# One-pot preparation of isomeric acetyl- and 2,2,2-trifluoroacetyl-azidothiophenes by selective bifunctionalization of dibromothiophenes *via* halogen–lithio exchange

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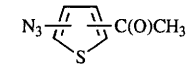
**A series of isomeric acetyl- (1) and 2,2,2-trifluoroacetyl-azidothiophenes (2) are prepared from 2,3-, 3,4- and 2,5-dibromothiophenes *via* a one-pot procedure entailing stepwise halogen–lithium exchange and successive reaction of the resulting thienyllithium derivatives with *N*,*N*-dimethylacetamide (or *N*,*N*-diethyl-2,2,2-trifluoroacetamide) and tosyl azide.**

Azides, including heteroaromatic azides, are a very important class of compounds with physical, industrial and biochemical applications.[1] In recent years we have been interested in the investigation and synthetic application of azides derived from five-membered heteroaryl systems, especially azido-thiophenes and -benzo[*b*]thiophenes, now readily available through reaction of the lithiated heteroaromatics with tosyl azide.[2] However, many polar substituents on the thiophene ring (*e.g.* formyl, acyl, nitro, cyano) limit the scope of this procedure and therefore force the preparation of azidothiophenes *via* nucleophilic substitution reaction of the corresponding bromo [3] and nitro [4] derivatives with azido ion.

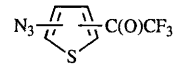
Our recent results suggest that α-azidobenzo[*b*]thiophene (2-BTA) [5] and α-azido-thiophene [6] and -selenophene [7] undergo unimolecular thermal decomposition and ring-opening. This observation is consistent with the assumption that both ground-state resonance conjugation of the azido group with the attached ring and the reorganization of the delocalized π-bond system play an important role in the cleavage of the azido $N–N_2$ bond. However, examples of electronic effects exerted by *ortho*- or *para*-like substituents upon unimolecular decomposition and ring cleavage of α-azidothiophenes (or other α-azidoheteroaryls) are very limited.†

We were therefore prompted to extend our study to thermal decomposition of 2,3-, 3,4- and 2,5-acyl-azidothiophenes. These azides were also of interest to us as straightforward precursors to synthetically useful (and hitherto unknown) acyl-substituted aminothiophenes.[11] Azidothiophenes can be selectively converted to the amines in high yields upon reaction with hydrogen sulfide [3,12] or other reagents.[11,13]

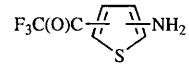
We now report a one-pot synthetic procedure to azidoacetylthiophenes **1a–c** and 2,2,2-trifluoroacetyl azidothiophenes **2a–c**, starting from 2,3-, 3,4- and 2,5-dibromothiophene. Single halogen–lithium exchange and subsequent reaction of the produced bromothienyllithium derivatives with *N*,*N*-dimethylacetamide (or *N*,*N*-diethyl-2,2,2-trifluoroacetamide, respectively) [14] results in the formation of intermediate bromothiophenes bearing a 'protected' carbonyl group.[15] These intermediates are then allowed to undergo a successive halogen–lithium exchange followed by reaction of the lithiated compounds with tosyl azide. Final treatment of the resulting acyltriazene dilithium salts with hydrochloric acid then tetrasodium pyrophosphate affords the azides **1a–c** and **2a–c**, whose structural assignments were made on the basis of IR, $^1H$ and $^{13}C$ NMR and mass spectral data (Table 1). Satisfactory yields of azides **1** and **2** were normally obtained by our present procedure. However, 2-acetyl-3-azidothiophene **1a** could be obtained only in *ca.* 10% yield. In this case **1a** was accompanied by major amounts of 2-azido-3-bromothiophene (38%) whose formation remains unclear at this stage.



