Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Studies on Pyrrolidinones. A Silylated Approach to Fused Triazoles

Benoit Rigo [a] , I. Gouni [a] , Samira El Ghammarti [a] , Philippe Gautret [a] & Daniel Couturier [b]

[a] Laboratoire Chimie Organique et Environnement , Ecole des Hautes Etudes Industrielles , 13 rue de Toul, 59046, Lille Cédex, France

[b] Laboratoire Chimie Organique et Environnement , Université des Sciences et Technologies de Lille , 59655, Villeneuve d'Ascq Cédex, France

Published online: 23 Sep 2006.

To cite this article: Benoit Rigo , I. Gouni , Samira El Ghammarti , Philippe Gautret & Daniel Couturier (1994) Studies on Pyrrolidinones. A Silylated Approach to Fused Triazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:21, 3055-3063, DOI: 10.1080/00397919408011318

To link to this article: http://dx.doi.org/10.1080/00397919408011318

SYNTHETIC COMMUNICATIONS, 24(21), 3055-3063 (1994)

STUDIES ON PYRROLIDINONES. A SILYLATED APPROACH TO FUSED TRIAZOLES.

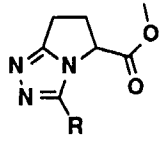
Benoît Rigo[a*], I. Gouni[a], Samira El Ghammarti[a], Philippe Gautret[a], Daniel Couturier[b]

Laboratoire Chimie Organique et Environnement

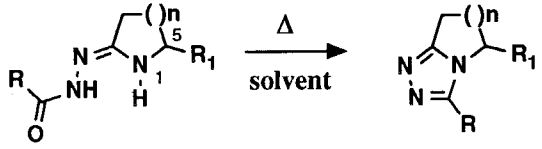
a) Ecole des Hautes Etudes Industrielles,
13 rue de Toul, 59046 Lille Cédex, France
b) Université des Sciences et Technologies de Lille,
59655 Villeneuve d'Ascq Cédex, France

Abstract : Starting from the readily available bis trimethylsilyl amidrazones derived from iminoether of methyl pyroglutamate, an easy high yield synthesis of functionalized fused triazoles is described.

We have already presented in a preliminary communication[1], the synthesis of compound **1a**. We now report that the same approach can be used for the preparation of triazoles **1b,c**.



1a R = Ph
1b R = Me
1c R = 3-Py



2	$R_1 = H$		**3**
7a	$R_1 = CO_2Me$	R = Ph	**1a**
7b	$R_1 = CO_2Me$	R = Me	**1b**

Scheme 1

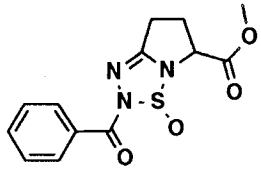
Compound \ Solvent	b R = Me		a R = 	
	MeOH [a]	AcOH [a]	MeOH [a]	AcOH [a]
3 n = 3, R_1 = H	5 h / 20° 100 %	2 h / 20° 100 %	6 h / Rfx 100 %	6 h / Rfx 100 %
3 n = 2, R_1 = H	2 h / 20° 100 %	2 h / 20° 100 %	12 h / Rfx 100 %	12 h / Rfx 100 %
3 n = 1, R_1 = H	24 h / Rfx 0 %	24 h / Rfx 70 %	24 h / Rfx 0 %	24 h / Rfx 95 %
1 n = 1, $R_1 = CO_2Me$	0 %	0 %	0 %	30 % [b]

a) NMR yield
b) Yield obtained on a 2 g scale ; there was also formation of acetyl benzydrazide. On a 10 g scale, the yield of triazole was very poor.

Table 1

Amidrazones **2** (R_1 = H) were shown to cyclize in triazoles **3** by refluxing in alcohols or in acetic acid[2,3] ; we have compared the results obtained for these compounds with those from the pyroglutamic acid serie **7** ($R_1 = CO_2Me$) ; it can be observed that the ring size is of prime importance for the cyclization, and that the N_1-lone pair is less disponible when there is a methoxycarbonyl group in the 5-position (Table 1). Such an influence of the ring size has already been reported for some reactions[4,5] (scheme 1).

