

Minas P. Georgiadis [1]

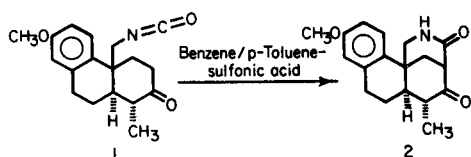
Agricultural University of Athens,
Athens, Greece

Received June 27, 1983

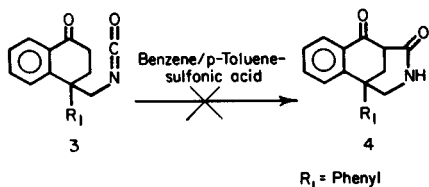
The use of sodium hydride for the synthesis of 1,5-methano-3-benzazocine derivatives, which involves the intramolecular acylation of the α -methylene group of tetralone by methylene isocyanate substituents, is discussed in detail.

J. Heterocyclic Chem., **21**, 611 (1984).

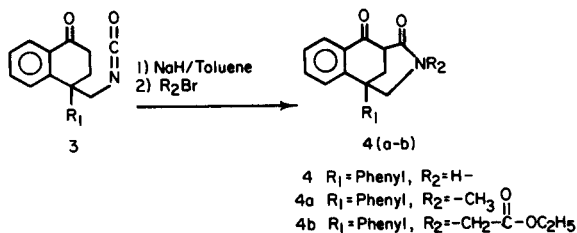
Wiesner and co-workers have reported a ring closure in the synthesis of atisine [2] which involves intramolecular acylation on the α -methylene group of intermediate **1** by isocyanate substituent.



When the above procedure suggested by Wiesner [3] was applied by the present author for the synthesis of 1-phenyl-1,5-methanobenzazocines **4**, it proved inadequate and practically useless.

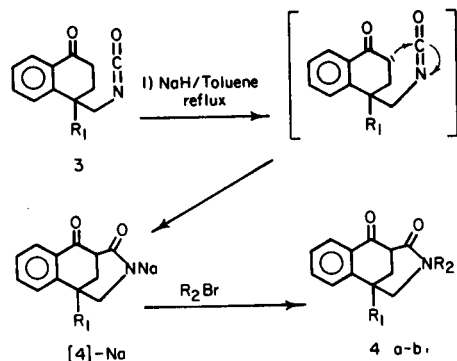


It was found, however, that the reaction **3** to **4**, which did not occur in the presence of *p*-toluenesulfonic acid, could be accomplished in high yield (80%) by the use of sodium hydride. In addition to the ring closure, the sodium hydride process allows the introduction *in situ* of a substituent on a nitrogen, as shown below:



After the discovery of the sodium hydride technique, the process was investigated and optimum conditions were found. This method was also used by Wiesner and co-workers [7,8,9]. However, the synthetic conditions were never properly discussed. Therefore, we present here detailed conditions of the sodium hydride process for the ring closure

mentioned above, together with a possible mechanism for this reaction, as shown in Scheme 1.



Scheme 1

EXPERIMENTAL

Optimum conditions for the ring closure depicted in Scheme 1 and essential points of the process are the following: 1) At least two moles of sodium hydride for each mole of **3** must be used. 2) The reaction must be followed by tlc; when the starting material disappears the *N*-sodium derivative formed (such as [4]-Na Scheme 1) remains at the origin on tlc (solvent benzene). At that point heating must be stopped or the mixture turns reddish and decomposition begins. The reaction mixture is cooled and water or water-acetic acid is added. If alkyl halide is added and the mixture is refluxed briefly, then an alkyl substituent is introduced on the nitrogen. 3) Using benzene as the solvent, the reaction is completed in five hours. In toluene the same reaction is completed within half an hour. Examples of the use of sodium hydride in the ring closure mentioned are the following:

1,2,3,4,5,6-Hexahydro-1,5-methano-1-phenyl-3-benzazocine-4,6-dione (**4**).