**1a** 2-Acetyl-3-azidothiophene
**1b** 4-Acetyl-3-azidothiophene
**1c** 5-Acetyl-2-azidothiophene



**2a** 2-(Trifluoroacetyl)-3-azidothiophene
**1b** 4-(Trifluoroacetyl)-3-azidothiophene
**1c** 5-(Trifluoroacetyl)-2-azidothiophene



**3**

*Reagents:* i, BuLi, $RC(O)NR'_2$; ii, BuLi, $TsN_3$

In general, our one-pot procedure appears to be more satisfactory when applied to the preparation of trifluoroacetyl azidothiophenes **2**, possibly due to a slightly greater stability of these compounds with respect to their acetyl analogues **1**. In fact, the azides **2a–c** are solid compounds which can be stored in the dark at 0 °C without any sign of decomposition, whereas the azides **1a–b**, and especially **1c**, require storing in a freezer. Apparently, the more strongly electron-withdrawing trifluoroacetyl substituent [whose $\sigma_p$ Hammet constant value and resonance parameter ($R$) is 0.80 and 0.26, respectively] [15] can confer a greater stabilization to the *ortho*- and *para*-like azido moiety than the acetyl group ($\sigma_p = 0.50$, $R = 0.17$).[16]

Finally, hydrogen sulfide reduction of the 2-azido-5-(2,2,2-trifluoroacetyl)thiophene **2c** to the corresponding amine **3** was shown to occur in virtually quantitative yield at 0 °C within 10 min.

## Experimental

### Preparation of azides 1a–c and 2a–c

A solution of appropriate dibromothiophene (0.016 mol) in dry diethyl ether (20 $cm^3$) was treated, with stirring under nitrogen at −70 °C, with butyllithium (1.6 mol $dm^{-3}$ in hexane; 10 $cm^3$). The reaction mixture was stirred for an additional 45 min, after which a solution of *N*,*N*-dimethylacetamide (or *N*,*N*-diethyl-2,2,2-trifluoroacetamide) (0.016 mol) in dry ether (10 $cm^3$) was added dropwise. After the addition was complete the resulting mixture was stirred at −30 °C for 1–3 h, again cooled to −70 °C and then treated with further butyllithium (1.6 mol $dm^{-3}$ in hexane; 10 $cm^3$) for 1 h. To the resulting mixture was

† Thermally induced ring-cleavage of 2-azido-5-oxofurans has been postulated to occur *via* a nitrene intermediate.[8] In addition, very recent kinetic investigations of thermal ring-cleavage of 5-azidopyrazoles [9] and 5-methyl- and 5-trimethylsilyl-2-azidothiophene [10] have been reported.

**Table 1** Yields and physical and IR and $\delta_H$ NMR spectral data of azidothiophenes

| Compound | Yield (%) | Mp/°C | IR | | δ (ppm) | | | | | $J_{HH}$/Hz |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $N_3$ | CO | H-2 | H-3 | H-4 | H-5 | $CH_3$ | |
| **1a** | 10 | 57–58 | 2130 | 1730 | | | 7.01 | 7.58 | 2.55 | 5.4 |
| **1b** | 32 | Oil | 2135 | 1760 | 6.91 | | | 8.04 | 2.53 | 3.4 |
| **1c** | 47 | 42–43 | 2130 | 1660 | | 6.63 | 7.48 | | 2.49 | 4.3 |
| **2a** | 45 | 26–27 | 2140 | 1760 | | | 7.09 | 7.84 | | 5.3 |
| **2b** | 58 | 36–38 | 2130 | 1715 | 7.02 | | | 8.33 | | 3.3 |
| **2c** | 60 | 24–25 | 2130 | 1685 | | 6.75 | 7.77 | | | 4.4 |

added tosyl azide (0.016 mol) in dry diethyl ether (20 $cm^3$). The pale yellow triazene salt which formed was stirred and allowed to reach 0 °C within 6–48 h, then rapidly filtered off and suspended in pentane. The suspension was treated at 0 °C for 10 min with hydrochloric acid (2 equiv.) in ice and then with tetrasodium pyrophosphate (0.016 mol) in water (20 $cm^3$). The yellow pentane layer was collected and the excess of solvent eliminated under vacuum to give a residue which was chromatographed on a 'Florisil' (BDH Type 100–200 U.S. mesh) column using hexane with increasing amounts of diethyl ether (up to 50%) as eluent.

