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Flash vacuum pyrolysis of 2-acetyl-3-azido[1]benzothiophene

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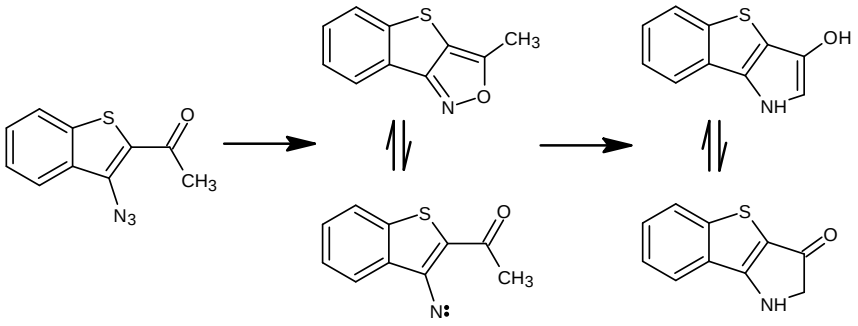
Abstract

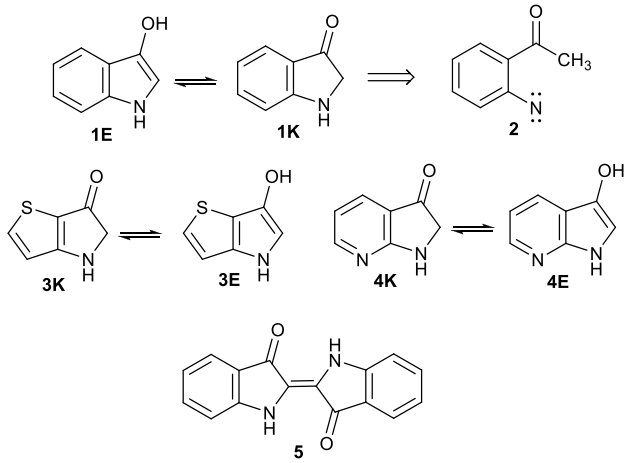
Flash vacuum pyrolysis (FVP) of 2-acetyl-3-azido[1]benzothiophene at 300 °C provides 3-methyl [1]benzothieno[3,2-c]isoxazole (72%). At higher temperatures, the heteroindoxyl 1,2-dihydro[1]benzo-thieno[3,2-b]pyrrol-3-one was obtained in low yield (ca. 10%). The heteroindoxyl exists as a mixture of keto and enol forms in DMSO solution. Because of the easy oxidative dimerisation of these products to indigotin (and its heteroanalogues), such reactions are excellent examples of the synthetic advantages of FVP with the monomeric products conveniently generated under vacuum in a solvent-free, air-free environment.



Keywords: Flash vacuum pyrolysis, FVP, heteroindoxyl, nitrene, fused heterocycles

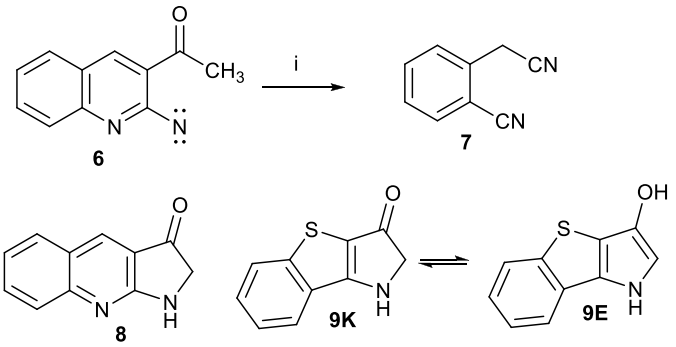
Introduction

We have recently employed a gas-phase nitrene insertion process to generate indoxyl (1)[1] and its heterocyclic analogues (**3**)[2] and (**4**)[3] under flash vacuum pyrolysis (FVP) conditions (Scheme 1). Azides or fused tetrazoles were used as precursors to the nitrene (*e.g.,* **2**).[1-3] Because of the easy oxidative dimerisation of these products to indigotin (**5**) (and its heterocyclic analogues) such reactions are excellent examples of the synthetic advantages of FVP with the monomeric products conveniently generated under vacuum in a solvent-free, air-free environment.



