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Facile Synthesis of 4,5-Dihydro-1,3,4-Thiadiazoles by 1,3-Dipolar Cycloaddition of Thioisomünchnones

Bárbara Sánchez,[A] *José Luis Bravo,*[A] *María José Arévalo,*[A] *Ignacio López,*[B] *Mark E. Light,*[C] *and Guadalupe Silvero*[B,D]

[A]Departamento de Química Orgánica e Inorgánica, Universidad de Extremadura, Badajoz E-06071, Spain.

[B]Departamento de Química Orgánica e Inorgánica, Universidad de Extremadura, Cáceres E-10071, Spain.

[C]School of Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK.

[D]Corresponding author. Email: gsilvero@unex.es

The present paper summarizes a straightforward synthesis of 4,5-dihydro-1,3,4-thiadiazoles by the 1,3-dipolar cycloaddition of thioisomünchnones. These reactions have been carried out in dichloromethane and are essentially complete within 60 min at room temperature. Under such mild conditions the asymmetric version has been explored as well. Unequivocal structure elucidation has been accomplished by means of one- and two-dimensional NMR techniques as well as X-ray structure analysis.

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1,3,4-Thiadiazole derivatives constitute a family of compounds that show a wide variety of biological effects, including anti-tumour, antibacterial, anti-inflammatory, and pesticide action, possibly due to the presence of the toxophoric N-C-S moiety.[1–3] Therefore, there is continued interest in developing new methodologies for obtaining 1,3,4-thiadiazoles.[1,4–9] We would like to report, herein, a new method for synthesizing a group of 1,3,4-thiadiazoles based on the 1,3-dipolar cycloaddition of thioisomünchnones with azodicarboxylates under mild conditions.

In our laboratory, we have been developing new methodologies for obtaining diverse heterocycles by means of 1,3-dipolar cycloadditions of thioisomünchnones (mesoionics having the structure of 1,3-thiazolium-4-olate). Remarkably, the introduction of a 2-dialkylamino group on the mesoionic ring has led to novel synthetic routes to highly functionalized, and often chiral three-,[10,11] four-,[11,12] five-,[13–16] and six-membered rings,[15,17] demonstrating the versatility of these compounds in synthesis.[18]

Following our studies, herein we describe a straightforward mild-condition methodology for the synthesis of 1,3,4-thiadiazoles from 2-[benzyl(methyl)amino]-3-(4-nitrophenyl)-5-phenyl-1,3-thiazolium-4-olate (**1**) and dialkylazodicarboxylates. Sheradsky et al. have previously studied the reaction of 2,5-diphenylthioisomünchnones with azodipolarophiles, reporting the formation of cycloadducts, open-chain products, and thiazolidines.[19] In the protocol described herein, equimolar reactions of **1** with azodicarboxylates **2a**–**c** in dichloromethane (DCM) at room temperature result in the formation of 4-alkoxycarbonyl-5-(*N*-alkoxycarbonyl-*N*-aryl)carbamoyl-5-phenyl-2-(*N*-methyl)benzylamino-4*H*,5*H*-1,3,4-thiadiazoles **3a**–**c**, respectively, in less than 60 min, as crystalline solids (Scheme 1).[20]

Spectroscopic data were fully consistent with the structures assigned to these thiadiazoles. Moreover, the structure of compound **3c** could be unequivocally elucidated by single-crystal X-ray analysis (Fig. 1).[21] Remarkably, this result differs from what was expected, illustrating the importance of an electron

Scheme 1. Compounds **2a**, **3a**: R = Me; **2b**, **3b**: R = ^{t}Bu; **2c**, **3c**: R = Et.