**5-Acetyl-2-azidothiophene 1c.** (7.2 mmol, 47%), mp 42–43 °C; $\nu_{max}/cm^{-1}$ 3130, 2130 ($N_3$), 1660 (CO); $\delta_H$(200 MHz; $CDCl_3$) 7.48 (1 H, d, *J* 4.3,‡ H-4), 6.63 (1 H, d, *J* 4.3, H-3) and 2.49 (3 H, s); $\delta_C$(50 MHz; $CDCl_3$) 190.1 (s, CO), 151.6 (s, C-2), 138.2 (s, C-5), 133.0 (d, C-4), 116.6 (d, C-3) and 26.1 (q, Me); *m*/*z* 167 ($M^+$, 6.6%), 139 (M–$N_2$, 0.7%), 111 (20.8), 110 (0.7), 97 (14.4), 96 (8.4), 69 (5.8), 45 (9.6) and 43 (100) (Found: $M^+$, 167.015 36. $C_6H_5N_3OS$ requires *M*, 167.015 33).

**5-(Trifluoroacetyl)-2-azidothiophene 2c.** (9.6 mmol, 60%), mp 24–25 °C; $\nu_{max}/cm^{-1}$ 3120, 2970, 2130 ($N_3$), 1685 (CO), 1240–1140 ($CF_3$); $\delta_H$(200 MHz; $CDCl_3$) 7.77 (1 H, dq, *J* 4.38 and 1.51, H-4) and 6.75 (1 H, d, *J* 4.38, H-3); $\delta_C$(50 MHz; $CDCl_3$) 172.8 (q, $J_{CF}$ 36.5, CO), 156.6 (s, $J_{CH}$ 12.8, C-2), 137.5 (d, $J_{CF}$ 4.0, $J_{CH}$ 172.0, C-4), 129.7 (s, $J_{CH}$ 10.5, C-5), 117.7 (d, $J_{CH}$ 173.4, C-3) and 116.6 (q, $J_{CF}$ 290.4, $CF_3$); *m*/*z* 221 ($M^+$, 36.3%), 193 (M–$N_2$, 13.7%), 96 (100), 69 (12.8) and 45 (13.6) (Found: $M^+$, 220.987 04. $C_6H_2F_3N_3OS$ requires *M*, 220.987 07).

**Preparation of 2-amino-5-(2,2,2-trifluoroacetyl)thiophene 3**

Following a standard procedure the reduction of the azide **2c** was carried out with hydrogen sulfide bubbled at 0 °C through a methanolic solution (5 $cm^3$) of the azide (1 mmol) containing a few drops of piperidine. The stream of hydrogen sulfide was continued at this temperature until TLC showed the absence of the starting azide (10 min), after which the precipitated sulfur was filtered off. The solvent was eliminated and the residue chromatographed on an aluminium oxide (Merck Type A. 1076) column using hexane with increasing amounts of diethyl ether (up to 80%) as eluent to give the title amine **3** (0.96 mmol, 96%) as a yellowish solid, mp 165–167 °C; $\nu_{max}/cm^{-1}$ 3310 and 3390 ($NH_2$), 1600 (CO), 1220–1140 ($CF_3$); $\delta_H$(200 MHz; $CDCl_3$) 7.60 (1 H, dq, *J* 4.65 and 1.60, H-4), 7.32 (2 H, br s) and 6.15 (1 H, d, *J* 4.65, H-3); $\delta_C$(50 MHz; $CDCl_3$) 170.2 (s, C-2), 168.6 (q, $J_{CF}$ 34.3, CO), 140.1 (d, $J_{CF}$ 3.6, C-4), 117.2 (q, $J_{CF}$ 290.1, $CF_3$) and 108.5 (d, C-3); *m*/*z* 195 ($M^+$, 14.3%), 126 (M–$CF_3$, 68.2%), 71 (35.0), 69 (13.7), 54 (100), 52 (8.2) and 45 (8.4) (Found: $M^+$, 194.996 59. $C_6H_4F_3NOS$ requires *M*, 194.996 57).

‡ *J* Values given in Hz.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