A one-pot synthesis of functionalised 1-azadienes containing 2-thioxoimidazolidin-4-ones

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The zwitterionic 1:1 intermediates generated by addition of alkyl isocyanides to acetylenic esters are trapped by 3-methyl-5,5-diaryl-2-thioxoimidazolidin-4-ones to yield dialkyl 2-[(alkylimino)(3-methyl-4-oxo-5,5-diaryl-2-thioxoimidazolidin-1-yl)methyl]but-2-enedioates in good yields.

Keywords: NH-acid, thiohydantoin, isocyanide, azadiene, acetylenic ester

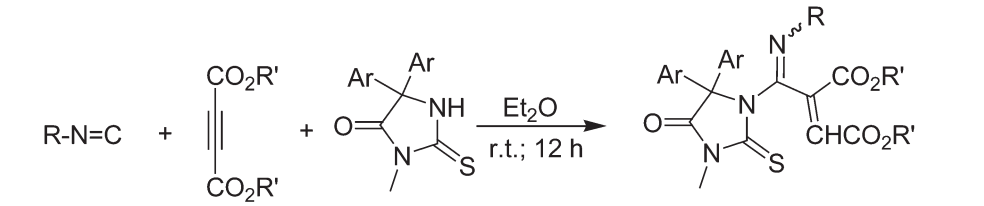
Thiohydantoin and its derivatives are important in organic and biological chemistry not only due to their presence as key structural units in many important pharmaceuticals,[1] but they can also be employed in synthetic chemistry as building blocks. Isocyanides are the only class of stable organic compounds with a formally divalent carbon atom.[2] Owing to its reactivity, the isocyanide group differs fundamentally from other functional groups. One of the classic applications in the chemistry of isocyanides is heterocyclic synthesis.[3,4]

As part of our current studies on the development of new routes in heterocyclic synthesis,[5-9] we now report the results of our studies involving the reaction of the zwitterionic intermediates derived from alkyl isocyanides **1** and acetylenic esters **2** with 3-methyl-5,5-diaryl-2-thioxoimidazolidin-4-ones **3**, which constitutes a synthesis of dialkyl 2-[(alkylimino)(3-methyl-4-oxo-5,5-diaryl-2-thioxoimidazolidin-1-yl)methyl]but-2-enedioates **4** in good yields (Scheme 1).

The ^{1}H NMR spectrum of **4a** exhibited four single sharp lines readily recognised as arising from N–Me (δ = 3.34 ppm), methoxy (δ = 3.64 and 3.85 ppm), and methine (δ = 6.89 ppm) protons, along with characteristic multiplets for the aromatic and cyclohexyl protons. The ^{1}H and ^{13}C NMR spectra of **4b–f** are similar to those of **4a** except for the alkyl and alkoxy moieties, which exhibited characteristic signals with appropriate chemical shifts. The structural assignments of compounds **4a–f** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest are the imine absorption bands at about 1650 cm^{-1} in all compounds.

A plausible rationalisation for the formation of functionalised 1-azadienes **4a–f** is shown in Scheme 2. Presumably, the zwitterionic intermediate **5**, formed from **1** and **2**, is protonated by the NH acidic compound **3**. Then, the positively charged ion **6** is attacked by the nitrogen atom of the bidentate anion **7**; direct addition leads to 1-azadiene **4** (Scheme 2). The absence of the strong ketenimine absorption bands at about 2050 cm^{-1} in the IR spectra of compounds **4**, excludes the conjugate addition of the anion **7** to the intermediate **6**.

In conclusion, the reaction of isocyanides, electron-deficient acetylenic esters, and 3-methyl-5,5-diaryl-2-thioxoimidazolidin-4-ones provides a simple one-pot entry into the synthesis of dialkyl 2-[(alkylimino)(3-methyl-4-oxo-5,5-diaryl-2-thioxoimidazolidin-1-yl)methyl]but-2-enedioates of potential synthetic interest. The present method may be considered as a practical route for the synthesis of functionalised 1-azadienes containing 2-thioxoimidazolidin-4-ones.



