Communications

Resin-Bound Isothiocyanates and Their Synthetic Equivalents as Intermediates for the Solid-Phase Synthesis of Substituted Thiophenes

Henrik Stephensen and Florencio Zaragoza*

Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

Received May 23, 1997

The development of new synthetic methodology for the automated solid-phase synthesis of small heterocyclic compounds continues to be a major focus in chemical research.[1]

We recently reported a solid-phase protocol for the preparation of 3-aminothiophenes and 2-methylenethiazoles.[2] In this synthesis a resin-bound cyanoacetamide was reacted with isothiocyanates under basic conditions. The resulting thioamides were then alkylated at sulfur with aromatic halo ketones to give methylenethiazoles. These could be directly cleaved from the support or cyclized to 3-aminothiophenes by treatment with DBU.[2]

In order to further exploit this powerful synthetic sequence, we considered to utilize resin-bound, amine-derived isothiocyanates or their synthetic equivalents as key intermediates. This was achieved with very satisfactory results in the following way (Scheme 1): treatment of resin-bound primary or secondary amines **1** with either carbon disulfide/tosyl chloride or thiophosgene in the presence of diisopropylethylamine led to the formation of thiocarbamoyl derivatives **2** or isothiocyanates **3**.[3] These intermediates **2**/**3** were then reacted with various acceptor-substituted acetonitriles, again under basic conditions, to yield thioamides **4**. *S*-Alkylation of the latter with α-halo ketones under slightly acidic conditions provided the resin-bound intermediates **5**.[4]

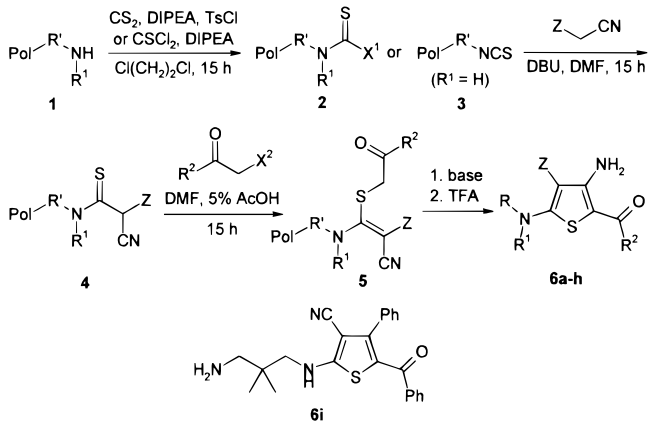
When these intermediates **5** were treated with a base (DBU or amines) and then cleaved from the support, pure thiophenes **6** were obtained. No major byproducts were observed.[5] The purities of the crude products, determined by HPLC (254 nm), ranged from 53% to 85% (Table 1).[6]

We encountered the following limitations for this reaction sequence: generally no thiophenes **6** resulted when aliphatic halo ketones or haloacetic esters were used for *S*-alkylation of the thioamides **4**.[7] On the other hand, a broad range of different acceptor-substituted acetonitriles could be used, such as aliphatic or aromatic sulfonylacetonitriles,[8] acylacetonitriles,[9] cyanoacetic esters and malononitrile, but not (cyanomethyl)phosphonates.

Apart from resin-bound diamines also α-amino acids, esterified with polystyrene-based Wang resin, gave the expected thiophenes. However, the purity of these α-amino acid derivatives was generally much lower than the purity of the diamine-derived products.

In conclusion a new, robust protocol for the solid-phase synthesis of thiophenes with variable substituents is

Scheme 1[a]



[a] Pol: polystyrene with Wang linker; R, R^1, R^2, Z: see Table 1; DIPEA: diisopropylethylamine; X^1: Cl, S−Ts; X^2: Cl, Br.

(1) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. Balkenhohl, F.; Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem.* **1996**, *108*, 2436. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. Früchtel, J. S.; Jung, G. *Ibid.* **1996**, *108*, 19 and **1996**, *35*, 17.

(2) Zaragoza, F. *Tetrahedron Lett.* **1996**, *37*, 6213.

(3) The structures of resin-bound intermediates could not be unambiguously determined spectroscopically (MAS-NMR). The proposed intermediates correspond to those obtained in solution.

(4) In the case where R^1 is hydrogen, this intermediate **5** may cyclize reversibly to a 4-hydroxythiazolidine. Cf. ref 2.

(5) All products were analyzed by HPLC-MS, ^{1}H and ^{13}C NMR, HPLC (254 nm and 214 nm), and IR spectroscopy. The molecular formulas were confirmed either by elemental analysis or by HRMS. We acknowledge Dr. D. Böhler and Dr. G. Remberg (University of Göttingen, Germany) for the measurement of HRMS spectra.

