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ORIGINAL PAPER

Reaction between benzoyl isothiocyanate and 2,6-dimethylphenyl isocyanide: synthesis of a sterically congested ten-membered ring containing the S–S–S moiety

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Abstract 2,6-Dimethylphenyl isocyanide reacts with benzoyl isothiocyanate in a clean one-pot reaction to afford a sterically congested ten-membered ring containing the S–S–S moiety in nearly quantitative yield. Dynamic effects are observed in the ^{1}H nuclear magnetic resonance (NMR) spectrum of this compound for the restricted rotation around two of the Ar–N single bonds.

Keywords Ugi reaction · Aryl isocyanide · Hindered rotation · Medium ring · Dynamic NMR

Introduction

Multicomponent reactions (MCRs) are useful organic reactions in which three or more starting materials react to give a product [1]. MCRs, by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention in combinatorial chemistry. Of pivotal importance in this area are the isocyanide-based MCRs, such as the versatile Ugi and Passerini reactions [2–5]. As part of our current studies on the development of new routes to heterocyclic systems [6–10], we report herein on the reaction between 2,6-dimethylphenyl isocyanide (**1**) and benzoyl isothiocyanate (**2**) in CH_2Cl_2, which leads to 9-(2,6-dimethylphenyl)-7,5′-bis[(2,6-dimethylphenyl)imino]-5,11,2′-triphenylspiro[9*H*-5,8,8-nitrilo-7*H*-oxazolo[4,5-g][1,4,5,6,9]-oxatrithiazundecen-4,4′(5*H*,5′*H*)-oxazol] (**3**) in nearly quantitative yield (Scheme 1).

Results and discussion

The reaction of 2,6-dimethylphenyl isocyanide with benzoyl isothiocyanate proceeded spontaneously at room temperature in CH_2Cl_2 and was finished within 2 h. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **3**. No product other than **3** could be detected by NMR spectroscopy. The methyl region of an equimolar solution of **1** and **2** in $CDCl_3$ was monitored by ^{1}H NMR spectroscopy (Fig. 1). The spectrum measured 5 min after mixing of these compounds showed, in addition to the single peak of compound **1**, the appearance of new small peaks. After 15 min, these new signals grew at the expense of the peak at $\delta = 2.38$ ppm. The reaction was complete after 2 h, and the signal due to **1** completely disappeared.

The product was characterized on the basis of spectroscopic data. At ambient temperature, the Ar–Me region of the ^{1}H NMR spectrum of **3** exhibits four single resonances at $\delta = 1.87$, 1.92, 2.25, and 2.47 ppm in 2:2:1:1 ratio. The line observed at 1.92 ppm is very broad at 25 °C. The proton-decoupled ^{13}C NMR spectrum of **3** showed 41 distinct resonances.

Unambiguous evidence for the structure and stereochemistry of **3** was obtained from single-crystal X-ray analysis. An ORTEP [11] diagram of **3** is shown in Fig. 2. There are two molecules of **3** in the unit cell. Also, there are two molecules of CH_2Cl_2 and 1.5 molecules of H_2O in the unit cell.

A plausible mechanism for the formation of **3** is proposed in Scheme 2. On the basis of the well-established

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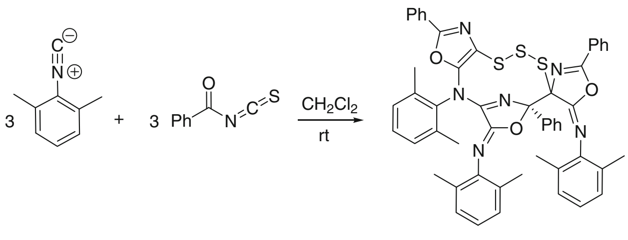