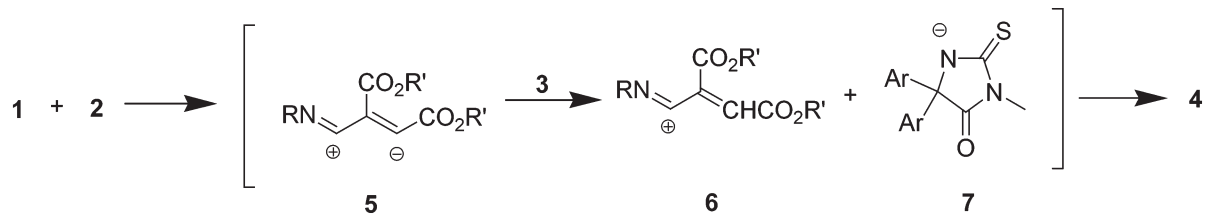
1a R = c-Hex **1b** R = $TsCH_2$ **1c** R = *t*-Bu

2a R' = Me **2b** R' = Et

3a Ar = Ph **3b** Ar = *p*-Tolyl

	R	R'	Ar	Yield (%)
4a	c-Hex	Me	Ph	85
4b	c-Hex	Et	Ph	88
4c	c-Hex	Me	*p*-Tolyl	82
4d	$TsCH_2$	Me	Ph	86
4e	$TsCH_2$	Et	Ph	90
4f	*t*-Bu	Me	Ph	94

Scheme 1



Scheme 2

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Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHNO-Rapid analyser. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance instrument with $CDCl_3$ as solvent at 300 and 75 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionisation potential of 70 eV. Compounds **1** and **2** were obtained from Fluka and were used without further purification. 3-Methyl-5,5-diphenyl-2-thioxoimidazolidin-4-one **1** was prepared by a known method.[10,11]

Preparation of **4***; typical procedure*

A solution of **1** (2 mmol) in 5 mL of Et_2O was added dropwise to a stirred solution of **2** (2 mmol) and **3** (2 mmol) in 5 mL of Et_2O at 5°C over 10 min. The reaction mixture was then allowed to warm to room temperature and stand for 12 h. The product was filtered and washed with cold Et_2O to afford the pure title compound.

Dimethyl 2-[(cyclohexylimino)(3-methyl-4-oxo-5,5-diphenyl-2-thioxoimidazolidin-1-yl)methyl]but-2-enedioate (**4a**): Cream powder; m.p. 224–226°C; yield: 0.91 g (85%); IR (KBr) (ν_{max}/cm^{-1}): 1741 and 1735 (C=O), 1643 (C=N) 1447 (C=C). Anal. Calcd for $C_{29}H_{31}N_3O_5S$ (533.64): C, 65.27; H, 5.86; N, 7.87; S, 6.01. Found: C, 64.90; H, 5.72; N, 8.03; S, 5.87%. MS: *m/z* (%): 533 (M$^+$, 23), 449 (11), 421 (42), 368 (100), 341 (60), 236 (26), 83 (15); ^{1}H NMR: 0.90–1.14 (6 H, m, 3CH_2), 1.45–1.47 (4H, m, 2CH_2), 2.86–2.88 (1H, m, CH), 3.34 (3H, s, MeN), 3.64 (3H, s, MeO), 3.85 (3H, s, MeO), 6.89 (1H, s, CH), 7.25–7.58 (10H, m, C_6H_5). ^{13}C NMR: 24.5 (CH_2), 24.6 (CH_2), 25.8 (CH_2), 29.0 (MeN), 33.2 (CH_2), 33.3 (CH_2), 52.2 (MeO), 53.4 (MeO), 59.6 (CH), 78.2 (C), 127.6 (2CH), 127.8 (2CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.3 (2CH), 131.1 (2CH), 135.3 (C), 136.1 (C), 136.5 (C), 142.4 (C=N), 164.6 (OC=O), 164.9 (OC=O), 174.6 (C=O), 181.1 (C=S).

