COMMUNICATION

Studies on isocyanides and related compounds: synthesis of benzo[*c*]-thiophenes by way of acid-induced three-component reactions

Ricardo Bossio,[a] Stefano Marcaccini,[a] Roberto Pepino[a] and Tomás Torroba *[,b]

[a] *CNR, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Dipartimento di Chimica Organica 'Ugo Schiff', Università di Firenze, Via Gino Capponi, 9, I-50121 Firenze, Italy*

[b] *Departamento de Química Orgánica, Facultad de Veterinaria, Universidad de Extremadura, 10071 Cáceres, Spain*

The 'diimino thioanhydrides' of cyclohex-1-ene-1,2-dicarboxylic acid have been synthesized in a very simple manner by allowing 2-(arylaminothiocarbonyl)cyclohexanones 1 and isocyanides 3 to react in an acidic medium. A mechanism for this three-component reaction, based on isocyanide chemistry, is proposed.

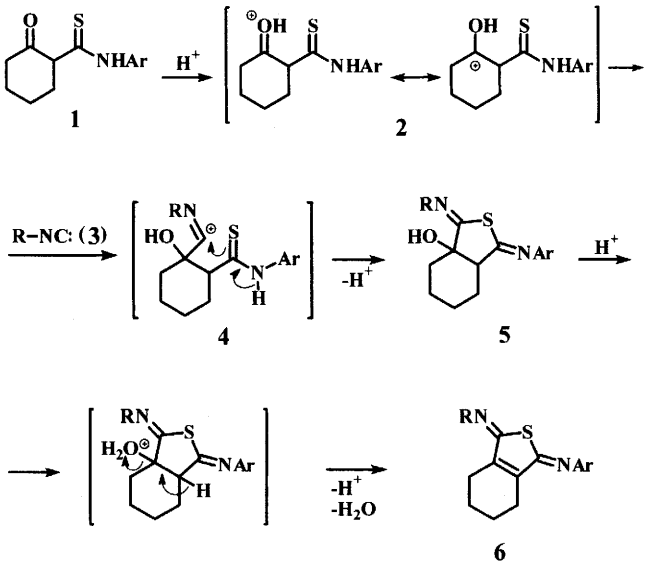
In his long and valuable studies, Ugi has noted that isocyanides have a marked tendency to participate in multi-component reactions.[1] With suitable reagents, intramolecular multi-component reactions can be induced which are of great importance in the synthesis of heterocyclic compounds [1–3] and antibiotics.[1d,4]

This paper deals with a novel intramolecular three-component condensation that leads to the formation of 1-arylimino-3-(*N*-substituted imino)-1,3,4,5,6,7-hexahydrobenzo[*c*]thiophenes **6**. These compounds, belonging to a hitherto unknown class of diimino thioanhydrides, were obtained by means of an experimentally simple one-pot procedure, consisting of a reaction between 2-(arylaminothiocarbonyl)cyclohexanones **1** and isocyanides **3** in an acidic medium.

In early experiments, performed with catalytic amounts of toluene-*p*-sulfonic acid, the yields of compounds **6** were only fair. Higher yields were obtained by employing stoichiometric amounts of benzoic acid and a slight improvement was achieved when salicyclic acid replaced the benzoic acid. With catalytic amounts of salicylic acid the reaction took place very slowly and, as expected, no reaction took place in the absence of acid. A possible reaction pathway is illustrated in Scheme 1.

In the reaction mechanism, the nucleophilic attack of the carbenoid carbon of the isocyanide onto the protonated carbonyl group appears to be reasonable in terms of known isocyanide chemistry. In fact, the protonated carbonyl group can be regarded as analogous to the immonium ion, which is the key intermediate in most isocyanide reactions. Nucleophilic attack of the thioamide sulfur on the imidoyl cation **4**, which prevents the nucleophilic attack of the acid anion and, consequently, the formation of the Passerini adduct, seems to be highly probable since it possesses good nucleophilic character and a five-membered cyclic product is formed. The elimination of water from compounds **5** takes place easily because of the highly conjugated nature of the final products.

