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

An Efficient Hydroxymethylation of Lactams

Bruno Jouglet [a] , Saïd Oumoch [a] & Gérard Rousseau [a]
[a] Laboratoire des Carbocycles, URA CNRS 478 , Institut de Chimie Moléculaire , d'Orsay B[acaron]t. 420, 91405, Orsay, France
Published online: 23 Sep 2006.

To cite this article: Bruno Jouglet , Saïd Oumoch & Gérard Rousseau (1995) An Efficient Hydroxymethylation of Lactams, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:23, 3869-3874, DOI: 10.1080/00397919508011462

To link to this article: http://dx.doi.org/10.1080/00397919508011462

SYNTHETIC COMMUNICATIONS, 25(23), 3869-3874 (1995)

AN EFFICIENT HYDROXYMETHYLATION OF LACTAMS

Bruno Jouglet, Saïd Oumoch and Gérard Rousseau *

Laboratoire des Carbocycles, URA CNRS 478, Institut de Chimie Moléculaire d'Orsay Bât. 420, 91405 Orsay, France

Abstract: N-Hydroxymethylation of lactams was achieved using paraformaldehyde in acetone in the presence of K_2CO_3 and water under sonication conditions.

N-Hydroxymethyl- and N-alkoxymethylamides are useful synthetic compounds mainly used in the α-amidoalkylation of aromatic, olefinic, acetylenic and activated methylene compounds.[1] The intramolecular version of these reactions has also been intensively studied.[2]

N-Hydroxymethylamides are usually prepared using an aqueous solution of formaldehyde or solid paraformaldehyde in the presence of sodium hydroxide, triethylamine or potassium carbonate.[3] When these bases are inefficient, cesium carbonate can be used.[4] However, this N-hydroxymethylation is limited to substrates such as imides or primary amides, owing to incomplete reactions and by-products.[3] Reactions with secondary amides appeared much more difficult, even if the preparation of the corresponding N-hydroxymethyl derivatives was reported.[5] In fact, it was subsequently found that these results were overestimated.[6] Closely related compounds such as N-acyloxymethyl-N-methylamides have been obtained by electrolysis of the corresponding N,N-dimethylamides,[7] and N-alkoxymethyl-

* To whom correspondence should be addressed

amides were prepared from the N-chloromethylamides,[8] which are sometimes more easily prepared.

When we started our work in this field,[9] almost no report was made concerning the hydroxymethylation of lactams.[1,3] Only the reactions with γ-butyrolactam,[10] and ε-caprolactam [11] were reported. With γ-substituted-γ-butyrolactams, we were unable to isolate the corresponding N-hydroxymethyl derivatives in both satisfactory yields and acceptable purity. These results led us to investigate a new method for their preparation. We found that these derivatives could be obtained using paraformaldehyde in acetone in the presence of catalytic amounts of potassium carbonate and water under ultrasonic irradiation. Our results are reported in the Table.

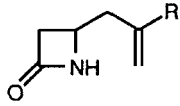
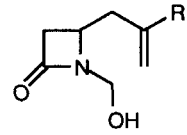
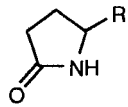
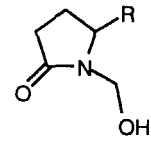
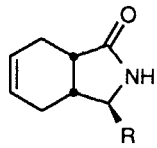
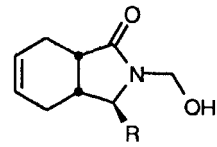
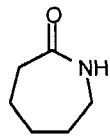
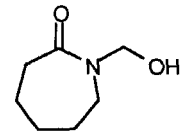
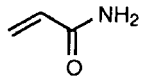
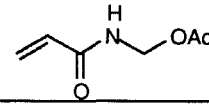
In the cases examined, excellent yields of N-hydroxymethyllactams were obtained after purification by liquid chromatography on silica gel. By-products or starting material could not be detected with tlc or ^{1}H- and ^{13}C-NMR spectroscopies. We must emphasise the necessity to correctly monitor the sonication time to avoid subsequent side reactions, such as formation of symmetrical ethers and (or) N,N'-methylenebislactams. With acrylamide (entry m) the alcohol formed was contaminated by ~20% of symmetrical ether by-product, which could not easily be separated by liquid chromatography. After acetylation (acetic anhydride, triethylamine in methylene chloride, 3 h) the corresponding acetate was obtained in satisfactory yield.