Scheme 1

Unfortunately, application of the method to the quinoline analogue (**6**) gave the dinitrile (**7**) as the major product. We believe this product is formed via a known nitrene insertion in the hetero ring[4], and subsequent rearrangements in which the elimination of ketene is the final step. Although the heteroindoxyl (**8**) could be reliably detected in the complex pyrolysate, it was never the major product and proved too unstable to isolate (Scheme 2).[3] In this paper, we complete our current studies of heteroindoxyls by using the nitrene strategy to achieve the successful synthesis of the benzothiophene analogue of **3**, *viz.* 1,2-dihydro[1]benzothieno[3,2-*b*]pyrrol-3-one (**9**). This example demonstrates that the presence of a fused benzene ring in the precursor does not necessarily preclude the formation of an indoxyl by the nitrene strategy. In addition, a detailed comparison is now possible between the behaviour of the azide precursors to **1**, **3** and **9** and the tautomeric properties of the products.



Scheme 2. *Reagents and conditions:* (i) FVP 600 °C.

Results and Discussion

A one-step route to 2-acetyl-3-amino[1]benzothiophene (**10**) is available[5]; this product was obtained in 80% yield after a 16 h reaction time (see Supplementary Material file, p. S2). Since the structure of the corresponding 2-acetyl-3-amino[1]benzofuran has been reported,[6] the X-ray crystal structure of **10** was obtained for comparison (Fig. 1); there are two molecules in the asymmetric unit (data for the second molecule and the benzofuran equivalent are shown in Table 1). The heavy atom skeleton of the molecule, as a whole, is planar {mean deviation from best plane 0.095 Å (0.034 Å). Maximum deviation from best plane is 0.0245 Å at C(11) [0.0895 Å at C(21)]. There is intramolecular hydrogen bonding between the NH and the C=O of the acetyl group {H(31)-O(10) 2.14 Å [H(131)-O(20) 2.16 Å]}; N(3)-O(10) 2.758(2) Å [N(13)-O(20) 2.7831(19) Å]; angle at hydrogen 126° (125°)} which means that C(2)-C(10) adopts an *s-E* configuration. With the exception of the region around the heteroatom, there are no significant differences in bond lengths between the benzothiophene (**10**) and the corresponding benzofuran.[6] Similarly, the expected push-pull conjugation between N(3) and the carbonyl group of **10** has little effect on the C(2)-C(3) bond length, by comparison with a 2-aroylbenzothiophene previously reported.[7]

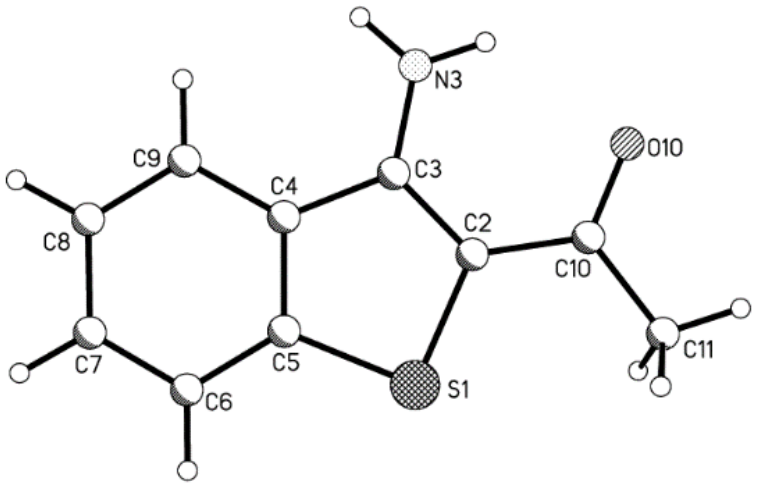
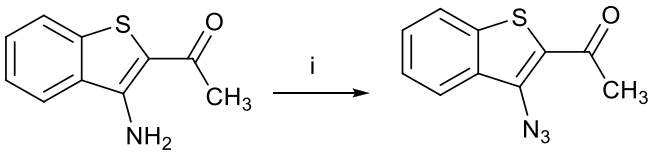


Figure 1. Plot of one of the molecules of **10** showing the crystallographic numbering scheme.

