

Nitrosation with Lithium Nitrite¹

M. F. CHEN² AND S. F. MACDONALD

Division of Biological Sciences, National Research Council of Canada, Ottawa, Ontario K1A 0R6

Received December 14, 1973

Alcoholic lithium nitrite and 1 mol of HCl may be used to nitrosate ketones. The yields are comparable to those obtained when alkyl nitrites are used with catalytic amounts of HCl.

On peut utiliser le nitrite de lithium alcoolique avec 1 mol de HCl pour effectuer la nitrosation des cétones. Les rendements se comparent avantageusement avec ceux obtenus lorsque cette réaction est effectuée avec des nitrites d'alkyles en présence d'une quantité catalytique de HCl.

[Traduit par le journal]

Can. J. Chem., 52, 1760 (1974)

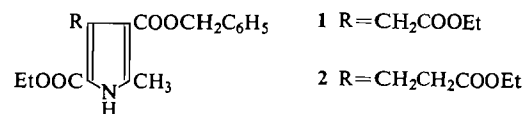
There are disadvantages attending the use of alkyl nitrites and HCl in nitrosating reactive methylene groups (1, 2). Alkyl nitrites are toxic and unstable, the lower members are gases, and the higher ones leave an alcohol in the product. The solubility of lithium nitrite in dimethylformamide makes it the reagent of choice for converting alkyl halides to nitro compounds (3). We find that its solubility in alcohols can be exploited similarly to generate *in situ* the alkyl nitrites required for nitrosations. Lithium nitrite is ridiculously expensive but it is easily obtained from barium nitrite and lithium sulfate. The examples below show that typical nitrosations, usually carried out with an alkyl nitrite and HCl, are conveniently done with alcoholic solutions of lithium nitrite and molar amounts of HCl.

2-Butanone and 3-pentanone were nitrosated in this way. We also attempted to nitrosate *n*-butyraldehyde because aldehydes, in contrast to ketones, do not appear to have been nitrosated directly (*cf.* ref. 4). The nature of the product suggests an explanation. Whether lithium nitrite and ethanolic HCl were used or the latter alone, the n.m.r. spectrum of the product showed that it was the polymeric aldehyde, presumably *m*- or *p*-butyraldehyde (*cf.* ref. 5).

Levulinic acid and its ethyl ester give their 5-chloro-5-oximino derivatives (5%) with nitrosyl chloride (6) but the 3- and 5-oximino derivatives are obtained indirectly by nitrosating acetyl-succinic acid (40%) (7) and β -ketoadipic acid (8), respectively. The lithium nitrite method converted ethyl levulinate into ethyl 3-oximino-4-

oxo-pentanoate (60%), the structure of which was confirmed by its conversion to 2,4-dimethyl-3-carbethoxy-5-carbethoxymethylpyrrole.

We were particularly interested in the pyrroles **1** and **2** obtained by nitrosating diethyl 3-oxoglutarate and diethyl β -ketoadipate, respectively, then reducing the crude products and benzyl acetoacetate with zinc dust and acetic acid (Knorr synthesis) (9). When lithium nitrite was used instead of amyl nitrite, the yields of **1** were somewhat lower but those of **2** were higher. The use of sodium nitrite and acetic acid resulted, as expected, in definitely lower yields, 25 and 46%, respectively. We took this occasion to confirm our suspicion that the ritual addition of ammonium acetate has no effect on these Knorr syntheses.



Experimental

Lithium Nitrite (10, 11)

A solution of lithium nitrite, free of barium and sulfate ions, was obtained by mixing equivalent amounts of saturated aqueous barium nitrite (City Chemical Corp.) and lithium sulfate. After removing the barium sulfate (centrifuge), the solution was evaporated (rotary), and the residue was dried over KOH (20°, 0.2 mm). Titration with permanganate (12) revealed the nitrite content and thus the degree of hydration (Li NO₂·*ca.* 1H₂O). The solubilities of the monohydrate and of the anhydrous salt in absolute ethanol are about 0.6 and 0.4 mol per 100 ml, respectively; both are more soluble in methanol.