Sodium hydride (1 g, 54% suspension in mineral oil) was refluxed in dry toluene using a Dean-Stark water separator and some toluene was distilled off. (4-Phenyl-1-tetralone-4)-methylisocyanate (**3**) (2.1 g) was added and refluxing was continued for 20-25 minutes until tlc (benzene-ether, 95:5) showed that the reaction was complete. The mixture was cooled and water was added cautiously. Neutralization with acetic acid, washing with water, back extraction with chloroform, drying, and evaporation of the solvents yielded the title compound (1.7 g, 80%), mp 241-242° after recrystallization from benzene-ethanol; ir (chloroform): ν max 3400, 1702, 1665 cm⁻¹; uv (ethanol): λ max 248 [ϵ (1%, cm) 242], 295 [ϵ (1%, cm) 84] m μ .

Anal. Calcd. for C₁₈H₁₅O₂N: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.30; H, 5.45; N, 5.13.

1,2,3,4,5,6-Hexahydro-1,5-methano-*N*-methyl-1-phenyl-3-benzazocine-4,6-dione (**4a**).

4-Phenyl-1-tetralone-4-methylisocyanate (**3**) (500 mg) and sodium hydride (400 mg) were refluxed in dry toluene for 20-25 minutes, at which time tlc (benzene-ether 95:5) showed disappearance of the starting material. The reaction mixture was removed from heating and methyl iodide (2 g) was added dropwise. After the addition of methyl iodide refluxing was continued for three hours. Water was added to the cooled mixture and it was worked up as before, to give the title compound (410 mg, 78%), mp 230° after recrystallization from toluene; ir (chloroform): ν max 1642, 1698, 1678 cm^{-1} ; uv: 247 (ϵ 1110), 295 (ϵ 2500) $\text{m}\mu$.

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_2\text{N}$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.41; H, 5.90; N, 4.96.

1,2,3,4,5,6-Hexahydro-1-phenyl-*N*-(carbethoxymethyl)-1,5-methano-3-benzazocine-4,6-dione (**4b**).

4-Phenyl-1-tetralone methylisocyanate (about 5 g) and sodium hydride (4 g, 54% suspension in mineral oil) were refluxed in dry toluene for about half an hour at which time tlc indicated no starting material remained. The reaction mixture was removed from heating and ethyl bromoacetate (10 ml) dissolved in 30 ml of dry toluene was added dropwise over a period of ten minutes. The mixture was refluxed for three hours and was worked up as before yielding 4 g of crude product which upon recrystallization yielded the title compound (3.5 g, 75%); mp 197° analytically pure; ir (chloroform): ν max 1738, 1650, 1700; uv: 246 (ϵ 10400), 295 (ϵ 2378) $\text{m}\mu$.

Anal. Calcd. for $\text{C}_{22}\text{H}_{21}\text{O}_4\text{N}$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.66; H, 5.93; N, 4.10.

REFERENCES AND NOTES

- [1] Senior Research Chemist, Ayerst Research Laboratories, Montreal, Canada, 1965-72.
- [2] R. W. Guthrie, Z. Valenta and K. Wiesner, *Tetrahedron Letters*, 4646 (1966).
- [3] Consultant at Ayerst Research Laboratories at the time of the sodium hydride process discovery (Dec 1965-Jan 1966).
- [4] Private communication with M. A. Davis, group leader at Ayerst Research Laboratory at the time.
- [5] After prolonged treatment of **3** in benzene/*p*-toluenesulfonic acid the starting material was recovered practically unaltered. A faint spot (a suspicion of a spot) with the same value with **4** prepared by sodium hydride process appeared on tlc only when zylene/*p*-toluenesulfonic acid was used and thus, though practically useless, this process was mentioned in reference [6].
- [6] M. P. Georgiadis, M. A. Davis and K. Wiesner, U. S. Patent 3,535,322, October, 1970; *Chem. Abstr.*, **74**, 13025q (1971).
- [7] K. Wiesner, J. G. McCluskey, J. K. Chang and V. Smula, *Can. J. Chem.*, **49**, 1092 (1971).
- [8] K. Wiesner, J. G. McCluskey, U. S. Patent 3,687,937, August, 1972; *Chem. Abstr.*, **77**, 152008m (1972).
- [9] The sodium hydride procedure used in references 7 and 8 was supplied to Wiesner and co-workers by R. Deghenghi, Research Director of Ayerst Laboratories (1966).