Table 1. Bond lengths of benzothiophene molecules of **10** found in asymmetric units of crystal structure (crystallographic numbering)

Bond	Benzothiophene (Asymmetric Unit 1)	Benzothiophene (Asymmetric Unit 2)	Benzofuran Equivalent
S1–C5	1.7353(15)	1.7300(16)	1.360(3)
S1–C2	1.7548(14)	1.7581(15)	1.404(3)
C2–C10	1.434(2)	1.430(2)	1.420(4)
C2–C3 (b)	1.387(2)	1.390(2)	1.378(3)
C3–C4 (	1.445(2)	1.447(2)	1.447(4)
C3–N3	1.351(2)	1.346(2)	1.355(3)
C4–C9	1.399(2)	1.399(2)	1.394(4)
C4–C5	1.407(2)	1.406(2)	1.399(3)
C5–C6	1.398(2)	1.398(2)	1.381(4)
C6–C7	1.382(3)	1.380(3)	1.380(4)
C7–C8	1.398(3)	1.397(3)	1.399(4)
C8–C9	1.383(2)	1.384(2)	1.381(4)
C10–C11	1.504(2)	1.505(3)	1.489(4)
C10–O10	1.242(2)	1.247(2)	1.245(3)

Due to the low solubility of **10** in dilute HCl, standard diazotization conditions gave only recovered starting material. When phosphoric acid was used instead, however, the increased solubility of **10** (and its phosphate salt) in the medium allowed diazotization and reaction with sodium azide to provide the azidobenzothiophene (**11**) in 47% yield, initially as a foam which could be purified by recrystallisation (Scheme 3).



10 **11**

Scheme 3. *Reagents and conditions:* (i) NaN_3, H_3PO_4, 0-20 °C, 47%.

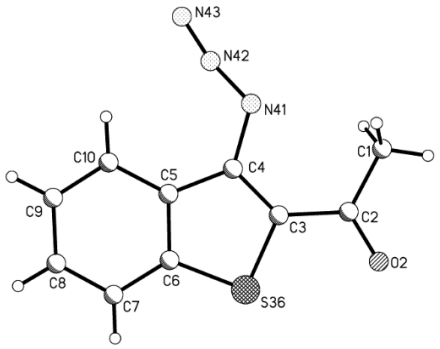
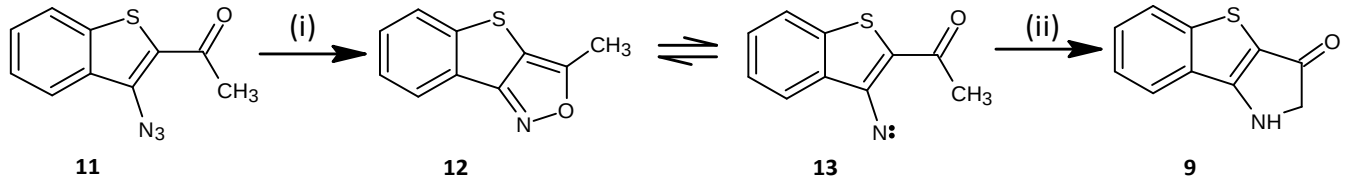


Figure 2. Plot of one of the molecules of **11** showing crystallographic numbering scheme.