Diethyl 2-[(cyclohexylimino)(3-methyl-4-oxo-5,5-diphenyl-2-thioxoimidazolidin-1-yl)methyl]but-2-enedioate (**4b**): Cream powder; m.p. 148–150°C; yield: 0.98 g (88%); IR (KBr) (ν_{max}/cm^{-1}): 1747 and 1727 (C=O), 1648 (C=N), 1441 (C=C); Anal. Calcd for $C_{31}H_{35}N_3O_5S$ (561.69): C, 66.29; H, 6.28; N, 7.48; S, 5.71. Found: C, 66.02; H, 6.39; N, 7.36; S, 5.91%. MS: *m/z* (%): 561 (M$^+$, 17), 477 (10), 449 (42), 396 (100), 369 (61), 236 (25), 83 (15); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89–1.11 (4H, m, 2CH_2), 1.08–1.10 (2H, m, CH_2), 1.13 (3H, t, ^3J = 7.0 Hz, Me), 1.38 (3H, t, ^3J = 7.0 Hz, Me), 1.47–1.49 (2H, m, CH_2), 1.77–1.79 (2H, m, CH_2), 2.86 (1H, m, CH), 3.34 (3H, s, MeN), 3.95 (2H, q, ^3J = 7.0 Hz, CH_2O), 4.31 (2H, q, ^3J = 7.0 Hz, CH_2O), 6.89 (1H, s, CH), 7.27–7.60 (10H, m, 2C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (Me), 14.6 (Me), 24.5 (CH_2), 24.6 (CH_2), 29.0 (CH_2), 33.2 (CH_2), 33.3 (CH_2), 59.5 (CH), 61.3 (CH_2O), 62.5 (CH_2O), 78.2 (C), 127.5 (2CH), 127.8 (2CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 129.4 (2CH), 131.2 (2CH), 135.8 (C), 136.2 (C), 136.4 (C), 142.8 (C=N), 164.1 (OC=O), 164.4 (OC=O), 174.7 (C=O), 181.0 (C=S).

Dimethyl 2-[(cyclohexylimino)(3-methyl-4-oxo-5,5-di-p-tolyl-2-thioxoimidazolidin-1-yl)methyl]but-2-enedioate (**4c**): Cream powder; m.p. 140–142°C; yield: 0.92 g (82%); IR (KBr) (ν_{max}/cm^{-1}): 1741 and 1735 (C=O), 1447 (C=C); Anal. Calcd for $C_{31}H_{35}N_3O_5S$ (561.69): C, 66.29; H, 6.28; N, 7.48; S, 5.71. Found: C, 66.15; H, 6.35; N, 7.32; S, 5.80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92–1.14 (6H, m, 2CH_2), 1.46–1.48 (4H, m, CH_2), 2.37 (3H, s, Me), 2.38 (3H, s, Me), 2.86–2.88 (1H, m, CH), 3.32 (3H, s, MeN), 3.39 (3H, s, MeO), 3.87 (3H, s, MeO), 6.89 (1H, s, CH), 7.08–7.48 (10H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (2 Me), 24.5 (CH_2), 24.6 (CH_2), 25.8 (CH_2), 29.0 (MeN), 33.2 (CH_2), 33.3 (CH_2), 52.2 (MeO), 53.4 (MeO), 59.6 (CH), 78.2 (C), 127.6 (2CH), 127.8 (2CH), 128.4 (CH), 129.3 (2CH), 131.1 (2CH), 135.3 (C), 136.1 (C), 136.5 (C), 140.1 (C), 141.1 (C), 142.3 (C=N), 164.6 (OC=O), 164.9 (OC=O), 174.6 (C=O), 181.1 (C=S).

Dimethyl 2-[(3-methyl-4-oxo-2-thioxo-5,5-diphenylimidazolidin-1-yl)-(tosylmethylimino)methyl]but-2-enedioate (**4d**): Cream powder; m.p. 186–188°C; yield: 1.06 g (86%); IR (KBr) (ν_{max}/cm^{-1}): 1749 and 1729 (C=O), 1663 (C=N), 1442 (C=C); Anal. Calcd for $C_{31}H_{29}N_3O_7S_2$ (619.71): C, 60.08; H, 4.72; N, 6.78; S, 10.35. Found: C, 60.16; H, 4.65; N, 6.82; S, 10.47%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (3H, s, Me), 3.32 (3H, s, MeN), 3.50 (3H, s, MeO), 3.87 (3H, s, MeO), 4.19 (1H, d, ^1J = 14.5 Hz, CH), 4.27 (1H, d, ^1J = 14.5 Hz, CH), 6.95 (1H, s, CH), 6.98–7.45 (14H, m, 2C_6H_5, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (Me), 29.3 (MeN), 52.7 (MeO), 53.8 (MeO), 71.9 (C), 90.1 (CH_2), 127.9 (2CH), 128.5 (2CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.2 (2CH), 129.3 (2CH), 129.9 (2CH), 130.7 (2CH), 135.1 (C), 135.2 (C), 135.3 (C), 135.6 (C), 144.7(C), 150.3 (C=N), 163.1 (OC=O), 164.0 (OC=O), 174.0 (C=O), 181.1 (C=S).