We were also interested to remove the introduced N-hydroxymethyl groups. We found that this could be achieved in 70-80% yields by heating at 200 °C under vacuum (10 to 10^{-1} mmHg). However, this procedure was inadequate with β-lactams due to their low thermal stability (entries a-d). In these cases we used an excess of conc. ammonia in MeOH at room temperature (50-80% yields),[12] or lithium hydroxide (2 equiv.) in presence of a catalytic amount of hydrogen peroxide in tetrahydrofuran-water mixture (3:1; 50% yields).

Experimental Section

The β-lactams used in this study were prepared by reaction of 4-acetoxy-2-azetidinone with the corresponding allylsilanes.[13] The preparation of γ-butyrolactams was also reported.[9] Satisfactory elemental analysis have been obtained for the N-acetyloxymethyl lactams, but not for the N-

Table: Preparation of N-hydroxymethyllactams

entry	substrate	sonication time (min)	product	yield (%)
				
a	R = H	90		95
b	R = Ph	60		80
c	R = CH_2SPh	90		80
d	R = CH_2COOMe	75		95
				
e	R = H	30		96
f	R =CH_3	30		94
g	R = C_3H_7	30		87
h	R = C_5H_{11}	30		96
i	R = $CH(CH_3)_2$	40		94
				
j	R = OC_2H_5	180		89
k	R = C_3H_7	180		77
l		60		96
m		95		70 [a]

[a] after acetylation

hydroxymethyllactams. The sonications were carried out in a Sonoclean TK 52 (Bransonic) cleaning bath at 60 KHz and 80-160 Wl^{-1}.

General procedure for the N-hydroxymethylation of lactams: In a 50 mL one necked flask were placed the lactam (6 mmol), acetone (25 mL), paraformaldehyde (0.211 g, 9 mmol), potassium carbonate (20 mg) and water (0.2 mL). The flask was closed and placed in a sonication bath. After completion of the reaction, followed by tlc (entries a-d, m) or ^{1}H-NMR (entries c-l) the mixture was filtered, dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by liquid chromatography on silica gel (CH_2Cl_2-MeOH) which led to the N-hydroxymethyllactams reported in the Table.

4-Allyl-1-hydroxymethyl-2-azetidinone: ^{1}H-NMR (200 MHz, $CDCl_3$): 2.40 (m, 1H), 2.60 (m, 1H), 2.70 (dd, J = 2.0 and 11.1 Hz, 1H), 3.10 (dd, J = 4.4 and 11.1 Hz, 1H), 3.20 (m, 1H), 3.85 (m, 1H), 4.61 (dd, A part of ABX system, J = 8.8 and 5.3 Hz, 1H), 4.78 (dd, B part of ABX system, J = 8.8 and 4.0 Hz, 1H), 5.15 (m, 2H), 5.80 (m, 1H). ^{13}C-NMR ($CDCl_3$): 167.6, 132.6, 118.2, 63.34, 49.7, 41.5, 37.1.

1-Hydroxymethyl-4-(2-phenyl-2-propenyl)-2-azetidinone: ^{1}H-NMR (200 MHz, $CDCl_3$): 2.60 (dd, J = 2.5 and 15.0 Hz, 1H), 2.80 (d, J = 7.0 Hz, 1H), 3.00 (dd, J = 5.1 and 15 Hz, 1H), 3.10 (d, J = 6.0 Hz, 1H), 3.90 (m, 1H), 4.60 (AB system, J_{AB} = 11 Hz, 2H). ^{13}C-NMR ($CDCl_3$): 167.7, 144.3, 140.2, 128.4, 127.7, 125.8, 114.6, 63.5, 49.4, 42.4, 39.2.