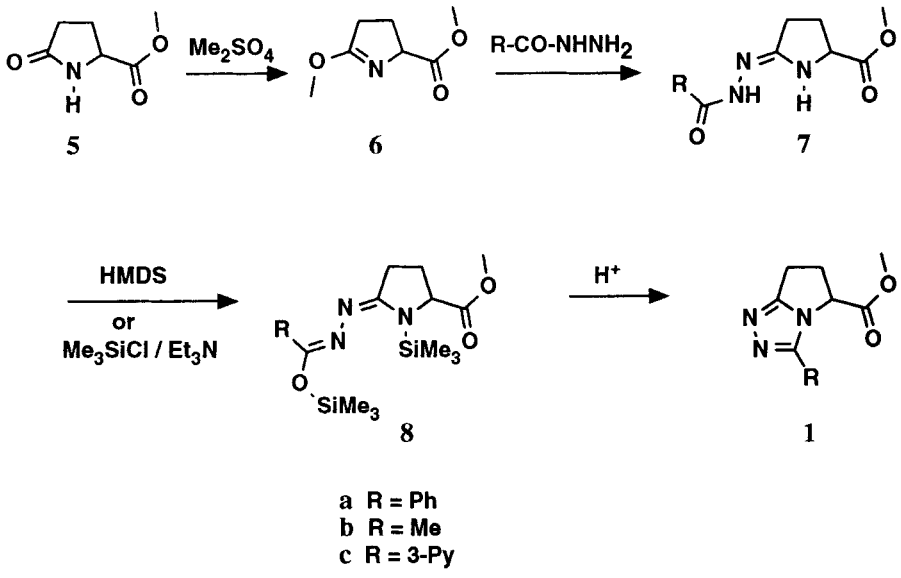
Cyclization of pyroglutamic amidrazone **2a** ($R_1 = CO_2Me$) was also tried by heating in chlorobenzene. In this case, formation of dibenzoylhydrazine was mainly observed. From these reactions, it can be concluded that the water formed during the cyclisation step hydrolyses the amidrazone, giving rise to benzoylhydrazine which is either acylated by the solvent or dismuted to dibenzoylhydrazine[6]. The use of a dehydrating agent such as phosphorus pentoxide does not give a better result. With thionyl chloride, as in other cases[7], only the heterocycle **4** was obtained.



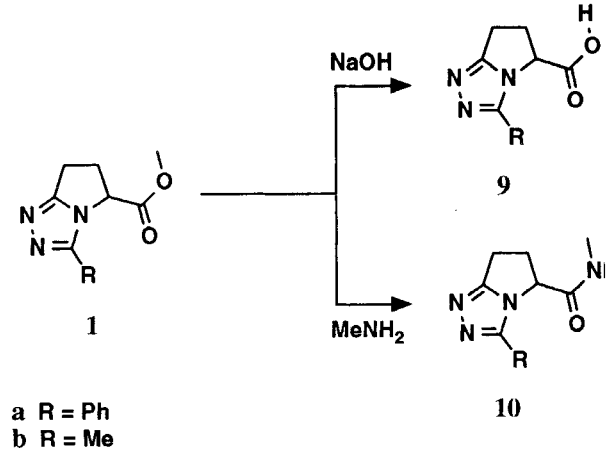
4

We then turned to the use of the cyclisation of disilylated compounds because we have already showed that these cyclisation methods which does not form water are often carried out in milder conditions than their thermal counterpart[1, 8-10] (scheme 2).

Reactions of hydrazides with iminoether **6**, easily obtained from methylpyroglutamate **5**[12], give amidrazones **7** in 80-90% yield. The silylation steps were realized with trimethylsilyl chloride in triethylamine (yield 85-95%). The distilled disilylated esters **8** were then cyclized by heating at 90°C in chlorobenzene in the presence of a catalytic amount of triflic acid (yield 75-92%). Alternatively the cyclization of amidrazones **7** can be realized without



Scheme 2



Scheme 3

isolation of **8** by heating them with hexamethyldisilazane in chlorobenzene (CF_3SO_3H as a catalyst). Generally speaking, these one-step reactions give lower yields in triazoles **1**.