2-Oxo-3-oximinobutane

Lithium nitrite monohydrate (7.2 g, 0.1 mol) in 15 ml of ethanol and HCl (4 g, 1.1 mol) in 10 ml of ethanol

¹Issued as NRCC No. 13863.

were added in alternate portions to 2-butanone (7.2 g, 0.1 mol), stirring at 15–20°. The solution was then stirred 1 h longer, ethanol was removed (rotary), and the residue was sublimed (65°, 12 mm) as colorless crystals, 65% (lit. (1) 50–74% using alkyl nitrites), m.p. 75–76° (lit. (13) m.p. 76.5°).

2-Oximino-3-oxo-pentane

3-Pentanone (0.1 mol) was nitrosated as above but at 30–35° and with methanol (2 × 10 ml) as the solvent. The residue left after removing the methanol was shaken with ether and water. The dried (MgSO₄) ether layer was concentrated and the crystalline product was filtered off. Yield 55% (lit. (1) 30–70% using amyl nitrite), m.p. 60–61° (lit. (4) m.p. 59–62°, (14) m.p. 69–72°).

Ethyl 3-Oximino-4-oxo-pentanoate

Solutions of lithium nitrite (0.05 mol) and of HCl (0.055 mol) in ethanol were gradually added to ethyl levulinate (0.05 mol) at 25–35°. The temperature was then allowed to rise while stirring continued until the KI–starch test was negative. The ethanol was removed (rotary, 35°), the residue was shaken with ether and water, and the dried (Na₂SO₄) ether layer was evaporated. The solution of the residue in ether–hexane (1:10) was filtered through a column of activated silica gel, the solvent was removed, and the residue distilled at 1 × 10^{−4} mm. Ethyl levulinate (1.4 g, b.p. 63°) was followed by the product (5.4 g, 60%, b.p. 97°). It was a pale yellow oil which darkened on standing; n.m.r. (CDCl₃) CH₃ at δ 2.35, no CH₂CH₂ at 2.7.

Anal. Calcd. for C₇H₁₁NO₄: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.52; H, 6.55; N, 8.03.

2,4-Dimethyl-3-carbethoxy-5-carbethoxymethylpyrrole

(a) A Knorr synthesis (*cf.* below) was carried out with ethyl-3-oximino-4-oxo-pentanoate (1.73 g), ethyl acetoacetate (1.43 g), acetic acid (10 ml), and zinc dust (2.5 g) at 65°. The crude product was recrystallized as colorless needles (43%), m.p. 86–87°, Ehrlich's reaction positive.

Anal. Calcd. for C₁₃H₁₉NO₄: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.47; H, 7.66; N, 5.68.

(b) (By reductive alkylation (*cf.* 15).) 2,4-Dimethyl-3-carbethoxypyrrole (1 g) was dissolved in a stirred solution made up from acetic anhydride (5 ml), hydriodic acid (66%, 5 ml), and hypophosphorous acid (50%, 1.5 ml). Glyoxylic acid (1 g) was then added in portions at 20°, after which stirring was continued for 1 h. The solution was poured into water to precipitate 2,4-dimethyl-3-carbethoxy-5-carboxymethylpyrrole (60%), m.p. 157–159° (lit. (16) m.p. 152–153°). This was left overnight in 10% ethanolic HCl at 20°. The ethanol was evaporated and the residue was stirred with water, separated, dried, and recrystallized from hexane (thimble). The product formed colorless needles (79%), m.p. 86–87°.

The products of *a* and *b* had identical n.m.r. spectra and the mixture m.p. was unchanged.