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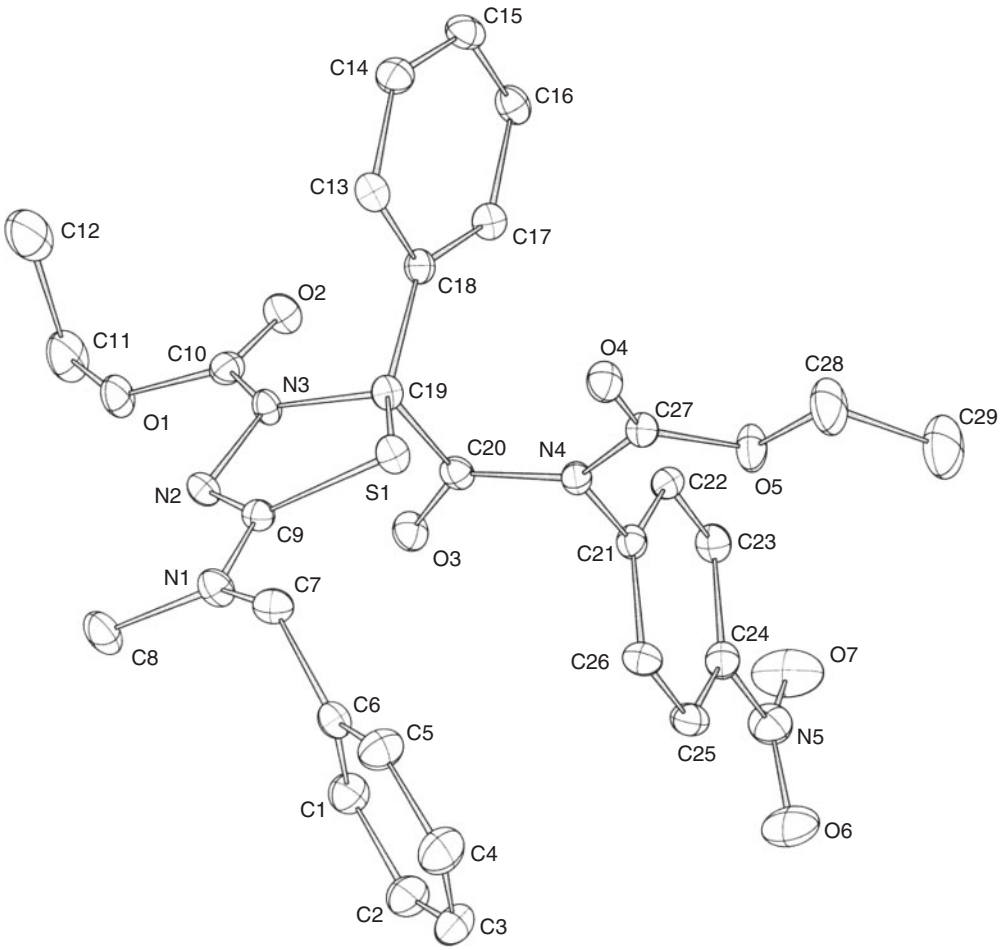
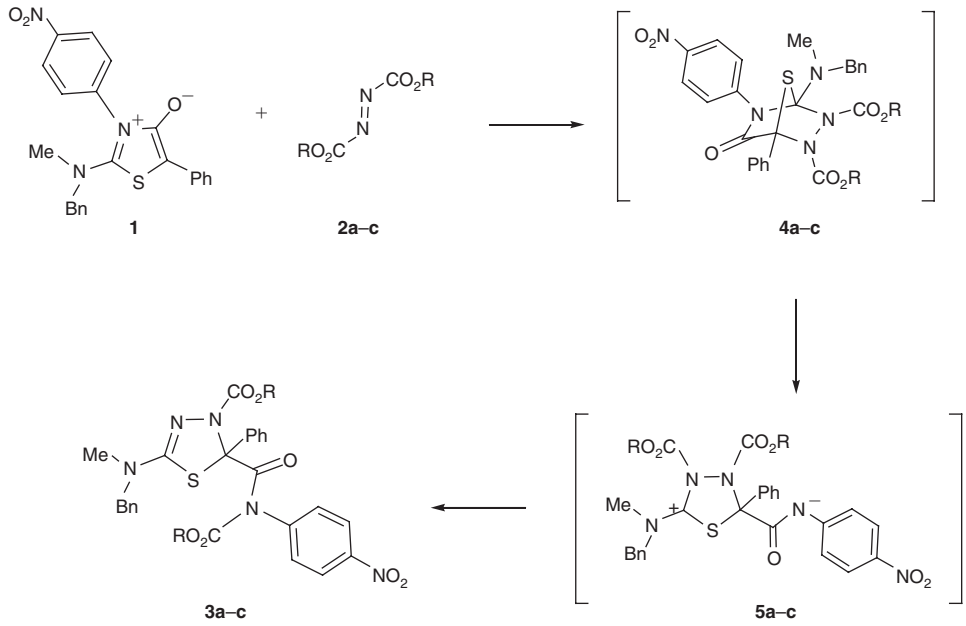
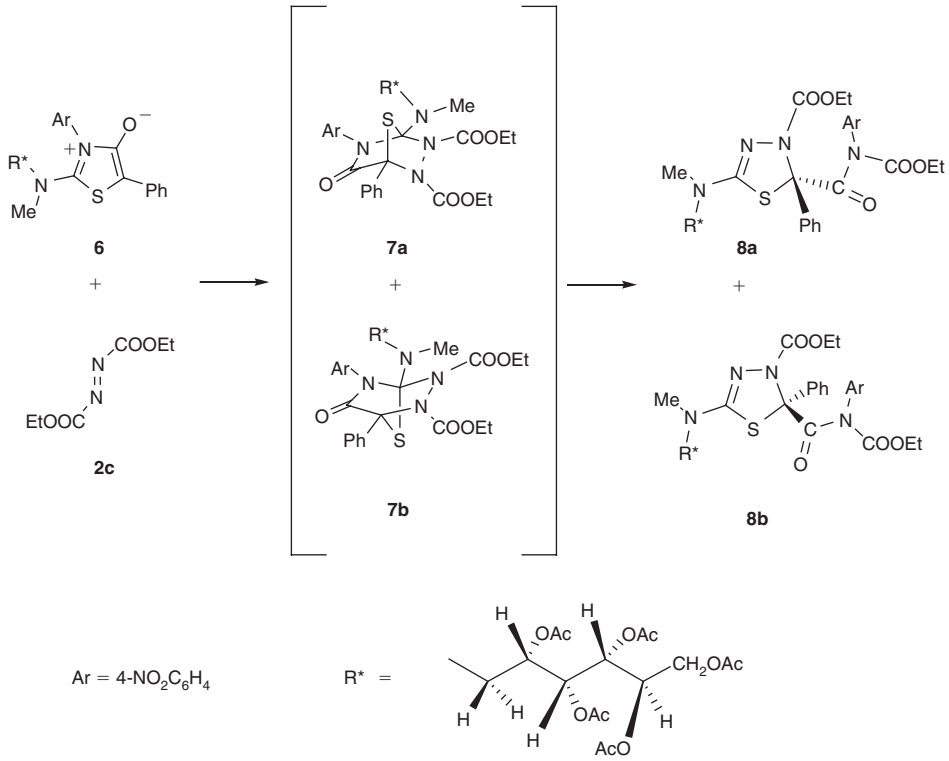