Reactions performed in the presence of toluene-*p*-sulfonic acid gave no evidence for the formation of the intermediates **5**, whereas those employing benzoic or salicylic acid gave mixtures of **5** and **6** by work-up of the reaction mixture after short reaction periods. The solid product that separated out in the reaction between 2-(anilinothiocarbonyl)cyclohexanone **1a** and cyclohexyl isocyanide **3b** in the presence of salicylic acid, after a period of 24 h, was recognized as **5b**. Comparison of the



1, 2 Ar	4, 5, 6 Ar	R
a Ph	**a** Ph	c-C_5H_9
b 4-ClC_6H_4	**b** Ph	c-C_6H_{11}
	c Ph	$PhCH_2$
3 R	**d** Ph	4-$EtOC_6H_4$
a c-C_5H_9	**e** 4-ClC_6H_4	c-C_5H_9
b c-C_6H_{11}	**f** 4-ClC_6H_4	c-C_6H_{11}
c $PhCH_2$	**g** 4-ClC_6H_4	$PhCH_2$
d 4-$EtOC_6H_4$	**h** 4-ClC_6H_4	4-$EtOC_6H_4$

Scheme 1

^{1}H NMR spectral data of **5b** with those of *cis*- and *trans*-3a-hydroxy-1,3,3a,4,5,6,7,7a-octahydrobenzo[*c*]furan-1-one [5] suggested a *trans* ring fusion with the hydroxy group and the hydrogen at the ring junction in a *trans* diaxial conformation. This stereochemistry is in agreement with the proposed dehydration mechanism.

In conclusion, the present method provides a useful route to 1-arylimino-3-(*N*-substituted imino)-1,3,4,5,6,7-hexahydrobenzo[*c*]thiophenes, which can be regarded as 'diimino thioanhydrides' of cyclohex-1-ene-1,2-dicarboxylic acid. Consequently, these compounds seem to be of interest for their use as dienophiles in Diels–Alder reactions.

Experimental

Compound **1a** was prepared according to a literature method.[6] Compound **2b** was prepared from 4-chlorophenylisothiocyanate and 1-morpholinocyclohex-1-ene following the method described for **1a** except that the crude 2-(4-chloro-

anilino)thiocarbonyl-1-morpholinocyclohex-1-ene, obtained as a glass-like residue by evaporating the reaction mixture, was hydrolysed without further purification. Overall yield 47%, mp 98–101 °C from MeOH.

1-*Arylimino*-3-(N-*substituted imino*)-1,3,4,5,6,7-*hexahydrobenzo*[*c*]*thiophenes* **6a–h**. A mixture of compound **1** (6 mmol), compound **3** (6 mmol) and salicylic acid (829 mg, 6 mmol) in diethyl ether (50 cm^3) was stirred at 20 °C for 48 h after which it was evaporated to dryness. The glass-like residue was stirred with a little cold methanol to give a solid product which was filtered off and recrystallized from a suitable solvent. All compounds gave satisfactory analytical and spectra data.

Compound **6**. Yellow crystals, mp 103–104 °C (MeOH), 65% yield; δ_H(200 MHz, $CDCl_3$) 1.57–1.89 (12 H, m, 8 H cyclopentane + 5-CH_2 + 6-CH_2), 2.55–2.64 (4 H, m, 4-CH_2 + 7-CH_2), 3.55–3.68 (1 H, m, 1-H cyclopentane) and 6.99–7.41 (5 H, m, ArH).

Compound **6b**. Yellow crystals, mp 111–112 °C (MeOH), 70% yield; δ_H(200 MHz, $CDCl_3$) 1.23–1.82 (14 H, m, 10 H cyclohexane + 5-CH_2 + 6-CH_2), 2.57–2.64 (m, 4 H, 4-CH_2 + 7-CH_2), 3.03–3.13 (1 H, m, 1-H cyclohexane) and 7.00–7.42 (5 H, m, ArH).