Diethyl 2-[(3-methyl-4-oxo-5,5-diphenyl-2-thioxoimidazolidin-1-yl)-(tosylmethylimino)methyl]but-2-enedioate (**4e**): Cream powder; m.p. 176–178°C; yield: 1.16 g (90%); IR (KBr) (ν_{max}/cm^{-1}): 1749 and 1729 (C=O), 1663 (C=N), 1442 (C=C); Anal. Calcd for $C_{33}H_{33}N_3O_7S_2$ (647.76): C, 61.19; H, 5.13; N, 6.49; S, 9.90. Found: C, 61.24; H, 5.08; N, 6.38; S, 10.01%. ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (3H, t, ^3J = 7.1 Hz, Me), 1.43 (3H, t, ^3J = 7.1 Hz, Me), 2.46 (3H, s, Me), 3.32 (3H, s, MeN), 3.91 (2 H, q, ^3J = 7.1 Hz, CH_2), 4.17 (1H, d, ^1J = 14.6 Hz, CH), 4.30 (1H, d, ^1J = 14.6 Hz, CH), 4.38 (2 H, q, ^3J = 7.1 Hz, CH_2), 6.93 (1H, s, CH), 6.81–7.51 (14H, m, 2C_6H_5, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (Me), 14.4 (Me), 21.8 (Me), 29.3 (MeN), 61.7 (CH_2O), 62.2 (CH_2O), 71.6 (C), 90.1 (CH_2), 127.9 (2CH), 128.5 (2CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.2 (2CH), 129.3 (2CH), 129.9 (2CH), 130.7 (2CH), 135.1(C), 135.2 (C), 135.3 (C), 135.6 (C), 144.7(C), 150.3 (C=N), 163.1 (OC=O), 164.2 (OC=O), 174.0 (C=O), 181.0 (C=S).

Dimethyl 2-[(tert-butylimino)(3-methyl-4-oxo-5,5-diphenyl-2-thioxoimidazolidin-1-yl)methyl]but-2-enedioate (**4f**): Cream powder; m.p. 135–137°C; yield: 0.95 g (94%); IR (KBr) (ν_{max}/cm^{-1}): 1741 and 1735 (C=O), 1643 (C=N) 1447 (C=C); Anal. Calcd for $C_{27}H_{29}N_3O_5S$ (507.6): C, 63.89; H, 5.76; N, 8.28; S, 6.32. Found: C, 63.80; H, 5.67; N, 8.32; S, 6.50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (9H, s, CMe_3), 3.35 (3H, s, MeN), 3.41 (3H, s, MeO), 3.76 (3H, s, MeO), 6.92 (1H, s, CH), 7.25–7.48 (10H, m, 2C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.0 (MeN), 31.8 (CMe_3), 52.2 (MeO), 53.4 (MeO), 44.2 (CMe_3), 78.2 (C), 127.5 (2CH), 127.7 (2CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.3 (2CH), 131.1 (2CH), 135.3 (C), 136.1 (C), 136.5 (C), 142.3 (C=N), 164.6 (OC=O), 164.9 (OC=O), 174.6 (C=O), 181.1 (C=S).

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References

1 R. Kumar and M. Prem. S.C., *Tetrahedron Lett.,* 2008, **49**, 5475.
2 A. Dömling, *Chem. Rev.,* 2006, **106**, 17.
3 L. Weber, *Curr. Med. Chem*., 2002, **9**, 2085.
4 S. Marcaccini and T. Torroba, *Org. Prep. Proc. Int.,* 1993, **25**, 141.
5 I. Yavari, A.R. Alborzi and B. Mohtat, *J. Chem. Res.,* 2007, 397.
6 I. Yavari, M. Sabbaghan, M. Ghazanfarpour-Darjani and Z. Hossaini, *J. Chem. Res.,* 2007, 392.
7 I. Yavari, H. Zare and B. Mohtat, *J. Chem. Res.,* 2007, 152.
8 I.Yavari, A. Mirzaei, L. Moradi and A. Mokhtarporian-Sanandaj, *J. Chem. Res.,* 2007, 205.
9 B. Mohtat, S. Jabbar, A. Ghasemi and I. Yavari, *J. Chem. Res.,* 2008, 601.
10 J. Safari, H. Naeimi, M.M. Ghanbari and O. Sabzi-Fini, *Russ. J. Org. Chem*., 2009, **45**, 477.
11 G.G. Muccioli, J.H. Poupaert, J. Wouters, B. Norberg, W. Poppitz, G.K.E. Scriba and D.M. Lambert, *Tetrahedron,* 2003, **59**, 1031.

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