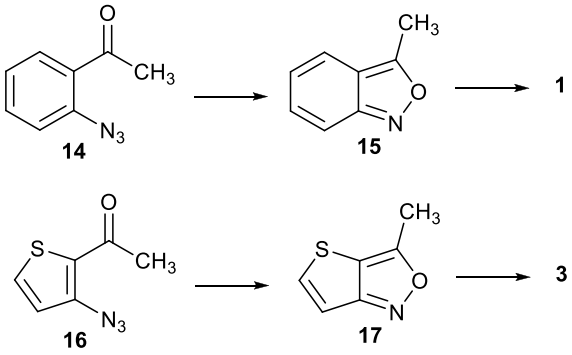
The X-ray crystal structure of the azide (**11**) again shows two molecules in the asymmetric unit. In common with other covalently-bonded azides,[8] the azide function itself is non-linear (data for the second molecule are given in parentheses) {N(41)-N(42)-N(43) 169.40(12)° [169.21(12)°]} and points in the opposite direction to the carbonyl of the acetyl group. In addition, the two N-N bonds have very different bond lengths {N(41)-N-42) 1.2425(13) Å [1.2397(14) Å]: N(42)-N(43) 1.1284(14) Å [1.1293(15) Å]}, another general feature of covalent azide geometry.[8] In the absence of hydrogen bonding, the acetyl group itself adopts the opposite (*s*-*Z*) configuration to that of the acetyl group of the amine (**10**) (*s*-*E*).

FVP of the azide (**11**) was complete at 300 °C, producing 3-methyl[1]benzothieno[3,2-*c*]isoxazole (**12**) (72%). The parent benzothienoisoxazole is the only previously known example of this ring system and it was prepared from 3-azido[1]benzothiophene-2-carboxaldehyde by a solution-phase nitrene insertion strategy.[9] FVP of **11** at higher temperatures (>500 °C) resulted in rearrangement to the poorly soluble heteroindoxyl (**9**) *via* the nitrene (**13**), accompanied by a range of more soluble byproducts which contributed to the low isolated yield of **9** (11%). FVP of the isoxazole (**12**) at 600 °C gave a similar, complex, pyrolysate. The product (**9**) was characterised by the CH_2 resonance of the keto form **9K** [δ_H(**9K**) 4.32 – *c.f.* δ_H(**3K**)[2] 4.22] and the CH resonance of the enol form [δ_H(**9E**) 6.62 – *c.f.* δ_H(**3E**)[2] 6.51]; both tautomeric forms of **9** were present in DMSO solution (see below).



Scheme 4. FVP of azidobenzothiophene (**11**) at (i) 300 °C and (ii) 500 °C.

The temperature profile for the decomposition of the azide (**11**) is shown in Fig. 3, and key parameters are listed in Table 2 with those for the sequences **14** → **15** → **1** and **16** → **17** → **3** listed for comparison (Scheme 5). Data for the benzothiophene sequence (**11** → **12** → **9**) are rather similar (within 25 °C) to those for the transformation of 2-acetylphenyl azide (**14**) to indoxyl (**1**) *via* anthranil (15)[1], but both differ from the corresponding parameters for the thiophene (**16** → **17** → **3**). In particular, the azide (**16**) requires a higher temperature than **11** or **14** for complete decomposition, and the onset of formation of the thienopyrrolone (**3**) occurs at a much lower temperature (≥125 °C) than for **1** or **9**, so there is no temperature at which the thieno[3,2-*c*]isoxazole **17** is the sole product.



Scheme 5. Comparison of ring systems.

The thermal reactivity of the azide (**11**), and stability of the isoxazole (**12**), relative to their monocyclic analogues (**16**) and (**17**), may be qualitatively rationalised by the maintenance of aromaticity in the benzene ring of **12**, whereas the aromaticity of the thiophene ring is lost in the formation of **17**. Despite the apparent *o*-quinonoid character of anthranil (**15**), it is known that such structures maintain significant aromatic character[10] which may account for the similarity in behaviour of **14** → **15** → **1** and **11** → **12** → **9**.

