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NITRILIMINE CYCLOADDITIONS TO THE CYANO GROUP IN AQUEOUS MEDIA

Giorgio Molteni* and Paola Del Buttero

Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, via Golgi 19, 20133 Milano, Italy

Abstract – Dipolar cycloadditions between nitrilimines (**2**) and the cyano group of activated nitriles (**3**) were exploited in aqueous sodium hydrogencarbonate as reaction media in the presence of a surfactant. Short reaction times and mild conditions were experienced affording 1-aryl-5-substituted 1,2,4-triazoles.

INTRODUCTION

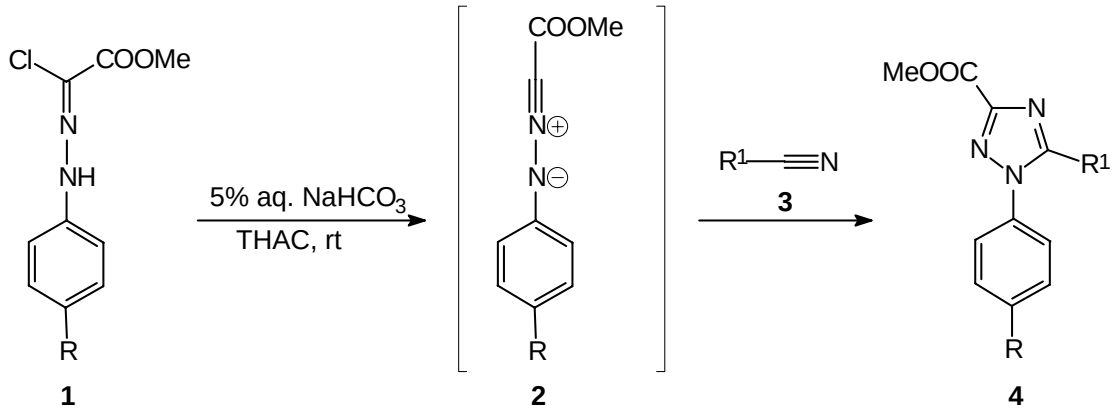
Nitrilimine cycloadditions to nitriles constitutes a valuable entry to 1,5-disubstituted 1,2,4-triazoles.[1] This regioselective reaction occurs in cases where the cyano function is activated by conjugation or by an oxygen atom in the α position.[2,3] The reported reaction conditions are usually severe, since prolonged times in boiling benzene or in boiling neat nitrile dipolarophile are required.

Recently, we developed an efficient and mild nitrilimine cycloaddition protocol onto a variety of alkenyl dipolarophiles in aqueous media.[4] Some advantages over usual procedures are concerned to this method: (*i*) reaction rates can be significantly increased; (*ii*) product separation can often be achieved by simple filtration of the crude reaction mixture; (*iii*) environmentally-friendly procedures can be successfully elaborated. We present here the first investigation on the behavior of variously substituted nitrilimines (**2**) onto cyano dipolarophiles (**3**) in aqueous media.

RESULTS AND DISCUSSION

Nitrilimine intermediates (**2**) were generated *in situ* from the corresponding hydrazonoyl chloride (**1**) in aqueous 5% sodium hydrogencarbonate at room temperature in the presence of tetrahexylammonium chloride (THAC) as the catalyst (see Scheme). Reaction times, product yields and eluants are collected in the Table. 1-Aryl-5-substituted 1,2,4-triazoles (**4**) were formed as the only regioisomers which were fully characterised by analytical and spectroscopic methods (see EXPERIMENTAL). As can be inferred from the Table, in the case of Entries **a**-**j** product isolation was actually achieved by filtration of reaction crudes

Scheme



R = H, Me, F, Cl, NO_2
R^1= COOEt, COOBn, CCl_3

Table. Cycloaddition between nitrilimines (**2**) and cyano dipolarophiles (**3**) in aqueous 5% sodium hydrogencarbonate.