Fig. 1. Crystal structure of compound **3c**.



2–5a: R = Me; **2–5b**: R = ^{t}Bu; **2–5c**: R = Et

Scheme 2. Proposed reaction mechanism for the formation of compounds **3a**–**c**.



Scheme 3. Formation of compounds **8a** and **8b**.

withdrawing substituent on the outcome of 1,3-dipolar cycloadditions of these systems.[18] Indeed, in our previous studies on the reactivity of 2-dialkylaminothioisomünchones towards azodipolarophiles, triazinones were obtained as sole reaction products.[17]

A plausible mechanism is proposed to account for the formation of these thiadiazoles (Scheme 2). The initial 1,3-dipolar cycloaddition would form the transient cycloadducts **4a**–**c**, which could not be isolated. Selective fragmentation by C-N bond cleavage would yield the zwitterions **5a**–**c**, with the negative charge presumably stabilized by the mesomeric effect of the 4-nitrophenyl group. The positive charge, however, would be delocalized between the carbon and the adjacent heteroatoms. Finally, intramolecular nucleophilic substitution would render the target thiadiazoles **3a**–**c**.

An asymmetric version of this novel synthetic protocol has been subsequently explored. Thus, thioisomünchnone **6**, bearing an acyclic *O*-protected carbohydrate side chain, was prepared by successive treatment with α-chlorophenylacetyl chloride and triethylamine of the thiourea formed by reaction of *N*-methyl-D-glucamine and 4-nitrophenylisothiocyanate. It was then trapped *in situ* with diethyl azodicarboxylate **2c** in DCM.[22] Again, no cycloadducts could be detected; instead, two products **8a** and **8b** were formed (Scheme 3).