Table 2. Key parameters from the temperature profiles of the FVP reactions of **11**, **14** and **16**

	>95% azide decomp	>5% isoxazole	>5% indoxyl	>95% indoxyl
Indoxyl series[1] (**14**→**15**→**1**)	300 °C	200 °C	400 °C	575 °C
Thiophene Series[2] (**16**→**17**→**3**)	325 °C	225 °C	250 °C	525 °C
Benzothiophene series (**11**→**12**→**9**)	275 °C	<200 °C	375 °C	525 °C

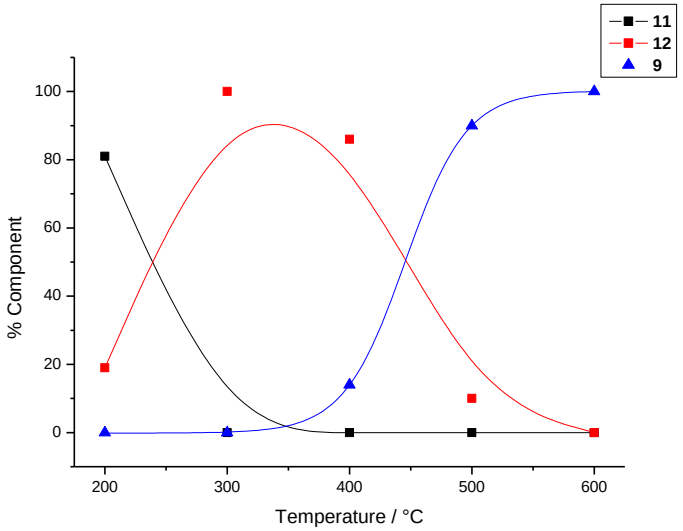


Figure 3. Temperature-conversion graph for FVP of **11**, showing the relative amounts of **11**, **12** and **9**.

Because of the low yield of **9** and its poor solubility, it was not possible to study its chemistry in detail. A complete NMR characterisation of both keto (**9K**) and enol (**9E**) forms, however, was carried out in DMSO solution. When first dissolved, the solution contained essentially 100% keto tautomer, suggesting that **9** exists in the keto form (**9K**) in the solid-state. After several hours in solution, the enol form (**9E**) predominated (*ca.* 80%). By comparison, indoxyl itself is present as the enol form (**1E**) almost exclusively (>95%) in DMSO, whereas the thiophene analogue (**3**) shows an unexpected preference for the keto form (**3K**) (80%) in the same solvent.[2]

Conclusions

This work has established that the nitrene strategy to heteroindoxyls under FVP conditions is compatible with the presence of a fused benzene ring in the precursor. Unlike its non-benzannulated anlogue, the kinetic product of the pyrolysis, 3-methyl[1]benzothieno[3,2-*c*]isoxazole (**12**), is stable over a range of temperatures. Rearrangement to the heteroindoxyl 1,2-dihydro[1]benzothieno[3,2-*b*]pyrrol-3-one (**9**) takes place at temperatures above 550 °C, but is accompanied by considerable decomposition leading to low yields. Both keto and enol tautomers, **9K** and **9E**, exist in equilibrium in DMSO solution.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 200 (or 250) and 50 (or or 63) MHz, respectively, for solutions in [^{2}H]chloroform unless otherwise stated. Coupling constants are quoted in Hz. ^{13}C NMR parameters refer to one CH signal unless otherwise stated. Mass spectra were recorded under electron impact conditions.

2-Acetyl-3-azido[1]benzothiophene (11)