In order to investigate the reactivity of these heterocycles, esters **1** were saponified into acids **9** and amides **10** ; in these reactions, the 5-methoxy carbonyl group proved to be very reactive (scheme 3).

Antitumor activity of triazoles **1** (R = Ph, 3-Py), **9** (R = Ph), **10** (R = Ph) have been tested *in-vitro* and none of them showed significant anticancer activity. Furthermore, compound **1** (R = Ph) has been tested *in-vitro* as inhibitor of the HIV virus and showed no activity. The tests were carried out at the National Cancer Institute (NCI) according to standard methods.

EXPERIMENTAL

Melting points are uncorrected ; the ir spectra were recorded on a Perkin Elmer 700 spectrometer and the NMR spectra on a Hitachi Perkin Elmer R-600 at 60 MHz using tetramethylsilane as an internal reference. Elemental analyses were performed by the Central Microanalytical Department of CNRS in Vernaison, France. Pyroglutamic acid was a gift of UCIB, Ivry- la-Bataille, France, which can provide this acid in bulk quantities.

Amidrazone 7b (R = Me)

Acetylhydrazide (25.8 g, 0.349 mol) was added to iminoether **6** (51.1 g, 0.317 mol). The mixture cristallized quickly ; methanol (40 ml) was then added and the mixture was heated for 1 hour at 40°C then kept at room temperature for 2 days. After solubilization in methanol, the product was precipited by addition of ether. Yield 80 %, mp 167-168°C (methanol). IR (KBr) ν : 3420, 3200 (NH), 1745, 1665, 1645 (C=O), 1615 (C=N) cm^{-1}. ^1H NMR (CD_3OD) δ : 1.95 (s, 3H), 2-2.7 (m, 4H), 3.71 (s, 3H), 4-4.5 (m, 1H) ppm. ^1H NMR ($CDCl_3$) δ : 2.03 (s, 1.5H), 2.16 (s, 1.5H), 2-3.8 (m, 4H), 3.75 (s, 3H), 4.1-4.5 (m, 1H), 5.9-6.9 (bs, 2H) ppm.

Anal. calcd for $C_8H_{13}N_3O_3$: C, 48.23, H, 6.58, N, 21.09, O, 24.09%.
Found : C, 48.01, H, 6.73, N, 20.79, O, 23.86.

The amidrazones **7a** (R = C_6H_5) and **7c** (R = 3-Py) were obtained with the same procedure.

Amidrazone 7a (R = Ph)

^{1}H NMR (dmso d_6) δ : 1.7-2.7 (m, 4H), 3.65 (s, 3H), 4-4.5 (m, 1H), 7.1-7.6 (m, 3H), 7.6-8 (m, 2H) ppm.

Amidrazone 7c (R = 3-Py)

^{1}H NMR (dmso d_6) δ : 1.8-2.8 (m, 4H), 3.66 (s, 3H), 4-4.5 (m, 1H), 7.2-7.5 (m, 1H), 7.9-8.2 (m, 1H), 8.4-8.6 (m, 1H), 8.8-8.9 (m, 1H) ppm.

Cyclisation in 2 steps :

Bis trimethylsilylamidrazone 8b (R = Me)

To a stirred mixture of amidrazone **7b** (R = Me)(16.9 g, 0.0853 mole) in triethylamine (180 ml), was added trimethylsilylchloride (42 ml)(nitrogen) ; the mixture was refluxed overnight. After filtration (nitrogen), the triethylamine hydrochloride was washed with anhydrous ether, the solvents were evaporated and the product was distilled, bp 90°C (0.18 mb), yield 85%. ^{1}H NMR δ : 0.26-0.27 (2s, 18H), 2.03 (s, 3H), 1.9-3 (m, 4H), 3.69 (s, 3H), 4-4.3 (m, 1H) ppm.