1 **2** **3**

Scheme 1

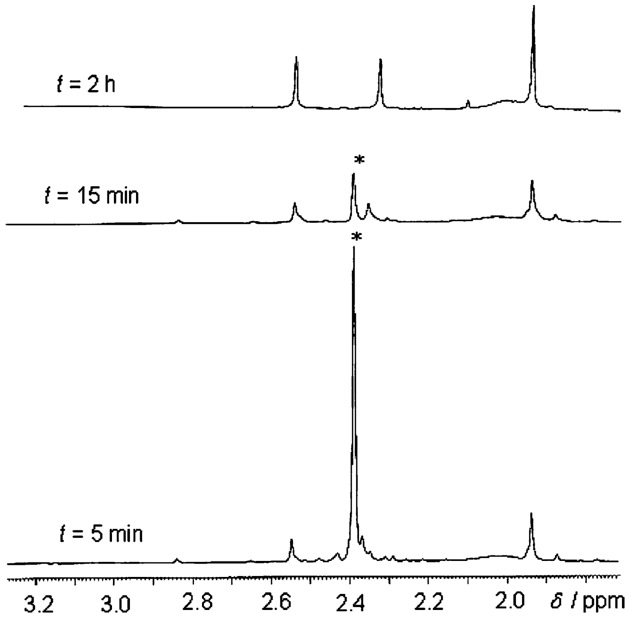


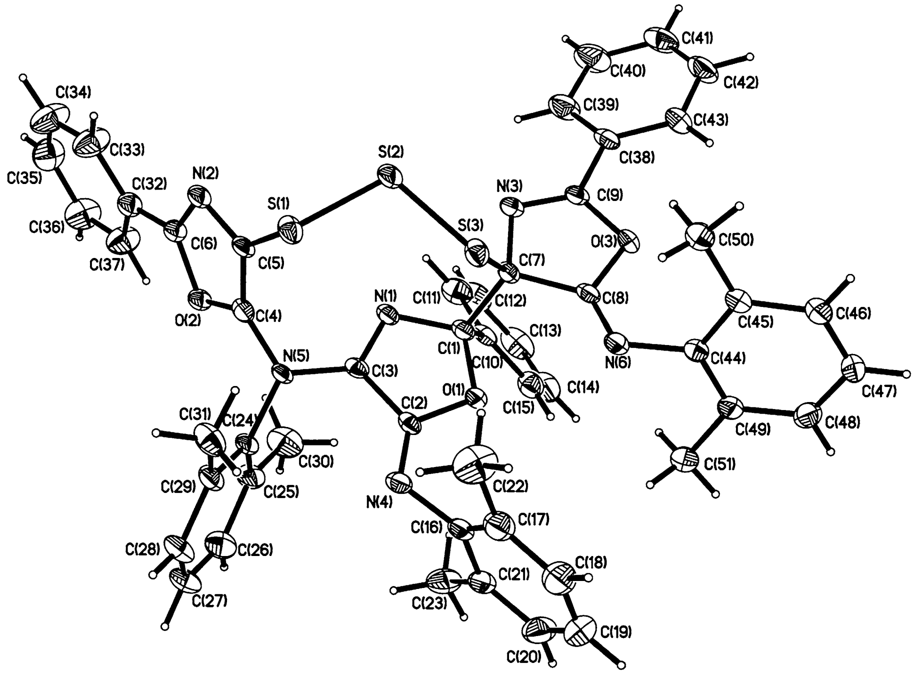
Fig. 1 ^{1}H NMR spectra (500 MHz) of an equimolar solution of **1** and **2** in CDCl$_3$ at different time points. Peaks marked with an *asterisk* belong to the Ar–Me group in isocyanide **1**

chemistry of isocyanides [4, 5], it is reasonable to assume that compound **3** results from nucleophilic addition of compound **1** to the *sp*-hybridized carbon atom of benzoyl isothiocyanate to produce intermediate **4** (Scheme 2). Intermediate **4** undergoes a three-component reaction to produce **3** via intermediates **5** and **6**.

