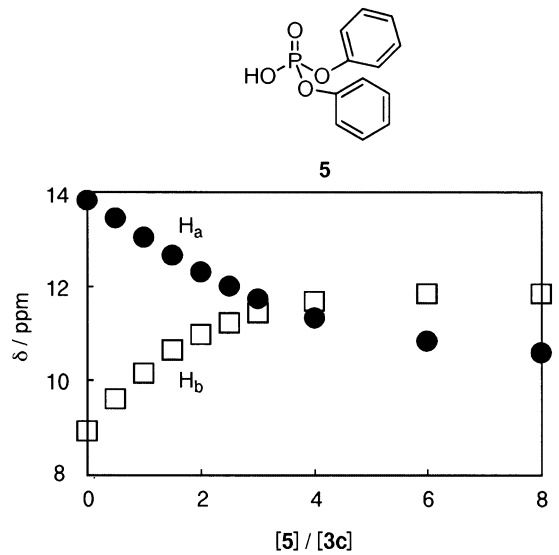


Figure 1. ^{1}H NMR chemical shifts of **3c** upon addition of diphenyl hydrogen phosphate **5**. [**3c**]=4 mM. See Fig. 2 for proton positions, H_a and H_b.

In conclusion, we have developed a convenient method for preparing a variety of *N*-pyridinothiourea derivatives using the high-pressure-promoted uncatalyzed condensation of isothiocyanates with aminopyridines. Our findings with this new class of compounds show that a pyridine–thiourea bifunctionality is effective for binding diphenyl hydrogen phosphate through hydrogen-bonding interactions. We believe that the present cogent synthetic method warrants future study.

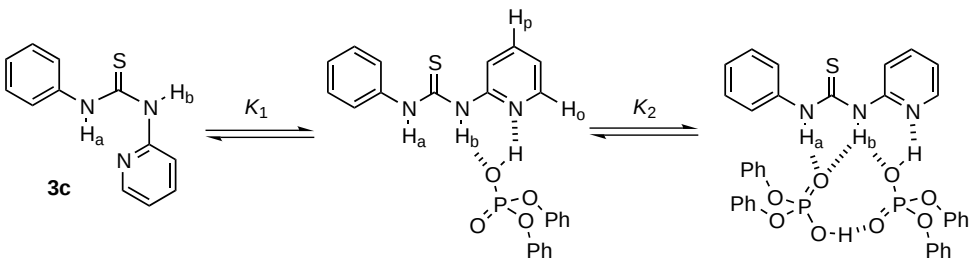


Figure 2. The plausible host–guest complexations.

Acknowledgements

This work was supported in part by The Nishida Research Fund for Fundamental Organic Chemistry (Y.K.).

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8. **Typical experimental procedure: preparation of 3a**. A mixture of phenylisothiocyanate (**2a**, 81 mg, 0.6 mmol) and 4-aminopyridine (**1a**, 47 mg, 0.5 mmol) in dry THF (1.5 mL) was placed in a Teflon reaction vessel and allowed to react at 0.6 GPa and 40°C for 24 h. After evaporation of the solvent, the crude product was purified by preparative TLC ($CHCl_3$/MeOH = 9:1) to give **3a** (77 mg, 67%) as a colorless powder. **3a**: FTIR (KBr) ν 3160, 1595, 1535, 1508, 1487 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.15 (1H, dt, J = 8.0, 1.2 Hz), 7.35 (2H, dt, J = 8.0, 1.2 Hz), 7.47 (2H, d-like, J = 8.0 Hz), 7.61 (2H, AA′XX′, J_{AX} = 4.8 Hz), 8.40 (2H, AA′XX′, J_{AX} = 4.8 Hz), 10.17 (2H, br s); ^{13}C NMR (CD_3OD) δ 117.2 (×2), 125.4 (×2), 126.9, 129.9 (×2), 139.9, 149.5, 150.2 (×2), 181.4. Anal. calcd for $C_{12}H_{11}N_3S$: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.62; H, 4.84; N, 18.19%.
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