Stereoselective Synthesis of *trans*-2,3-Disubstituted 5-Amino-4-cyano-2,3-dihydrothiophenes

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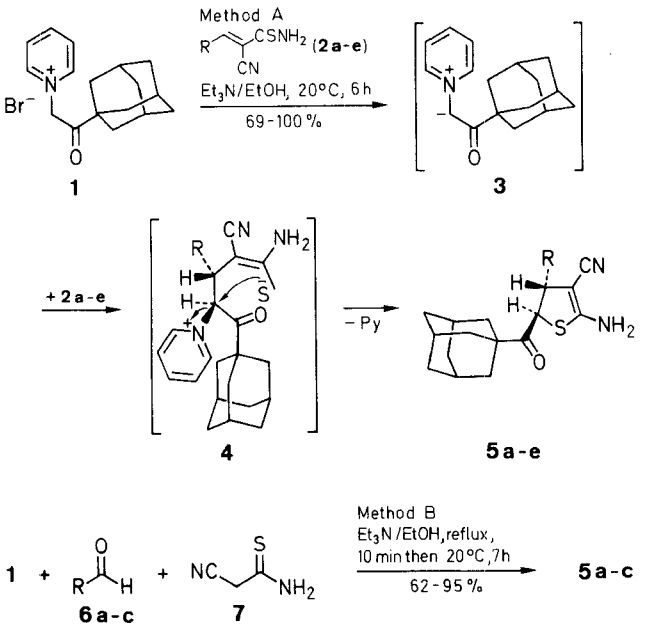
Interaction of 1-(1-adamantylcarbonylmethyl)pyridinium bromide (**1**) with arylmethylenecyanothioacetamides **2** proceeds stereoselectively with formation of 2-(1-adamantylcarbonyl)-5-amino-3-aryl-4-cyano-2,3-dihydrothiophenes. Dihydrothiophenes were obtained in a good yield by three-component condensation of pyridinium bromide **1**, aldehydes and cyanothioacetamide in presence of triethylamine.

Thiophenes containing the 5-amino-4-cyano substituted fragment have wide application in the synthesis of industrially useful compounds: dyes, pesticides and medical preparations.[1-4] Gewald[1-5] and Thorpe[1,4,6,7] reactions are frequently used in the synthesis of these thiophenes. However, no example of stereoselective synthesis of hydrogenated thiophenes with the 5-amino-4-cyano substituted fragment have been reported.

The present paper reports a new reaction of 1-(1-adamantylcarbonylmethylene)pyridinium ylide **3** with arylmethylenecyanothioacetamides, yielding dihydrothiophenes **5**. The pyridinium ylide was not isolated but was formed in the reaction mixture in ethanol at 25°C during the treatment of the corresponding salt **1** by an equimolar amount of triethylamine. Further reaction of pyridinium ylide **3** with compounds **2** proceeds through the formation of unstable Michael adducts **4**. Adducts **4** can not be isolated in these reaction, but undergo regio- and stereocontrolled intramolecular 1,5-cycloelimination of pyridine to form *trans*-2-(1-adamantylcarbonyl)-5-amino-3-aryl-4-cyano-2,3-dihydrothiophenes **5** (Method A, Table 1).



2, 4–6	a	b	c	d	e
R	4-Py	4-FC_6H_4	4-ClC_6H_4	4-BrC_6H_4	4-$MeOC_6H_4$

According to IR and ^{1}H-NMR spectroscopy, the above reactions proceed with a high selectivity (Table 1). The ^{1}H-NMR spectra of these compounds shows a pair of doublets for H-3 and H-2 at $\delta = 3.74–4.76$ ($^3J = 4.5–5.2$ Hz). Hence H-3 and H-2 of hydrogen are in a *trans* position, similarly to substituted 2,3-dihydrofurans[8]. A characteristic feature of the structure of compounds in the IR spectra is the presence of a conjugated adsorption band at $\nu = 2184\,cm^{-1}$. The NH_2 group adsorption bands are observed at $\nu = 1624–1650$ and $3212–3452\,cm^{-1}$.

***trans*-2-(1-Adamantylcarbonyl)-5-amino-3-aryl-4-cyano-2,3-dihydrothiophenes 5; General Procedures:**

Method A (for dihydrothiophenes **5a–e**): A mixture of **1** (3.36 g, 10 mmol), **3a–e** (10 mmol) and Et_3N (1.01 g, 10 mmol) in EtOH (20–30 mL) is heated to boiling and filtered through a folded filter paper. The solution is stirred at 20 °C for 6 h. The precipitate is filtered, washed with H_2O, EtOH and hexane. It is recrystallized from EtOH to afford thiophenes **5a–e**.