These diastereomers were obtained as a nearly 1:1 mixture that could not be resolved. This absence of facial selectivity suggests that the conformational freedom of the sugar moiety and its distance from the new stereogenic centres prevent it from exerting any noticeable effect. The structural elucidation of these substances has also been accomplished by comparing their ^{1}H- and, mainly, ^{13}C-NMR data with those of compounds **3a** and **3c**.

The most significant ^{13}C-NMR values of these 1,3,4-thiadiazoles are shown in Table 1, corresponding to their main structural features. Thus, in all cases the tetrahedral C5 resonance appears within a 0.13 ppm range from δ 88.70 to 88.83. The trigonal C2 atom also shows a narrow range of chemical shift values, δ 150.37–151.00; the same applies for the exocyclic amide-like carbon, with δ values between 167.90 and 168.21 ppm. The CH_3-N shows chemical shifts in the 37–38 ppm range, due to the vicinity of the sugar (compounds **8a**,**b**) or benzyl moieties (compounds **3a**,**c**).

Table 1. **^{13}C-NMR shifts of selected carbons for compounds 3a, 3c and 8a/8b[A]**

Compound	C5	C2	N(CH_3)	C=O-(C5)
3a	88.83	151.00	37.15	168.08
3c	88.74	150.77	37.12	168.21
8a/**8b**	88.70/88.81	150.37/150.47	38.18/38.31	167.90/168.06

[A] ^{13}C-NMR spectra recorded in $CDCl_3$ at 100 MHz.

To sum up, we have described a facile methodology for the synthesis of 1,3,4-thiadiazole derivatives, a family of products which display an interesting array of bio-pharmaceutical activities. Our protocol suggests a one-pot 1,3-dipolar cycloaddition followed by a cascade of cycloadduct fragmentation, driven by the 4-nitrophenyl group on the mesoionic ring, and a later intramolecular nucleophilic substitution. Products are obtained under mild reaction conditions as crystalline solids in moderate to good yields. New experiments as well as calculations by quantum methods are under way in order to gain insight into this new synthetic process. Results will be published in due course.

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[20] Typical Procedure (**3**): To a solution of **1** (1.0 mmol) in CH_2Cl_2 (3 mL) was added the corresponding azodicarboxylate (**2**, 1.0 mmol) and the reaction mixture was stirred at room temperature for 60 min. After removal of the solvent under vacuum, the product crystallized from diethyl ether in moderate to good yields (40–65%, not optimized). Spectrocopic data: (**3a**) Mp 179°C (dec.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35–7.26 (14H, m, ar), 4.45 (2H, s, CH_2), 3.65 (3H, s, $COOCH_3$), 3.37 (3H, s, $COOCH_3$), 2.96 (3H, s, NCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.08 (C=O(C-5)), 153.70 (C=O(OCH_3)), 152.43 (C=O(OCH_3)), 151.00 (C-2), 147.45, 143.51, 136.69, 136.41, 129.35, 128.92, 128.77, 128.56, 127.98, 127.86, 127.74, 127.68, 127.53, 125.89, 125.04, 124.68, 119.70 (ar), 88.83 (C-5), 56.95 (CH_2), 54.44 (CH_3OOC), 53.34 (CH_3OOC), 37.15 (NCH_3). IR ν_{max}/cm^{-1} 1743, 1688, 1528, 1353, 1254. HRMS (CI) $C_{27}H_{25}N_5O_7S$ requires $[M+Na]^+$ 586.1372; Found 586.1405. (**3b**) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37–7.12 (14H, m, ar), 4.47 (2H, s, CH_2), 2.91 (3H, s, NCH_3), 1.52 (9H, s, $C(CH_3)_3$), 1.28 (9H, s, $C(CH_3)_3$). (**3c**) Mp 154°C. Elemental analysis found: C 58.88, H 4.92, N 11.83, S 5.24. $C_{29}H_{29}N_5O_7S$ requires C 58.88, H 4.94, N 11.84, S 5.41%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.34–7.26 (14H, m, ar), 4.44 (2H, s, CH_2), 4.04 (2H, bm, CH_2), 3.89 (1H, m, $J_{H,H'}$ 11.2, J_{CH_2,CH_3} 7.1, CH_2), 3.78 (1H, m, $J_{H,H'}$ 11.1, J_{CH_2,CH_3} 7.2, CH_2), 2.96 (3H, *s*, NCH_3), 1.17 (3H, bs, CH_3), 0.91 (3H, t, *J* 7.0, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.21 (C=O(C-5)), 153.22 (C=O(OCH_2CH_3)), 151.97 (C=O(OCH_2CH_3)), 150.77 (C-2), 147.32, 143.71, 137.02, 136.50, 129.30, 128.72, 127.81, 127.65, 127.59, 124.59 (ar), 88.74 (C-5), 64.22 (OCH_2), 62.16 (OCH_2), 56.86 (NCH_2), 37.12 (NCH_3), 14.33 (CH_3), 13.64 (CH_3). IR ν_{max}/cm^{-1} 1740, 1720, 1690, 1620, 1520, 1250, 740, 730, 700.