1-Hydroxymethyl-4-(2-thiophenylmethyl-2-propenyl)-2-azetidinone: ^{1}H-NMR (200 MHz, $CDCl_3$): 2.49 (dd, A part of ABX system, J = 13.3 and 6.6 Hz, 1H), 2.70 (dd, B part of ABX system, J = 13.3 and 4.4 Jz, 1H), 2.61 (dd, J = 2.2 and 11.1 Hz, 1H), 3.10 (dd, J = 4.4 and 11.1 Hz, 1H), 3.60 (s, 2H), 4.00 (m, 1H), 4.55 (dd, A part of ABX system, J = 8.8 and 6.6 Hz, 1H), 4.78 (dd, B part of ABX system, J = 8.8 and 4.4 Hz, 1H), 4.90 (s, 1H), 5.00 (s, 1H), 7.30 (m, 5H). ^{13}C-NMR ($CDCl_3$): 168.0, 140.3, 135.0, 130.1, 128.6, 126.4, 115.2, 63.3, 48.6, 42.6, 40.6, 37.8.

1-Hydroxymethyl-4-(2-methoxycarbonylmethyl-2-propenyl)-2-azetidinone : ^{1}H-NMR (200 MHz, $CDCl_3$): 2.40 (dd, A part of ABX system, J = 16.0 and 6.6 Hz, 1H), 2.62 (d, B part of ABX system, J = 16 Hz, 1H), 2.65 (dd, J = 2.5 and 14.6 Hz, 1H), 2.90 (dd, J = 6.8 and 8.2 Hz, 1H), 3.07 (m, 1H), 3.12 (s, 2H), 3.70 (s, 3H), 4.00 (m, 1H), 4.65 (dd, A part of ABX system, J = 11.7 and

8.3 Hz, 1H), 4.79 (dd, B part of ABX system, J = 11.7 and 6.8 Hz, 1H), 5.05 (s, 1H), 5.15 (s, 1H). ^{13}C-NMR ($CDCl_3$): 171.4, 167.4, 138.0, 115.7, 63.1, 51.6, 48.3, 42.3, 41.5, 39.2.

1-Hydroxymethyl-5-methyl-2-pyrrolidinone: ^{1}H-NMR (250 MHz, $CDCl_3$): 1.30 (d, J = 6.3 Hz, 3H), 1.55 - 1.7 (m, 1H), 2.20 - 2.30 (m, 1H), 2.35 - 2.50 (m, 2H), 2.75 - 3.00 (br s, 1H), 3.90 (s, J = 6.3 Hz, 1H), 4.65 (d, J = 10.5 Hz, 1H), 5.00 (d, J = 10.5 Hz, 1H).

1-Hydroxymethyl-5-propyl-2-pyrrolidinone: ^{1}H-NMR (250 MHz, $CDCl_3$): 0.98 (t, J = 6.9 Hz, 3H), 1.20 - 1.50 (m, 2H), 1.60 - 1.90 (m, 2H), 2.10 - 2.45 (m, 3H), 3.35 - 3.52 (m, 1H) ; 3.70 - 3.90 (m, 1H), 4.65 (dd, J = 9.2 Hz, 1H), 4.95 (dd, J = 9.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$) : 176.6, 64.5, 57.0, 35.7, 30.4, 24.1, 17.9, 14.0.

5-Butyl-1-hydroxymethyl-2-pyrrolidinone : ^{1}H-NMR (250 MHz, $CDCl_3$): 0.93 (t, J = 6.9 Hz, 3H), 1.20 - 1.50 (m, 4H), 1.60 - 1.90 (m, 2H), 2.10 - 2.50 (m, 3H), 3.05 - 3.20 (m, 1H), 3.70 - 3.82 (m, 1H), 4.65 (dd, J = 8.2 Hz, 1H), 4.95 (dd, J = 8.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$): 176.3, 64.1, 56.9, 33.0, 30.4, 26.6, 24.0, 22.5, 13.8.

1-Hydroxymethyl-5-isopropyl-2-pyrrolidinone: ^{1}H-NMR (250 MHz, $CDCl_3$): 0.80 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.70 - 2.05 (m, 2H), 2.10 - 2.22 (m, 1H), 2.32 - 2.45 (m, 1H), 3.60 - 3.70 (m, 1H), 3.72 - 3.85 (m, 1H), 4.58 - 4.70 (m, 1H), 4.90 - 5.03 (m, 1H).