Benzyl 2-Methyl-4-(2-carbethoxymethyl)-5-carbethoxypyrrole-3-carboxylate (I)

Diethyl β-ketoglutarate (202 g, 1 mol) (17) was stirred and cooled in an ice bath while solutions of lithium nitrite (71 g, 1 mol) in 200 ml of ethanol and HCl (40 g) in 100 ml of ethanol were dropped in at a rate which main-

tained the temperature at 20°. The reaction was completed (KI–starch test) by stirring for a further 2 h at 20°.

Acetic acid (1 l) and benzyl acetoacetate (200 g) were stirred in a bath of ice water while the above solution and zinc dust (250 g) were added at a rate which kept the temperature at 65°. The bath was then removed and more zinc was added until there was no further temperature rise. The mixture was then maintained 2 h at 95° and the supernatant was added to 5 l of ice water, the zinc being washed with hot acetic acid. When the oil solidified it was separated and recrystallized from 300 ml of ethanol. Yield 49–51%, m.p. 119–120°, remelt 125° (lit. (9) 55%, m.p. 120–125°).

Benzyl 2-Methyl-4-(2-carbethoxyethyl)-5-carbethoxypyrrole-3-carboxylate (2)

As in the preceding preparation, diethyl β-ketoadipate (0.7 mol) (obtained by method *ii* in ref. 18) was nitrosated with lithium nitrite (0.7 mol) in 105 ml of ethanol and HCl (0.77 mol) in 70 ml of ethanol. This product was converted into the pyrrole using 700 ml of acetic acid, 140 g of benzyl acetoacetate, 150 g of zinc dust, and 3.5 l of ice water. The pyrrole was separated, dried, and recrystallized from 1.1 l of ethanol. Yield 75%, m.p. 143–146° (lit. (9) 68%, m.p. 140–142°). Using amyl nitrite and adding ammonium acetate we regularly get 60–65%, m.p. 145–146°, in 2.5 *M* runs.

- O. TOUSTER. *Org. React.* **7**, 327 (1953).
- H. METZGER. In *Methoden der organischen Chemie*. Edited by E. Muller. Georg Thieme Verlag, Stuttgart. 1968. Vol. X, part 1, p. 897; Vol. X, part 4, p. 7.
- N. KORNBLUM, H. O. LARSON, R. K. BLACKWOOD, D. D. MOOBERRY, E. P. OLIVETO, and G. E. GRAHAM. *J. Am. Chem. Soc.* **78**, 1497 (1956).
- L. CLAISEN and O. MANASSE. *Chem. Ber.* **22**, 526 (1889).
- A. FRANKE and H. WOZELKA. *Monatsh. Chem.* **33**, 349 (1912).
- H. RHEINOLDT and O. SCHMITZ-DUMONT. *Ann. Chem.* **444**, 113 (1925).
- O. DIELS and K. SCHLEICH. *Chem. Ber.* **49**, 284 (1916).
- D. SHEMIN, C. S. RUSSELL, and T. ABRAMSKY. *J. Biol. Chem.* **215**, 613 (1955).
- S. F. MACDONALD. *J. Chem. Soc.* 4176 (1952).
- W. C. BALL and H. H. ABRAM. *J. Chem. Soc.* **103**, 2130 (1913).
- J. BUREAU. *Ann. Chim. (Paris)*, [11], **8**, 5 (1937).
- W. W. SCOTT. *Standard methods of chemical analysis*. 2nd ed. Van Nostrand, New York. 1920. p. 521.
- Org. Syn. Col. Vol.* **2**, p. 204.
- E. JÄNECKE. *Chem. Ber.* **32**, 1095 (1899).
- M. W. ROOMI and S. F. MACDONALD. *Can. J. Chem.* **48**, 139 (1970).
- H. FISCHER and E. BARTHOLOMÄUS. *Chem. Ber.* **45**, 1919 (1912).
- D. M. MACDONALD and S. F. MACDONALD. *Can. J. Chem.* **33**, 573 (1955).
- S. F. MACDONALD and R. J. STEDMAN. *Can. J. Chem.* **33**, 466 (1955).