(6) Typical procedure. Preparation of thiophene **6h**: To Wang-resin-bound 1,3-diamino-2,2-dimethylpropane[10] (0.60 g, approximately 0.6 mmol, swollen in 1,2-dichloroethane) were added 1,2-dichloroethane (5.2 mL), carbon disulfide (0.8 mL), and diisopropylethylamine (0.52 mL). After shaking for 45 min a solution of tosyl chloride (1.32 g, 6.91 mmol) in 1,2-dichloroethane (1.5 mL) was added, and shaking was continued for 15 h. After filtration and washing of the resin with dichloromethane (5 × 8.0 mL), a solution of methanesulfonylacetonitrile (0.72 g, 6.04 mmol) in DMF (6.0 mL) was added, followed by the addition of DBU (0.84 mL). The resulting mixture was shaken for 15 h, filtered and washed with DMF (5 × 8.0 mL). The resin was then treated with a solution of 4-phenylphenacyl bromide (1.65 g, 6.00 mmol) in DMF (6.0 mL) and acetic acid (0.3 mL) for 15 h. The mixture was filtered, and the resin was washed with DMF (5 × 8.0 mL) and then suspended in a mixture of DMF (7.0 mL) and DBU (1.6 mL). After shaking for 15 h the resin was extensively washed with DMF, dichloromethane, and methanol. Cleavage from the support was effected by treatment with 50% trifluoroacetic acid in dichloromethane (6.0 mL) for 1 h. Concentration of the filtrate yielded 273 mg (80%) of **6h** (trifluoroacetate) as an oil (85% pure by HPLC, 254 nm), which crystallized upon addition of methanol (2.0 mL). Filtration and drying yielded 82 mg (24%) of slightly yellow crystals, 93% pure by HPLC (254 nm). Mp 216−218 °C (2-propanol); IR (KBr) 3459, 3313, 1677, 1549 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 0.98 (s, 6H), 2.74 (s, 2H), 3.16 (s, 2H), 3.25 (s, 3H), 7.42 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.3 Hz, 2H), 7.66−7.80 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) 22.25, 35.10, 43.43, 46.02, 54.37, 92.82, 99.29, 126.69, 127.41, 127.94, 128.99, 139.07, 140.08, 141.89, 155.52, 165.93, 183.81. Anal. Calcd for $C_{25}H_{28}F_3N_3O_5S_2$ (571.64): C, 52.53; H, 4.94; N, 7.35. Found: C, 52.60; H, 5.19; N, 7.13.

(7) Haloacetic esters have been used successfully for this reaction in solution. Gewald, K.; Hain, U.; Schmidt, M. *J. Prakt. Chem.* **1986**, *328*, 459. Augustin, M.; Dölling, W. *J. Prakt. Chem.* **1982**, *324*, 322. Laliberté, R.; Médawar, G. *Can. J. Chem.* **1971**, *49*, 1372.

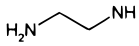
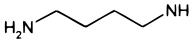
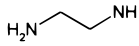
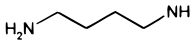
(8) Mehta, M. R.; Trivedi, J. P. *Indian J. Chem., Sect. B*, **1990**, *29*, 1146. Fishwick, B. R.; Rowles, D. K.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1171.

(9) When benzoylacetonitrile was used (entry **i**) no 3-aminothiophene but the 3-cyano-4-phenylthiophene **6i** was obtained.

(10) Prepared as described for resin-bound piperazine: Zaragoza, F.; Petersen, S. V. *Tetrahedron* **1996**, *52*, 5999.

S0022-3263(97)00915-8 CCC: $14.00

Table 1. Purities of the crude thiophenes 6, determined by HPLC (254 nm)

Entry	RR^1N	R^2	Z	Purity of **6**
a		phenyl	cyano	75%
b		phenyl	cyano	84%
c		phenyl	cyano	53%
d	1-piperazinyl	phenyl	cyano	68%
e		phenyl	4-chlorophenyl-sulfonyl	64%
f		phenyl	4-chlorophenyl-sulfonyl	82%
g		phenyl	4-chlorophenyl-sulfonyl	65%
h		4-biphenylyl	methylsulfonyl	85%
i		phenyl	benzoyl	85%

disclosed herein. This reaction sequence is based on easily available starting materials and can be realized at ambient temperature. It is therefore suitable for standard peptide synthesizers, thus permitting the fast preparation of numerous new compounds for high through put screening.

Supporting Information Available: Experimental details, including analytical and spectroscopic data for all new compounds (5 pages).

JO9709155