Triazole 1b (R = Me)

In a closed (septum) flask containing 15 ml of chlorobenzene were added successively (syringe) 5 g (0.0145 mole) of silylated amidrazone **7b** (R = Me) then 0.008g (0.53 mmol) of triflic acid. The mixture was heated at 90°C for 4 hours, giving a crude 100 % NMR yield. The product was washed with ether and then recristallized in ethyl acetate, giving a yield of 92 %, mp 118-120°C. IR (KBr) ν : 1740 (C=O), 1547-1520 (C=N), 1227 (C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$) : 2.37 (s, 3H), 2.8-3.3 (m, 4H), 3.81 (s, 3H), 4.6-5 (m, 1H) ppm.

Anal. calcd. for $C_8H_{11}N_3O_2$: C, 53.03, H, 6.12, N, 23.19, O, 17.66.
Found : C, 52.75, H, 6.15, N, 22.81, O, 18.05

Cyclisation in one-step :

Triazole 1a (R = Ph)

To stirred mixture of hydrazone **7a** (R = Ph), (20 g, 0.077 mole), hexamethyldisilazane (48.6 ml, 37.2 g, 0.228 mole) and chlorobenzene (200 ml) was added 0.6 ml of triflic acid ; after refluxing for 20 hours, the mixture was cooled (-20°C) and then filtered, yielding a 75 % yield of triazole, mp 170°C (MeCN). IR (nujol) ν : 1740 (C=O) cm^{-1}. ^1H NMR (DMSO d_6) δ : 2.5-3.1 (m, 4H), 3.63 (s, 3H), 5.3-5.7 (m, 1H), 7.3-7.55 (m, 3H), 7.55-7.9 (m, 2H) ppm. ^1H NMR ($CDCl_3$) δ : 2.6-3.3 (m, 4H), 3.62 (s, 3H), 4.8-5.2 (m, 1H), 7.1-7.45 (m, 3H), 7.45-7.8 (m, 2H) ppm.
Anal. calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19, H, 5.39, N, 17.27, O, 13.15.
Found : C, 64.31, H, 5.50, N, 17.02, O, 13.50.

Triazole 1c (R = 3-Py)

The above procedure was used for the synthesis of the triazole **1** (R = 3-Py), obtained in a 53 % yield after chromatography on silica ; mp 112°C (MeCN). ^1H NMR ($CDCl_3$) δ : 2.7-3.3 (m, 4H), 3.66 (s, 3H), 5-5.4 (m, 1H), 7.1-7.5 (m, 1H), 7.9-8.2 (m, 1H), 8.4-8.6 (m, 1H), 8.7-8.8 (m, 1H) ppm.
The best analysis obtained was :
Anal. calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01, H, 4.95, N, 22.94, O, 13.10.
Found : C, 57.43, H, 4.93, N, 22.94, O, 13.43.

Acid 9b (R = Me)

Ester **1b** (R = Me) (5 g, 0.0276 mole) was heated at 60°C for some minutes in 30 ml of 1N sodium hydroxyde. To the solution was neutralized with acidic resin Amberlite IR 120 (1,9 meq/ml). After filtration, the solution was evaporated under vacuum and the residue was washed with acetone giving 83 % crude yield; mp 236°C (MeOH). IR (KBr) ν : 3450 (OH), 1710 (C=O), 1560 (C=N), 1245 (C-O) cm^{-1}. ^1H NMR (DMSO d_6) δ : 2.19 (s, 3H), 2.6-3 (m, 4H), 4.6-5.1 (m, 1H), 6.4-7.5 (bs, 1H) ppm.

Anal. calcd. for $C_7H_9N_3O_2$, MeOH : C, 48.23, H, 6.58, N, 21.09, O, 24.09.
Found: C, 48.06, H, 6.51, N, 21.08, O, 24.39.