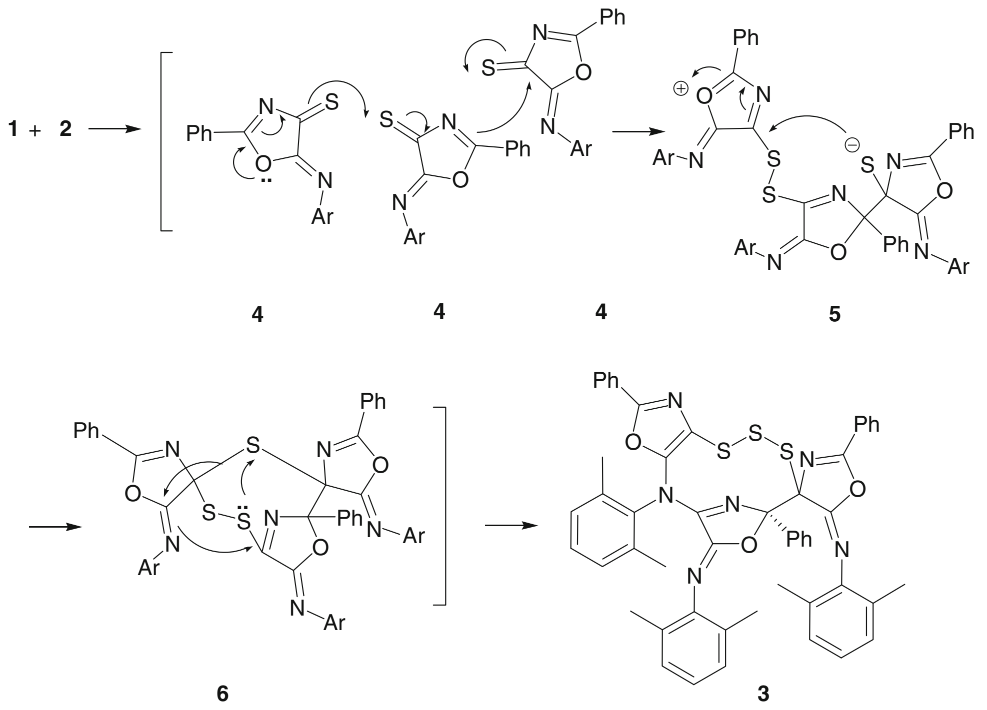
The noteworthy feature of the ^{1}H NMR spectrum of **3** in CDCl$_3$ solution at 298 K (Fig. 3) is the presence of four peaks in 1:1:2:2 ratio. The two sharp singlets ($\delta = 2.25$ and 2.47 ppm) with equal intensities belong to the methyl groups of an Ar moiety with slow rotation about the Ar–N bond. Rotation about the other Ar–N bonds is either fast (sharp peak at $\delta = 1.87$ ppm) or intermediate (broad peak at $\delta = 1.92$ ppm) on the NMR time scale at 298 K. At 333 K, the broad line became sharper. Decreasing the temperature to 243 K led to decoalescence of the peak at 1.92 ppm, and two fairly sharp singlets are observed at 218 K (process A). The decoalescence of the peak at 1.87 ppm occurs at about 218 K, and two very broad signals ($\delta = 1.69$ and 2.09 ppm) are observed at 213 K (process B), the lowest temperature investigated. From the coalescence of the methyl protons and using the expression $k = \pi\Delta v/\sqrt{2}$, the first-order rate constants (k) for processes A and B were calculated to be 970 and 420 s^{-1}. The free-energy barriers for processes A and B are calculated to be 51 and 42 kJ/mol. The signals observed at $\delta = 2.25$ and 2.47 ppm remained sharp when a solution of **3** in 1,2-dichlorobenzene was heated to 180 °C. Thus, the free-energy barrier for the third Ar–N bond rotation (process C) is estimated to be higher than 95 kJ/mol.

In conclusion, we revealed a novel transformation involving 2,6-dimethylphenyl isocyanide and benzoyl

Fig. 2 X-ray crystal structure of **3**. ORTEP-III plot [11]; arbitrary atom numbering



Scheme 2



isothiocyanate to afford a sterically congested ten-membered ring containing the S–S–S moiety. Dynamic effects are observed in the ^{1}H NMR spectrum of this compound for the restricted rotation around two of the Ar–N single bonds.

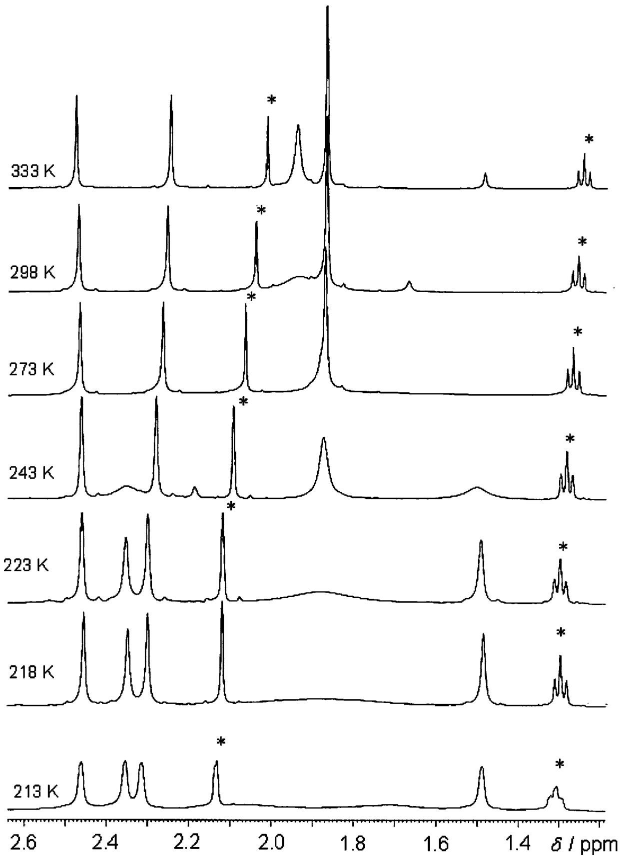


Fig. 3 Variable-temperature 500-MHz ^{1}H NMR spectra of **3** in $CDCl_3$. Peaks marked with an *asterisk* belong to EtOAc