Entry	R	R^1	Time (min)	Products and yields (%)		Eluant
				1	**4**	
a	H	COOEt	45	—	79	—
b	Me	COOEt	45	—	78	—
c	F	COOEt	45	—	95	—
d	Cl	COOEt	50	—	82	—
e	NO_2	COOEt	120	—	59	—
f	H	COOBn	50	—	76	—
g	Me	COOBn	55	—	74	—
h	F	COOBn	40	—	84	—
i	Cl	COOBn	40	—	74	—
j	NO_2	COOBn	105	—	67	—
k	H	CCl_3	240	37	46	AcOEt/Hexane 7:3
l	Me	CCl_3	180	39	41	AcOEt/Hexane 7:3
m	F	CCl_3	220	34	49	$CHCl_3$/Hexane 20:1
n	Cl	CCl_3	280	27	56	$CHCl_3$
o	NO_2	CCl_3	360	65	24	$CHCl_3$

while in the case of Entries **k**-**o** chromatographic workup was needed. The extent of the cycloaddition was somewhat dependent on the electronic features of both nitrilimines (**2**) and nitriles (**3**). For a given cyano dipolarophile, the cycloaddition outcome was less satisfactory with electron-poor nitrilimine (R = NO_2); this behavior reflects the usual HOMO-dipole (LUMO-dipolarophile) control of nitrilimine cycloadditions.[5] On the other hand, conjugated nitriles (R^1 = COOEt, COOBn) gave better results as compared with unconjugated one (R^1 = CCl_3). Notwithstanding 1,3-dipolar cycloadditions are regarded as

solvent-insensitive processes,[6] we experienced a dramatic increase of reaction rates compared with available literature data.[3] In order to account for the observed rate enhancements, our mechanistic picture[7] implies that the hydrophobic effect[8] gives rise to close association of organic reactants. Nitrilimine intermediate should be generated into the organic aggregate, which is characterised by a high local concentration of the dipolarophile. In this context, THAC acts as a genuine phase transfer catalyst driving the basic agent from the bulk aqueous media into the organic aggregate. As a limitation in scope, it needs to be added that nitrilimines (**2**) fail to react with alkyl nitriles (methyl cyanide, benzyl cyanide) and benzonitrile in the above conditions. This is not surprising, however, in the light of the known poor reactivity of unactivated nitriles as dipolarophiles.[9] As concluding remarks, some advantages concerned to the present aqueous media cycloaddition protocol should be pointed out: (*i*) cleaner and faster transformations were experienced compared to non-aqueous synthesis; (*ii*) reaction conditions were mild and (*iii*) the use of organic solvents was suppressed in the cycloaddition reaction.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1725 X spectrophotometer. MS spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz.

Nitriles (**3**) were used as purchased by Aldrich without any further purification. Hydrazonoyl chlorides (**1**) were synthesised according to literature procedures.[10]

Cycloaddition between hydrazonoyl chlorides (1) and nitriles (3) in aqueous sodium hydrogen carbonate; General Procedure. A mixture of hydrazonoyl chloride (**1)** (1.0 mmol), the appropriate nitrile (**3**) (10.0 mmol), THAC (38 mg, 0.1 mmol) and aqueous 5% sodium hydrogencarbonate (5.0 mL) was stirred at rt for the time indicated in the Table.

In the case of Entries **a**-**j** the mixture was filtered; the solid material was washed with water (25 mL) and dried. Subsequent crystallisation gave pure **4a**-**j**.

1-Phenyl-3-methoxycarbonyl-5-ethoxycarbonyl-1,2,4-triazole (**4a**) (79%) as pale yellow needles having mp 119-120°C (from hexane/toluene); IR (nujol): 1740 (cm^{-1}); ^{1}H-NMR: 1.37 (3H, t, *J*=6.7), 3.93 (3H, s), 4.38 (2H, q, *J*=6.7), 7.3-7.5 (5H, m); MS: 275 *m/z* (M^+). *Anal.* Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.77; H, 4.78; N, 15.32.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-1,2,4-triazole (**4b**) (78%) as colorless needles