Acid 9a (R = Ph)

A mixture of ester **1a** (R = Ph)(4.1 g, 0.017 mole) and sodium hydroxyde (0.7 g, 0.0175 mole) in water (20 ml) was stirred for a night, then acidified with dilute HCl, giving a 78 % yield of acid, mp > 260°C (water). ^1H NMR (D_2O / NaOD) δ : 2.5-3.1 (m, 4H), 4.6-4.9 (m, 1H), 7.2-7.7 (m, 5H) ppm.
The best analysis obtained was :
Anal. calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87, H, 4.84, N, 18.33, O, 13.96.
Found : C, 61.99, H, 4.84, N, 18.21, O, 14.14.

Amide 10b (R = Me)

A stirred mixture of ester **1b** (R = Me) (5 g, 0.0276 mole) in 40 % aqueous methylamine (7 ml, 0.0838 mole) was heated at 60°C for 10 minutes ; the solid obtained after evaporation of the solution was washed with acetone, yielding 93 % of crude amide, mp 184-185°C (MeOH). IR (KBr) ν : 3500, 3400, 3300 (NH), 1660 (C=O), 1555 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ : 2.31 (s, 3H), 2.86, 2.93 (2s, 3H), 2.5-3.2 (m, 4H), 4.5-4.9 (m, 1H), 7.6-8.2 (bs, 1H, exchangeable).
Anal. calcd. for $C_8H_{12}N_4O$: C, 53.32, H, 6.71, N, 31.09, O, 8.88.
Found : C, 52.95, H, 6.48, N, 31.55, O, 8.99.

Amide 10a (R = Ph)

The above procedure was used for the synthesis of the amide **10a** (R = Ph), 80%, mp 230°C (MeCN). ^1H NMR ($CDCl_3$ / dmso d_6) δ : 2.58, 2.66 (2s, 3H ; becoming 2.62, s, 3H by addition of D_2O), 2.7-3.2 (m, 4H), 4.8-5.3 (m, 1H), 7.8-8.4 (bs, 1H, D_2O exchangeable).
Anal. calcd. for $C_{13}H_{14}N_4O$: C, 64.45, H, 5.82, N, 23.12, O, 6.60.
Found : C, 63.93, H, 5.56, N, 22.84, O, 6.92.

REFERENCES

(1) Rigo, B., Valligny, D., Taisne, S., D. Couturier, D., *Synth. Commun.*, 1988, **18**, 167..

(2) Petersen, S., Tietze, E., *Chem. Ber.*, 1957, **90**, 909.
(3) Farbenfabriken Bayer, Brit. Patent 871765, 1956.
(4) Granik,V.G., *Russ. Chem. Rev.*, 1982, **51**, 119.
(5) Celerier, J.P., Deloisy-Marchalant, E., Lhommet, G., *J. Heterocyclic Chem.*, 1984, **21**, 1633.
(6) Herbst, R.M., Garrison, J.A., *J. Org. Chem*, 1953, **18**, 872.
(7) Reimlinger, H., Vandewalle, J.J.M., Lingier, W.R.F., *Chem. Ber.*, 1970, **103**, 1934.
Bartsch, H., Erker, T., Neubauer, G., *J. Heterocyclic Chem.*, 1989, **26**, 205.
(8) Rigo, B., Cauliez, P., Fasseur, D., Couturier, D., *Synth. Commun.*, 1986, **16**, 1665.
(9) Rigo, B., Cauliez, P., Fasseur D., Couturier, D., *Synth. Commun.*,1988, **18**, 1247.
(10) Rigo, B., Fasseur, D., Cauliez, P., Couturier, D., *Synth. Commun.*, 1989, **19**, 2321.
(11) Fasseur, D., Rigo, B., Leduc, C., Cauliez, P., Couturier, D., *J. Heterocyclic Chem.*, 1992, **29**, 1285.
(12) Cauliez, P., Rigo, B., Fasseur D., Couturier, D., *J. Heterocyclic Chem.*, 1991, **28**, 1143.

(Received in the UK 15 April 1994)