Experimental

All purchased solvents and chemicals were of analytical grade and used without further purification. Melting points and infrared (IR) spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker DRX-500 Avance instrument using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard at 500 and 125.7 MHz, respectively. Mass spectra were recorded on a HP (Agilent Technology) GCMSQP5050A. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Their values (C, H, and N) were in good agreement with the calculated ones.

9-(2,6-Dimethylphenyl)-7,5′-bis[(2,6-dimethylphenyl)-imino]-5,11,2′-triphenylspiro[9H-5,8,8-nitrilo-7H-oxazolo[4,5-g][1,4,5,6,9]-oxatrithiazundecen-4,4′(5H,5′H)-oxazol] (**3**, $C_{51}H_{42}N_6O_3S_3$)

To a stirred solution of 0.48 g **2** (6 mmol) in 10 cm^3 CH_2Cl_2 was added dropwise at −10 °C over 10 min a solution of 0.78 g **1** (6 mmol) in 5 cm^3 CH_2Cl_2.

The reaction mixture was then allowed to warm up to room temperature and stand for 2 h. The solvent was removed under reduced pressure, and the residual solid recrystallized from Et_2O. Compound **3** was obtained as colorless crystals. Yield 0.91 g (98%); m.p.: 193–194 °C; IR (KBr):$\bar{\nu} = 1{,}716, 1{,}620, 1{,}568, 1{,}459\ \text{cm}^{-1}$; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.87$ (s, 2 Me), 1.92 (br s, 2 Me), 2.25 (s, Me), 2.47 (s, Me), 6.82 (t, $^3J = 7.3$ Hz, CH), 6.86–6.97 (m, 5 CH), 7.02–7.08 (m, 5 CH), 7.14 (t, $^3J = 7.5$ Hz, CH), 7.26 (t, $^3J = 7.8$ Hz, CH), 7.40–7.50 (m, 4 CH), 7.57 (d, $^3J = 6.7$ Hz, 2 CH), 7.70 (d, $^3J = 7.7$ Hz, 2 CH), 7.97 (d, $^3J = 7.1$ Hz, 2 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 18.2$ (2 Me), 18.3 (2 Me), 18.5 (Me), 19.2 (Me), 65.8 (N–C–O), 85.4 (C_{spiro}), 104.9 (C), 122.9 (C), 123.3 (C), 124.2 (C), 125.1 (C), 126.4 (2 CH), 126.7 (CH), 127.1 (CH), 127.4 (CH), 127.5 (2 CH), 127.6 (2 CH), 127.8 (2 CH), 128.5 (2 CH), 128.6 (2 CH), 128.69 (2 CH), 128.71 (2 CH), 128.8 (2 CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 130.5 (C), 131.0 (C), 133.0 (C), 135.9 (C), 136.1 (C), 137.2 (C), 138.8 (C), 143.0 (C), 143.9 (C), 146.7 (C), 151.7 (C), 153.0 (C), 155.3 (C), 158.4 (C), 162.9 (C) ppm; EI–MS: $m/z = 883$ (M^{+}, 2), 430 (10), 130 (25), 105 (90), 77 (75), 43 (100).

CCDC-284910 contains the supplementary crystallographic data for $\mathbf{3}\cdot CH_2Cl_2\cdot 0.75H_2O$ ($C_{52}H_{45.5}ClN_6O_{3.75}S_3$), $F_w = 946.07$, triclinic, space group P-1, $Z = 2$, $a = 10.262(9)$ Å, $b = 10.583(9)$ Å, $c = 24.02(2)$ Å, $\alpha = 98.66(7)°$, $\beta = 95.67(7)°$, $\gamma = 94.53(7)°$, $V = 2{,}554(4)$ Å^3, $D_{calcd} = 1.230$ g/cm^3, $R = 0.0650$, $R_w = 0.1289$, $0 \le h \le 12$, $-13 \le k \le 13$, $-29 \le l \le 29°$, Mo ($\lambda = 0.71073$ Å), $T = 193(2)$ K. These data can be obtained free of charge from Cambridge Crystallography Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

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