2-Acetyl-3-aminobenzo[*b*]thiophene (**10**)[5] (570 mg, 2.98 mmol) was dissolved in hot conc. phosphoric acid (10 cm^{3}) and cooled to 0 °C. A solution of sodium nitrite (296 mg, 4.29 mmol) in the minimum amount of water was added dropwise, and the mixture was stirred for 30 min keeping the temperature at 0 °C. A solution of sodium azide (365 mg, 5.62 mmol) in the minimum amount of water was added dropwise, and the solution stirred for a further 30 min. The resulting precipitate was filtered and washed with water to yield 2-acetyl-3-azidobenzo[*b*]thiophene (**11**) (306 mg, 47%); mp 60-62 °C (from ethanol). (Found: M^{+}, 217.0310, $C_{10}H_7N_3OS$ requires *M* 217.0310); δ_H 2.67 (3H, s, acetyl), 7.49 (1H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.79 (1H, m, Ar-H) and 8.00 (1H, m, Ar-H); δ_C 29.7 (CH_3), 123.1, 123.1, 125.1, 127.3 (quat), 128.4, 134.2 (quat), 134.3 (quat), 138.5 (quat) and 191.3 (quat); *m/z* 217 (M^{+}, 6%), 189 (92), 161 (100), 146 (55), 103 (46) and 59 (38). The crystallographic data has been deposited at the Cambridge Crystallographic Data Centre and assigned the code number CCDC 1408196.

Flash vacuum pyrolysis reactions

The precursor was volatilized under vacuum through an empty, electrically heated silica tube (35 × 2.5 cm) and the products were collected in a U-tube cooled with liquid nitrogen, situated at the exit point of the furnace. CAUTION: aryl azides are potentially explosive when heated. Although we experienced no problems with the reactions reported here, the following precautions were always taken: 1. Each individual pyrolysis was carried out on a scale no greater than 250 mg., 2. A metal inlet heater was always used, and 3. The apparatus was protected by a blast shield while in use. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent and removed from the trap. The precursor, pyrolysis conditions [quantity of precursor, furnace temperature (T_f), inlet temperature (T_i), pressure (P) and pyrolysis time (t)] and products are quoted.

FVP of 2-acetyl-3-azido[1]benzothiophene (11)

FVP of 2-acetyl-3-azido[1]benzothiophene (**11**) (60 mg, 0.27 mmol, T_f 300 °C, T_i 60 °C, P 2.8 × 10^{-2} Torr, t 10 min) yielded 3-methyl[1]benzothieno[3,2-*c*]isoxazole (**12**) (38 mg, 72%); (Found: M^{+}, 189.0246. $C_{10}H_7NOS$

requires *M* 189.0248); δ_H 2.62 (3H, s, acetyl), 7.41 (1H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.64 (1H, m, Ar-H) and 8.09 (1H, m, Ar-H); δ_C 12.0 (CH_3), 113.9 (quat), 124.00, 124.1, 124.16 (quat), 125.2, 129.7, 147.6 (quat), 159.5 (quat) and 166.6 (quat); *m/z* 189 (M^+, 100%), 161 (95), 146 (78), 130 (29), 103 (61) and 76 (25).

The pyrolysate of the FVP of 2-acetyl-3-azido[1]benzothiophene (**11**) (100 mg, 0.47 mmol, T_f 600 °C, T_i 60 °C, P 2.6 × 10^{-2} Torr, t 12 min) was washed through first with chloroform then acetone to and the solvent evaporated to yield a residue of pure 1,2-dihydro[1]benzothieno[3,2-*b*]pyrrol-3-one (**9**) (*ca.* 10 mg, 11%). (Found: M^+, 189.0244. $C_{10}H_7NOS$ requires *M* 189.0248); ^{1}H NMR spectroscopy in [$^2H_6$]DMSO equilibrated at 80% enol and 20% keto tautomer. δ_H ([$^2H_6$]-DMSO, 360 MHz, enol tautomer **9E**); 6.62 [1H, s, H(2)], 7.18 [1H, m, H(6)], 7.34 [1H, m, H(7)], 7.79 [1H, m, H(8)] and 7.81 [1H, m, H(5)]; δ_H ([$^2H_6$]DMSO, 360 MHz, keto tautomer **9K**); 4.32 (2H, s, CH_2), 7.51 [1H, m, H(7)], 7.60 [1H, m, H(6)], 7.98 [1H, m, H(5)], 8.05 [1H, m, H(8)] and 8.32 [1H, br s, NH]; δ_C ([$^2H_6$]-DMSO, 90 MHz, enol tautomer **9E**) 107.0 [C(2)], 109.9 [quat, C(3a)], 118.5 [C(8)], 122.4 [C(6)], 124.1 [C(7)], 124.2 [C(5)], 127.8 [quat, C(8a)], 129.9 [quat, C(8b)], 137.1 [quat, C(3)], and 140.7 [quat, C(4a)]; δ_C ([$^2H_6$]-DMSO, 90 MHz, keto tautomer **9K**) 60.1 [CH_2, C(2)], 109.5 [quat, C(3a)], 123.6 [C(8)], 125.0 [C(7)], 125.2 [C(5)], 126.0 [quat, C(8a)], 129.5 [C(5)], 148.0 [quat, C(4a)], 171.4 [quat, C(8b)] and 190.4 [quat, C(3)]; *m/z* 189 (M^+, 100%), 188 (82), 176 (91), 161 (48), 105 (78) and 77 (49).