Compound **6c**. Yellow crystals, mp 58–59 °C (MeOH), 66% yield; δ_H(200 MHz, $CDCl_3$) 1.76–1.90 (4 H, m, 5-CH_2 + 6-CH_2), 2.58–2.70 (4 H, m, 4-CH_2 + 7-CH_2), 4.66 (2 H, s, CH_2Ph) and 7.06–7.40 (10 H, m, ArH).

Compound **6d**. Yellow crystals, mp 97–99 °C (MeOH), 78% yield; δ_H(200 MHz, $CDCl_3$) 1.39 (3 H, t, *J* 6.9,† CH_3), 1.70–1.82 (4 H, m, 5-CH_2 + 6-CH_2), 2.63–2.74 (4 H, m, 4-CH_2 + 7-CH_2), 4.03 (2 H, q, *J* 6.9, OCH_2) and 6.82–7.37 (9 H, m, ArH).

Compound **6e**. Yellow crystals, mp 128–129 °C (MeOH), 70% yield; δ_H(200 MHz, $CDCl_3$) 1.58–1.95 (12 H, m, 8 H cyclopentane + 5-CH_2 + 6-CH_2), 2.53–2.64 (4 H, m, 4-CH_2 + 7-CH_2), 3.53–3.67 (1 H, m, 1-H cyclopentane) and 6.13–7.35 (4 H, m, ArH).

Compound **6f**. Yellow crystals, mp 112–113 °C (MeOH), 75% yield; δ_H(200 MHz, $CDCl_3$) 1.21–1.85 (14 H, m, 10 H cyclohexane + 5-CH_2 + 6-CH_2), 2.52–2.63 (4 H, m, 4-CH_2 + 7-CH_2), 3.00–3.12 (1 H, m, 1-H cyclohexane) and 6.92–7.36 (4 H, m, ArH).

Compound **6g**. Yellow crystals, mp 93–94 °C (MeOH–DMF), 68% yield; δ_H(200 MHz, $CDCl_3$) 1.79–1.87 (4 H, m, 5-CH_2 + 6-CH_2), 2.58–2.69 (4 H, m, 4-CH_2 + 7-CH_2), 4.66 (2 H, s, CH_2Ph) and 6.96–7.37 (9 H, m, ArH).

† *J* Values in Hz.

Compound **6h**. Yellow crystals, mp 141–142 °C (EtOH), 83% yield; δ_H(200 MHz, $CDCl_3$) 1.40 (3 H, t, *J* 7.1, CH_3), 1.81–1.92 (4 H, m, 5-CH_2 + 6-CH_2), 2.62–2.76 (4 H, m, 4-CH_2 + 7-CH_2), 4.01 (2 H, q, *J* 7.1, OCH_2) and 6.84–7.31 (8 H, m, ArH).

Compound **5b** was obtained by allowing **1a** and **3b** to react as described above, except that the reaction time was 24 h. The reaction mixture was filtered and the solid product collected was recrystallized from EtOH: white crystals, mp 198–199 °C, 25% yield; δ_H(300 MHz, $CDCl_3$) 1.15–2.00 (16 H, m, 10 H cyclohexane + 5-CH_2 + 6-CH_2 + 7-CH_2), 1.90 (1 H, s, OH), 2.20–2.33 (m, 4-CH_2), 2.64 (1 H, dd, *J* 3.2, 7a-H), 2.91–3.00 (1 H, m, 1-H cyclohexane) and 7.05–7.45 (5 H, m, ArH).

Calculations performed with Spartan 3.1 (Wavefunction Inc., Irvine, CA, USA) using the semi-empirical molecular orbital AM1 method[7] suggested a *Z* geometry at both the nitrogen atoms of compounds **6a–h** and **5b**.

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