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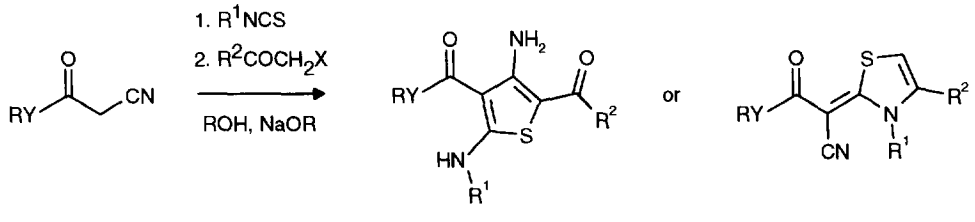
Solid-Phase Synthesis of Substituted 3-Aminothiophenes and 2-Methylene-2,3-dihydrothiazoles

Florencio Zaragoza

Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark
Telefax: (+45) 4466 3450, e-mail: flo@novo.dk

Abstract: Diversely substituted 3-aminothiophenes and 2-methylene-2,3-dihydrothiazoles have been synthesized on a solid support. A resin-bound cyanoacetamide reacted efficiently with aliphatic or aromatic isothiocyanates in DMF/DBU. The resulting intermediates were then alkylated at sulphur with different α-haloketones under acidic conditions. Acidolytic cleavage from the support yielded 2-methylene-2,3-dihydrothiazoles in purities up to 88% (HPLC). Alternatively, treatment of the resin-bound, S-alkylated intermediates with DBU, followed by acidolytic cleavage, yielded 3-aminothiophene derivatives in purities up to 91% (HPLC). Copyright © 1996 Elsevier Science Ltd

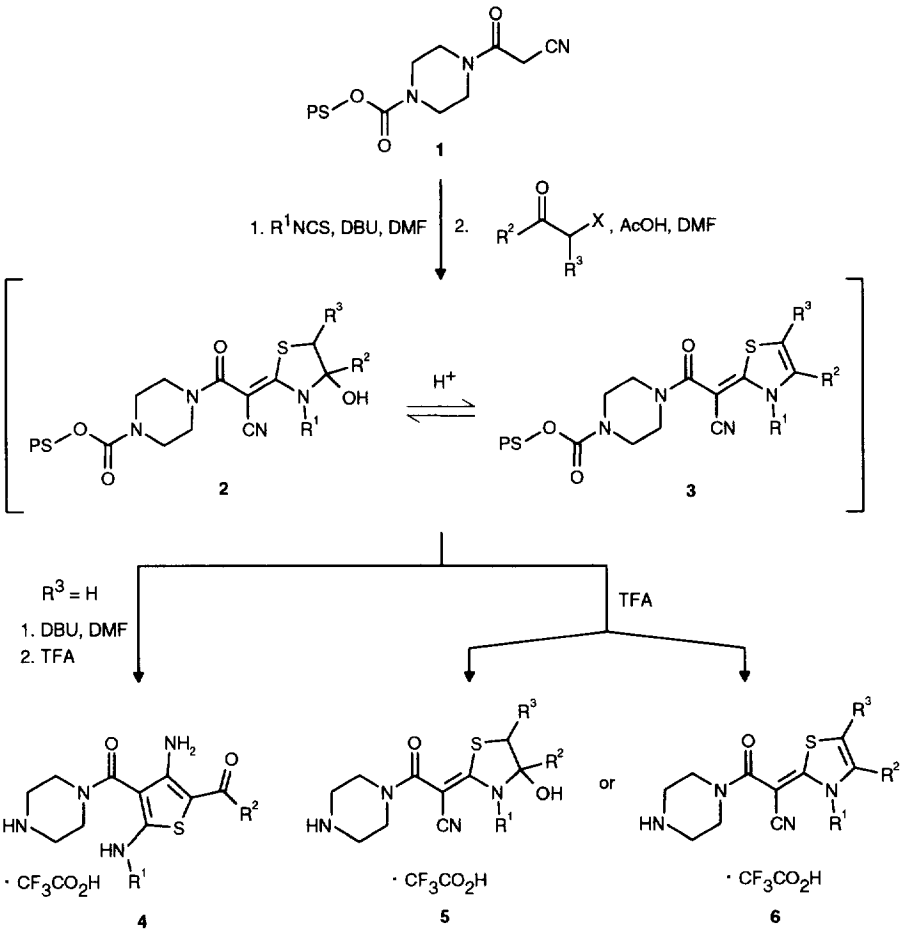
As part of a continuing program which is concerned with the development of solid-phase syntheses of heterocyclic compounds,[1] we became interested in the thiophene-synthesis shown in scheme 1, first reported by R. Laliberté[2] and coworkers.