Temperature Profile of FVP of 2-acetyl-3-azido[1]benzothiophene (11)

The pyrolyses were carried out (typically 31 mg, 0.14 mmol, T_i 60 °C, P 1.9 × 10^{-2} Torr, t 6 min) at the temperatures described in the following table, with the following peaks in the ^{1}H NMR spectrum of the product mixture used to calculate the product ratio: 2-acetyl-3-azido[1]benzothiophene thiophene (**11**) [2.67 (3H, s, acetyl), 7.79 (1H, m, Ar-H) and 8.00 (1H, m, Ar-H)] and 3-methyl[1]benzo]thieno[3,2-*c*]isoxazole (**12**) [2.62 (3H, s, acetyl), 7.64 (1H, m, Ar-H) and 8.09 (1H, m, Ar-H)]; 1,2-dihydro[1]benzothieno[3,2-*b*]pyrrol-3-one (**9**) as its enol tautomer [6.62 (1H, s, H(2)]. At higher temperatures unidentified thermal decomposition products appeared in the product mixture (see Discussion section).

Table 2. Data for the temperature profile of **11**, forming **12** and **9**

Temperature /°C	200	300	400	500	600
11/%	81	0	0	0	0
12/%	19	100	86	10	0
9/%	0	0	14	90	100

Crystallography data

Diffraction data for **10** and **11** were collected with Mo-Kα radiation on a Bruker Smart Apex diffractometer equipped with an Oxford cryosystems low-temperature device operating at 150 K.

*Crystal data for **10**.* $C_{10}H_9NOS$, *M* = 191.25. Orthorhomic, space group $P2_12_12_1$. *a*= 10.1472(8), *b* = 12.5954(10), *c* = 14.3300(12) Å, *V* = 1831.5(3) Å^3, *Z* = 8. The structure was solved by Patterson methods (DIRDIF)[11] and refined by full matrix least squares against F^2 (Crystals).[12] All non-H atoms were refined with anisotropic displacement parameters and H-atoms were placed in calculated positions. The final *R* factor, based on *F* and 4416 out of 4495 data with $F > 4\sigma(F)$, was 0.0351. The final difference map extremes were $\pm$0.50 eÅ^{-3}.

*Crystal data for **11**.* $C_{10}H_7N_3OS$, *M* = 217.25. Monoclinic, space group *P*-1. *a* = 7.7220(3), *b* = 9.7725(4), *c* = 13.7905(6) Å, α = 76.880(20)°, β = 77.566(2)°, γ = 74.225(2)°, *V* = 962.15(7) Å^3, *T* = 150 K, *Z* = 4. The structure

was solved by direct methods (Shelxs)[13] and refined by full matrix least squares against F^2 (Crystals). All non-H atoms were refined with anisotropic displacement parameters and H-atoms were placed in calculated positions. The final *R* factor, based on *F* and 1913 out of 4427 data with $F > 4\sigma(F)$, was 0.0399. The final difference map extremes were -0.27 and +0.38 eÅ^{-3}.

Acknowledgements

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Supplementary Material

Experimental procedure for compound 10, NMR analyses, and X-ray tables are available in the Supplementary Material file available on the publisher's website.

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