3-Ethoxy-2-hydroxymethyl-2,3,3a,4,7,7a-hexahydro-1-isoindolone: ^{1}H-NMR (250 MHz, $CDCl_3$): 1.25 (t, J = 6.9 Hz, 3H), 1.70 - 1.85 (m, 1H), 2.18 - 2.35 (m, 2H), 2.40 - 2.60 (m, 2H), 2.95 - 3.05 (m, 2H), 3.55 - 3.68 (m, 2H), 4.70 (t, J = 9.2 Hz, 1H), 5.05 (dd, J = 4.6 and 4.6 Hz, 1H), 5.65 - 5.82 (m, 2H). ^{13}C-NMR ($CDCl_3$): 177.9, 126.2, 124.7, 93.3, 65.7, 63.5, 37.2, 35.6, 24.2, 21.4, 15.3.

2-Hydroxymethyl-3-propyl-2,3,3a,4,7,7a-hexahydro-1-isoindolone: ^{1}H-NMR (250 MHz, $CDCl_3$): 0.95 (t, J = 8.3 Hz, 3H), 1.15 - 1.25 (m, 1H), 1.25 - 1.75 (m, 5H), 1.75 - 1.92 (m, 1H), 2.08 - 2.30 (m, 4H), 2.30 - 2.48 (m, 1H), 2.70 - 2.80 (m, 1H), 3.25 - 3.33 (m, 1H), 4.52 (d, J = 10.1 Hz, 1H), 4.95 (d, J = 10.1 Hz, 1H), 5.62 - 5.78 (m, 2H). ^{13}C-NMR ($CDCl_3$): 177.3, 126.0, 125.5, 65.3, 63.1, 37.4, 34.0, 33.6, 26.4, 21.6, 19.2, 14.1.

N-Acetyloxymethylacrylamide: ^{1}H-NMR (250 MHz, $CDCl_3$): 2.05 (s, 3H), 5.30 (d, J = 7.4 Hz, 2H), 5.75 (dd, J = 1.4 and 10.2 Hz, 1H), 6.10 (dd, J = 10.2 and 17 Hz, 1H), 6.40 (dd, J = 1.4 and 17 Hz, 1H), 6.9 (br s, 1H).

References

1. Zaugg, H.E. *Synthesis* **1984**, 85 and 181.
2. Speckamp, W.N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. Hiemstra, H.; Speckamp, W.N. in *Comprehensive Organic Synthesis* Trost, B.M. Ed.; Pergamon Press New York **1991**, Vol. 2, p. 1047.
3. Zaugg, H.E.; Martin, W.G. *Organic Reactions* **1965**, *14*, 52.
4. Gambaryan, N.; Zeitman, Y. *Izv. Akad. Nauk SSR, Ser. Khim* **1969**, 2059. Gobao, R.A.; Bremmer, M.L.; Weinreb, S.M. *J. Am. Chem. Soc.* **1982**, *104*, 7065.
5. Böhme, H.; Dick, A.; Driesen, G. *Chem. Ber.* **1961**, *94*, 1879.
6. a) Chupp, J.P.; Speziale, A.J. *J. Org. Chem.* **1963**, *28*, 2592. b) Tyka, R.; Hägele, G. *Synthesis* **1984**, 218.
7. Ross, S.D.; Finkelstein, M.; Peterson, R.C. *J. Org. Chem.* **1966**, *31*, 128.
8. Chupp, J.P.; Goodin, R.D. *U.S. Patent* 4,258,196. *Chem. Abstr.* **1981**, *95*, 42402.
9. Jouglet, B.; Rousseau, G. *Tetrahedron Lett.* **1993**, *34*, 2307.
10. Sidel'kovskaya, F.P.; Zelenskaya, M.G.; Shostakovskii, M.F. *Izvest. Akad. Nauk. SSSR., Otdel. Khim. Nauk.* **1959**, 892. *Chem. Abstr.* **1960**, *54*, 1286.
11. Benson, R.E.; Cairns, T.L. *J. Am. Chem. Soc.* **1948**, *70*, 2115.
12. Bagai, H.; Shiozawa, T.; Achiwa, K.; Terao, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1933.
13. Oumoch, S.; Rousseau, G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2841.

(Received in The Netherlands 19 May 1995)