having mp 123-124°C (from hexane/toluene); IR (nujol): 1740 (cm^{-1}); ^{1}H-NMR: 1.35 (3H, t, *J*=6.7), 2.48 (3H, s), 3.92 (3H, s), 4.36 (2H, q, *J*=6.7), 7.0-7.4 (4H, m); MS: 289 *m/z* (M^+). *Anal.* Calcd for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 58.16; H, 5.27; N, 14.59.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-1,2,4-triazole (**4c**) (95%) as colorless needles having mp 122-123°C (from hexane/toluene); IR (nujol): 1735 (cm^{-1}); ^{1}H-NMR: 1.37 (3H, t, *J*=6.7), 3.98 (3H, s), 4.43 (2H, q, *J*=6.7), 7.0-7.3 (4H, m); MS: 293 *m/z* (M^+). *Anal.* Calcd for $C_{13}H_{12}N_3O_4F$: C, 53.24; H, 4.12; N, 14.33. Found: C, 53.28; H, 4.08; N, 14.29.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-1,2,4-triazole (**4d**) (82%) as pale yellow needles having mp 130-131°C (from hexane/toluene); IR (nujol): 1735 (cm^{-1}); ^{1}H-NMR: 1.36 (3H, t, *J*=6.7), 3.96 (3H, s), 4.41 (2H, q, *J*=6.7), 7.2-7.6 (4H, m); MS: 309 *m/z* (M^+). *Anal.* Calcd for $C_{13}H_{12}N_3O_4Cl$: C, 50.41; H, 3.91; N, 13.57. Found: C, 50.37; H, 3.93; N, 13.61.

1-(4-Nitrophenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-1,2,4-triazole (**4e**) (59%) as pale yellow needles having mp 150-151°C (from hexane/chloroform); IR (nujol): 1735 (cm^{-1}); ^{1}H-NMR: 1.38 (3H, t, *J*=6.7), 4.01 (3H, s), 4.45 (2H, q, *J*=6.7), 7.4-7.8 (4H, m); MS: 320 *m/z* (M^+). *Anal.* Calcd for $C_{13}H_{12}N_4O_6$: C, 48.75; H, 3.78; N, 17.49. Found: C, 48.72; H, 3.81; N, 17.53.

1-Phenyl-3-methoxycarbonyl-5-benzyloxycarbonyl-1,2,4-triazole (**4f**) (76%) as pale yellow needles having mp 134-135°C (from hexane/toluene); IR (nujol): 1740, 1735 (cm^{-1}); ^{1}H-NMR: 3.96 (3H, s), 5.28 (2H, s), 7.2-7.5 (10H, m); MS: 337 *m/z* (M^+). *Anal.* Calcd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 64.13; H, 4.50; N, 12.42.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-benzyloxycarbonyl-1,2,4-triazole (**4g**) (74%) as white needles having mp 137-138°C (from hexane/toluene); IR (nujol): 1745, 1735 (cm^{-1}); ^{1}H-NMR: 2.39 (3H, s), 3.96 (3H, s), 5.31 (2H, s), 7.2-7.4 (9H, m); MS: 351 *m/z* (M^+). *Anal.* Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.91; H, 4.90; N, 12.02.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-benzyloxycarbonyl-1,2,4-triazole (**4h**) (84%) as colorless needles having mp 120-121°C (from hexane/toluene); IR (nujol): 1745, 1735 (cm^{-1}); ^{1}H-NMR: 3.94 (3H, s), 5.33 (2H, s), 7.1-7.4 (9H, m); MS: 355 *m/z* (M^+). *Anal.* Calcd for $C_{18}H_{14}N_3O_4F$: C, 60.85; H, 3.97; N, 11.83. Found: C, 60.88; H, 4.00; N, 11.87.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-benzyloxycarbonyl-1,2,4-triazole (**4i**) (74%) as pale yellow needles having mp 134-135°C (from hexane/toluene); IR (nujol): 1745, 1735 (cm^{-1}); ^{1}H-NMR: 4.03 (3H, s), 5.24 (2H, s), 7.2-7.5 (9H, m); MS: 371 *m/z* (M^+). *Anal.* Calcd for $C_{18}H_{14}N_3O_4Cl$: C, 58.15; H, 3.80; N, 11.30. Found: C, 58.19; H, 3.81; N, 11.34.