Method B (for dihydrothiophenes **5a–c**): A mixture of **1** (3.36 g, 10 mmol), **6a–e** (10 mmol), **7** (1.00 g, 10 mmol) and Et_3N (1.01 g, 10 mmol) is boiled in EtOH (20–30 mL) for 10 min. Then the mixture is allowed to cool to 20 °C and is stirred for 7 h. The precipitate is treated as for method A.

Table. 2,3-Disubstituted 5-Amino-4-cyano-2,3-dihydrothiophenes **5** Prepared

Product	Yield (%) (Method)	Molecular Formula[a]	mp (°C)	IR (KBr)[b] ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[c] δ, J (Hz)
5a	100 (A), 95 (B)	$C_{21}H_{19}N_3OS$ (361.59)	205–208	1650, 1696, 2184, 2852, 2904, 3212, 3324, 3388	1.63, 1.70, 1.92 (m, 15$H_{adamantyl}$), 4.46 (d, 1 H, ^3J = 4.5, H-3), 4.76 (d, 1 H, H-2), 7.27 (d, 2 H, ^3J = 6.2, H-3,5$_{pyridyl}$), 7.30 (s, 2 H, NH_2), 8.56 (d, 2 H, H-2,6$_{pyridyl}$)
5b	70 (A)	$C_{22}H_{23}FN_2OS$ (382.5)	156–158	1624, 1692, 2180, 2848, 2904, 3232, 3360	1.62, 1.70, 1.92 (m, 15$H_{adamantyl}$), 4.46 (d, 1 H, ^3J = 4.7, H-3),4.67 (d, 1 H, H-2), 7.14–7.42 (m, 6 H, H_{arom}, NH_2)
5c	69 (A), 73 (B)	$C_{22}H_{23}ClN_2OS$ (398.9)	170–172	1624, 1690, 2184, 2848, 2908, 3212, 3360	1.62, 1.70, 1.93 (m, 15$H_{adamantyl}$), 4.45 (d, 1 H, ^3J = 4.8, H-3), 4.69 (d, 1 H, H-2), 7.18 (s, 2 H, NH_2), 7.24 (d, 2H_{arom}, ^2J = 7.8), 7.38 (d, 2H_{arom})
5d	78 (A)	$C_{22}H_{23}NrN_2OS$ (443.4)	191–193	1624, 1684, 2184, 2848, 2900, 3352, 3452	1.68, 1.74, 1.92 (m, 15$H_{adamantyl}$), 4.46 (d, 1 H, ^3J = 4.7, H-3), 4.68 (d, 1 H, H-2), 7.18 (s, 2 H, NH_2), 7.25 (d, 2H_{arom}, ^3J = 8.0), 7.58 (d, 2H_{arom})
5e	82 (A)	$C_{23}H_{26}N_2O_2S$ (394.5)	207–209	1626, 1682, 2184, 2848, 2900, 3220, 3316, 3344	1.62, 1.68, 1.92 (m, 15$H_{adamantyl}$), 3.74 (s, 3 H, CH_3), 4.38 (d, 1 H, ^3J = 5.2, H-3), 4.62 (d, 1 H, H-2), 6.90 (d, 2H_{arom}, ^3J = 8.3), 7.12 (s, 2 H, NH_2), 7.18 (d, 2H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.23, H ±0.12, N ±0.30, S ±0.28.

[b] Recorded on a Perkin-Elmer 577 spectrophotometer.

[c] Obtained on a Bruker WM-250 (250 MHz) spectrometer.

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The stereoselectivity of this process is determined by stereoselective addition of pyridinium ylide **3** to compounds **2** and formation of *trans*-adduct **4**. The regioselectivity of reactions is determined by the prevalence of the intramolecular 1,5-cycloelimination in adduct **4** over 1,3 or 1,6-eliminations. Such a regioselectivity may be a result of the steric hindrance of the carbonyl group caused by the adamantyl residue.

Taking into account these results we have simplified the synthesis of compounds **5**. Thiophenes **5a–c** were obtained in good yields by three-component condensation of pyridinium salt **1**, aldehydes **6a–c** and cyanothioacetamide **7** in ethanol at 25 °C (Method B, Table 1).

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