[21] The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Crystal data for **3c** (CCDC-146112), $C_{29}H_{29}N_5O_7S$, Mr = 590.63, monoclinic, $P2_1/c$, $a = 12.127(6)$, $b = 19.843(10)$, $c = 12.262(3)$ Å, $V = 2931(2)$ Å^3, $Z = 4$, $D_{calcd} = 1.341$ g cm^{-3}, λ(MoKα) = 0.71073 Å, $\mu = 0.165$ mm^{-1}, $F(000) = 1240$, $T = 150(2)$ K, GooF^2 = 0.985, independent reflections = 5179 [$R_{int} = 0.0471$] of a total of 9415 collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2) = 0.0445$, $wR(F^2) = 0.0931$, R(all data) = 0.0822, $wR(F^2) = 0.1074$.

[22] To a solution of (2*S*,3*R*,4*S*,5*S*)-*N*-(2,3,4,5,6-pentaacetoxy)hexyl-*N*-methyl-*N*′-(4-nitrophenyl)thiourea (1.0 g, 1.7 mmol) in dry chloroform (20 mL) was added α-clorophenylacetyl chloride (0.8 mL, 5.0 mmol) and was refluxed for 1 h. After, the reaction mixture was concentrated under vacuum and washed with dry diethyl ether. Chloroform (40 mL) and triethylamine (0.5 mL, 3.6 mmol) were then added to the residue obtained and the mixture was refluxed for 10 min. The crude product was then washed with distilled water, dried over magnesium sulfate, and concentrated under reduced pressure to afford a viscous oil. This product was dissolved in dry chloroform (10 mL), treated with diethylazodicarboxylate (0.3 mL, 2.0 mmol), and left to react at room temperature for 1 h. Subsequent purification by column chromatography (ethyl acetate/petroleum ether, 2:3) afforded a nearly 1:1 diastereomeric mixture of **8a** and **8b** (38% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33–7.30 (9H, m, ar), 5.44–5.34 (6H, m, H-2′, H-3′, H-4′), 5.03 (2H, m, H-5′), 4.32–3.78 (12H, m, H-6′, H-6″, CH_2), 3.52 (4H, m, H-1′, H-1″), 3.00 (3H, CH_3), 2.13 (3H, CH_3), 2.12 (3H, CH_3), 2.11 (3H, CH_3), 2.08 (3H, CH_3), 2.06 (3H, CH_3), 2.04 (3H, CH_3), 2.03 (3H, CH_3), 2.01 (3H, CH_3), 1.26–083 (12H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.48, 170.18, 170.11, 169.81, 169.76, 168.06 (C=O(C-5)), 167.90 (C=O(C-5)), 153.20, 152.94, 150.47 (C-2), 150.37 (C-2), 143.69, 137.10, 129.39, 129.28, 128.36, 127.82, 127.71, 127.56, 124.57 (ar), 88.81 (C-5), 88.70 (C-5), 69.11 (2C, C-4′), 68.97 (2C, C-5′), 68.74 (2C, C-3′), 68.25 (2C, C-2′), 64.17 (2C, C-6′), 62.00 (C-1′), 61.40 (C-1′), 52.47 (CH_2), 52.18 (CH_2), 38.31 (NCH_3), 38.18 (NCH_3), 20.71, 20.63, 20.47 (10C, CH_3(OAc)), 14.30 (CH_3), 13.64 (CH_3). IR ν_{max}/cm^{-1} 1750, 1720, 1700, 1610, 1390, 1350, 1220, 1150, 1025, 950, 810, 690, 620.