1-(4-Nitrophenyl)-3-methoxycarbonyl-5-benzyloxycarbonyl-1,2,4-triazole (**4j**) (67%) as yellow needles having mp 154-155°C (from hexane/chloroform); IR (nujol): 1750, 1735 (cm^{-1}); ^{1}H-NMR: 4.05 (3H, s), 5.29 (2H, s), 7.2-7.8 (9H, m); MS: 382 *m/z* (M^+). *Anal.* Calcd for $C_{18}H_{14}N_4O_6$: C, 56.55; H, 3.69; N, 14.65

Found: C, 56.58; H, 3.71; N, 14.70.

In the case of Entries **k-o** the mixture was taken up with chloroform (25 mL). The organic layer was washed with water (2 x 20 mL), dried over sodium sulfate and evaporated. The residue was chromatographed on a silica gel column with the eluant reported in the Table. Unreacted **1** was eluted first, followed by 1,2,4-triazole (**4**).

1-Phenyl-3-methoxycarbonyl-5-trichloromethyl-1,2,4-triazole (**4k**) (46%) as pale yellow needles having mp 90-91°C (from hexane/toluene); IR (nujol): 1735 (cm^{-1}); ^{1}H-NMR: 3.93 (3H, s), 7.2-7.4 (5H, m); MS: 319 *m/z* (M^+). *Anal.* Calcd for $C_{11}H_8N_3O_2Cl_3$: C, 41.21; H, 2.52; N, 13.11. Found: C, 41.24; H, 2.50; N, 13.14.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-trichloromethyl-1,2,4-triazole (**4l**) (41%) as pale yellow needles having mp 94-95°C (from hexane/toluene); IR (nujol): 1730 (cm^{-1}); ^{1}H-NMR: 2.38 (3H, s), 3.98 (3H, s), 7.2-7.4 (4H, m); MS: 333 *m/z* (M^+). *Anal.* Calcd for $C_{12}H_{10}N_3O_2Cl_3$: C, 43.08; H, 3.01; N, 12.56. Found: C, 43.11; H, 2.98; N, 12.60.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-trichloromethyl-1,2,4-triazole (**4m**) (49%) as white needles having mp 90-91°C (from hexane/toluene); IR (nujol): 1735 (cm^{-1}); ^{1}H-NMR: 3.94 (3H, s), 7.0-7.3 (4H, m); MS: 337 *m/z* (M^+). *Anal.* Calcd for $C_{11}H_7N_3O_2F$: C, 39.03; H, 2.08; N, 12.41. Found: C, 38.99; H, 2.05; N, 12.44.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-trichloromethyl-1,2,4-triazole (**4n**) (56%) as white needles having mp 98-99°C (from hexane/toluene); IR (nujol): 1735 (cm^{-1}); ^{1}H-NMR: 3.95 (3H, s), 7.2-7.5 (4H, m); MS: 354 *m/z* (M^++1). *Anal.* Calcd for $C_{11}H_7N_3O_2Cl_4$: C, 37.21; H, 1.99; N, 11.84. Found: C, 37.18; H, 2.01; N, 11.89.

1-(4-Nitrophenyl)-3-methoxycarbonyl-5-trichloromethyl-1,2,4-triazole (**4o**) (24%) as yellow needles having mp 111-112°C (from hexane/chloroform); IR (nujol): 1740 (cm^{-1}); ^{1}H-NMR: 4.01 (3H, s), 7.4-7.8 (4H, m); MS: 364 *m/z* (M^+). *Anal.* Calcd for $C_{11}H_7N_4O_4Cl_3$: C, 36.14; H, 1.93; N, 15.32. Found: C, 36.17; H, 1.90; N, 15.35.

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