Scheme 1. Y = O, NR'; R = methyl, ethyl; R' = hydrogen, alkyl, aryl; R^1, R^2 = alkyl, aryl; X = Cl, Br.

The realization of this reaction on a solid support would provide non-peptidic, non-oligomeric compounds with up to three independently variable groups, thus being a potentially valuable process for the parallel and combinatorial preparation of small molecules for high volume throughput screening.[3]

We have found, that this reactions sequence[4] can indeed be realized on a polystyrene support, if the original procedure is modified in the way shown in scheme 2. We were pleased to find, that the outcome of the reaction could easily be controlled by adjustment of the reaction conditions.



Scheme 2. Abbreviations: PS: polymeric support [polystyrene with *p*-benzyloxybenzylalcohol (Wang) linker]; DBU: 1,8-diazabicyclo-[5.4.0]undec-7-ene; TFA: trifluoroacetic acid

Treatment of the resin-bound (cyanoacetyl)piperazine **1**[1] with aliphatic or aromatic isothiocyanates in the presence of DBU, followed by S-alkylation with α-haloketones under slightly acidic or neutral conditions resulted in the formation of the intermediates **2/3**. In contrast to the experimental results of Laliberté,[2] no uniform product formation was observed, if the S-alkylation was performed under basic conditions (e.g. in the presence of tertiary amines or alcoholates). In view of the experimental results given below, we assume that the intermediates **2/3** have the structures as shown in scheme 2, the predominant form being determined by the electronic properties of the substituents R^1-R^3.

When these intermediates **2/3a-h** were treated with DBU in DMF, ensued by acidolytic cleavage of the Wang linker with trifluoroacetic acid, the 3-aminothiophenes **4a-h** were obtained as trifluoroacetates in purities up to 91% (HPLC, see table 1).[5] Direct treatment of the intermediates **2/3a-h** with trifluoroacetic acid

yielded the 2-methylene-2,3-dihydrothiazoles **5/6a-h** (of unknown configuration).

Table 1. Purities[a] of 3-Aminothiophenes **4a-h** and 2-Methylenethiazoles **5/6a-h**.

Entry	R^1	R^2	R^3	Purity of 4[b]	Purity of 5[c]	Purity of 6[c]
a	phenyl	phenyl	H	76%	-	88%
b	phenyl	3,4-dihydroxyphenyl	H	-	-	81%
c	phenyl	2,4-dichlorophenyl	H	91%	-	87%
d	ethyl	2,4-dichlorophenyl	H	76%	-	87%
e	4-dimethylaminophenyl	phenyl	H	-	-	69%
f	ethyl	phenyl	methyl	-	-	86%
g	phenyl	ethoxycarbonyl	H	-	72%	-
h	phenyl	trifluoromethyl	H	90%	91%	-

[a]Purities of crude products, determined by HPLC (254 nm). [b]The thiophenes **4** were the only products obtained, when the intermediates **2/3** were treated with DBU and then cleaved from the support. [c]The thiazoles **5/6** were the only products obtained, when the intermediates **2/3** were directly cleaved from the support by treatment with TFA.

We encountered the following limitations for the choice of substituents of thiophenes **4**: complex mixtures of products were obtained in those cases, where strongly electron-donating isothiocyanates or α-haloketones were used (e.g. **4b** or **4e**). Generally, no thiophenes resulted from aliphatic haloketones, 3-bromo-1,1,1-trifluoro-2-propanone being the only non-aromatic haloketone which led to a clean thiophene-formation.[6] The reaction sequence leading to the formation of the 2-methylenethiazoles **5/6a-h** showed a higher tolerance towards variation of the substitution pattern. Generally, pure products were obtained for both electron-donating and electron-withdrawing isothiocyanates or α-haloketones.[5] In most of the cases studied, the dehydrated 2-methylenethiazoles **6** were obtained as single products. 4-Hydroxythiazolidines of the type **5** resulted only in those cases where R^2 was a strongly electron-withdrawing group (**5g** and **5h**).

In conclusion, a solid-phase protocol for the synthesis of thiophenes and thiazoles with variable substituents is disclosed herein. This reaction sequence is based on easily available starting materials and can be realized at ambient temperature. Although only the conversion of the resin-bound (cyanoacetyl)piperazine **1** into different thiophenes or thiazoles has been described here, this sequence may also be applicable to other resin-bound cyanoacetamides [e.g. those derived from resin-bound α-amino acids, from other resin-bound diamines or from a support with a benzhydrylamine (Rink) linker], thus permitting the fast preparation of numerous, highly diverse compounds as potential new leads.

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5. *Typical procedure for the solid-phase synthesis of 3-aminothiophenes 4: Synthesis of [4-amino-5-(2,4-dichlorobenzoyl)-2-phenylaminothien-3-yl]piperazin-1-ylmethanone trifluoroacetate* (**4c**). A solution of DBU (0.7 mL) in DMF (2.5 mL) was added to the cyanoacetamide **1**[1] (0.2 g, approx. 0.2 mmol), followed by the addition of phenyl isothiocyanate (0.24 mL, 2.02 mmol). The mixture was shaken for 18 h, filtered, and the resin was extensively washed with DMF. A solution of 2,4-dichlorophenacyl chloride (0.48 g, 2.16 mmol) in DMF (2.0 mL) was added to the resin, followed by the addition of glacial acetic acid (0.2 ml), and the mixture was shaken for 20 h. After filtration and washing with DMF, the resin was suspended in a mixture of DBU (1.0 mL) and DMF (2.0 mL) and shaken for 20 h. After filtration the resin was carefully washed with DMF, methanol, dichloromethane and 10% AcOH in dichloromethane. It was suspended in dichloromethane (2.0 mL) and TFA (2.0 mL) and shaken for 3 h. Filtration, washing with dichloromethane and concentration of the filtrates yielded 145 mg (quant.) of the trifluoroactate of thiophene **4c** as an oil (slightly contaminated with DMF). HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitored at 254 nm): elution at 21.7 min, 91% pure. IR (film): 3450, 3000, 2700, 1680 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.10-3.20 (m, 4H), 3.55-3.80 (m, 4H), 7.12 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 7.8, 1.5 Hz, 1H), 7.69 (d, J = 1.5 Hz, 1H), 8.9 (s, br, 2H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 40.02 (t), 42.63 (t), 96.63 (s), 104.05 (s), 115.5 (q, J = 291 Hz, CF_3), 121.15 (d), 124.76 (d), 127.45 (d), 129.32 (d), 129.49 (d), 129.55 (d), 130.72 (s), 134.31 (s), 139.07 (s), 140.25 (s), 156.01 (s), 157.90 (s), 158.09 (q, J = 37 Hz, CF_3-CO_2), 162.85 (s), 180.70 (s); MS (EI) *m/z* 475, 477 (MH^+); HRMS calcd for $C_{22}H_{20}Cl_2N_4O_2S$ [M^+] 474.0681, found 474.0684. If in the previous procedure the final treatment with DBU was omitted, the corresponding thiazolidine trifluoroacetates **5g/h** or the 2-methylene-2,3-dihydrothiazole trifluoroacetates **6a-f** were obtained. Data for *3-oxo-2-(3,4-diphenyl-3H-thiazol-2-ylidene)-3-piperazin-1-ylpropionitrile trifluoroacetate hemihydrate (6a)*: Yellow solid, mp 233-235 °C (methanol); IR (KBr) 3445, 3120, 2171 (CN), 1666 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.08 (m, 4H), 3.54 (m, 4H), 7.12-7.42 (m, 11H), 8.90 (s, br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.52 (t), 64.65 (s), 109.64 (d), 116.57 (s), 128.00 (d), 129.06 (d), 129.13 (d), 129.52 (d), 129.63 (s), 129.86 (d), 130.10 (d), 136.73 (s), 142.47 (s), 168.16 (s), 169.57 (s); MS (EI) *m/z* 389 (MH^+), 303. Anal. Calcd. for $C_{24}H_{21}F_3N_4O_3S$ (502.51) + ½ H_2O: C, 56.35; H, 4.33; N, 10.95. Found: C, 56.18; H, 4.26; N, 10.82. The structural proposals for all the compounds listed in table 1 are based on ^1H NMR, ^{13}C NMR, MS and IR spectral data.
6. When haloacetic esters or haloacetamides were used as alkylating agents, no ring closure of the S-alkylated intermediate to either thiazolinones[4] or 3-aminothiophenes[2] was observed.

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