

A NEW ROUTE TO 1-ACYL-5-OXOPERHYDROAZOCINE CORE USING
1,2,3,5,6,7-HEXAHYDROPYRROLIZINIUM PERCHLORATES

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Abstract — A convenient simple method for the synthesis of 1-substituted 5-oxoperhydroazocines (1) is described. The method consists of N-acylation of 5-oxoperhydroazocine which is one of the tautomers of the pseudobase (3) generated by the treatment of 1,2,3,5,6,7-hexahydropyrrolizinium perchlorate with aqueous alkali.

Among various procedures for the synthesis of the title core, the fundamental structure of otonecine alkaloids¹, the methods adopted Dieckmann condensation², crisscross annulation³, and hydroboration-CO insertion⁴ are considered to be efficient, so far. These methods, however, suffer from disadvantages such as high-dilution condition, multistage of the reaction, or formation of an isomeric product, respectively.

We communicate here a general strategy for such heterocycles represented as the general formula 1. The method is featured by the simplicity and the ready availability of the starting material, 1,2,3,5,6,7-hexahydropyrrolizinium perchlorates(2)^{5,6}.

For instance, the treatment of the perchlorate (2a) with phenyl isocyanate (1.0 eq.) in the presence of sodium hydroxide (3 eq.) in water at room temperature for 0.5 - 1 h afforded the product (1a)(77 %); m/z (high resolution FAB) 247.14495 (MH⁺, C₁₄H₁₉N₂O₂); ir(CHCl₃) 1700 (C₅=O) and 1670 cm⁻¹ (C=O on N₁); ¹H-nmr δ (CDCl₃, TMS) 1.90-2.53 (8H, m, aliphatic protons), 3.42 (4H, t, J=5.7 Hz), 6.45 (1H, br s, -NHCO-), and 6.88-7.44 (5H, m, aromatic protons). ¹³C-nmr δ (CDCl₃, TMS) 27.17 (C₃ and C₇), 40.08 (C₄ and C₆), 47.45 (C₂ and C₈), 120.79, 123.29, 128.65, 139.06 (aromatic carbons), 155.39 (C=O on N₁),

and 213.13 ($C_5=O$). This procedure has been found to be applicable into the synthesis of various 1-acyl-5-oxoperhydroazocines.⁷ The validity of the procedure could be exemplified by the synthesis of N-benzyloxycarbonyl-4-methyl-5-oxoperhydroazocine(1f), a crucial key intermediate for the synthesis of ($\pm$)-dihydrodesoxyotonecine(5)⁸, which has been prepared by multistage synthesis involving crisscross annulation. Thus, 1f could now be quite easily prepared in high yield from the iminium salt (2b) and benzyl chloroformate under the same reaction conditions described above (see Table).

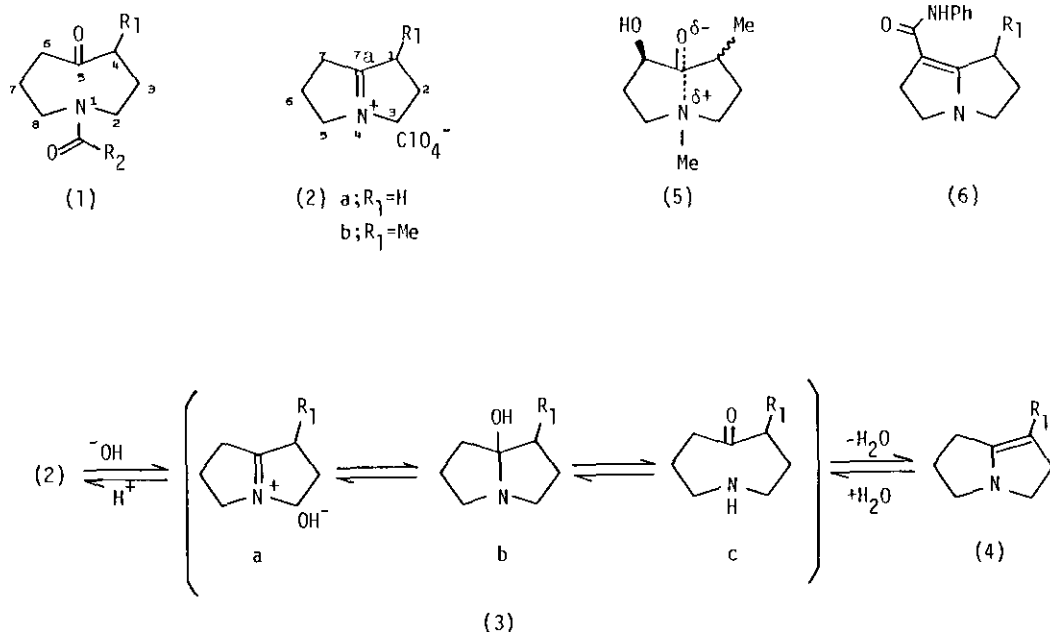
In ir spectra ($CHCl_3$), the fact that all products (1a-1f) showed a strong absorption of the ring carbonyl at 1700-1705 cm^{-1} indicates little contribution of a transannular effect between N_1 and $C_5=O$ ^{9,10}, and also may allow one to propose that, taking the steric bulkiness of substituents on N_1 into consideration, the products require a boat-chair conformation as the sole conformation¹¹. Of particular interest is the following ^{13}C -nmr spectral behavior of the products. Thus, at room temperature (35°C), the product (1a) showed only four ^{13}C resonances [$C_2(C_8)$, $C_3(C_7)$, $C_4(C_6)$, and C_5] for the ring carbons. In the case of the compounds 1b, 1c, and 1d, each of the ^{13}C lines, with the exception of C_5 carbon, splitted at 35°C into almost equal-intensity doublets, which would be attributable to the rotation of an amide functionality [N_1-COR]¹². In fact, at slightly elevated temperature ($\sim 60^\circ C$), all of these compounds showed only four ^{13}C resonances. Such ^{13}C -nmr behavior resulted from an amide rotation was also observed in the compound (1f).

On the contrary, when the reaction of freshly prepared enamine (4, $R_1=Me$)⁶ with phenyl isocyanate (1.1 eq.) was carried out in dry ether, the C-acylated compound (6) was obtained predominantly (64 %); m/z 242.14169 (M^+ , $C_{15}H_{18}N_2O$); ir(KBr) 3280 (NH) and 1640 $cm^{-1}(C=O)$; 1H -nmr δ ($CDCl_3$, TMS) 1.32 (d, $J=7.0$ Hz, Me), 1.70 -3.60 (9H, m, aliphatic protons), 6.71 (1H, br s, $-NHCO-$), and 6.86-7.78 (5H, m, aromatic protons); ^{13}C -nmr δ ($CDCl_3$, TMS) 18.28 (Me), 32.47(C_1), 32.83(C_6), 35.33(C_2), 47.39(C_3), 49.70(C_5), 93.20(C_7), [119.45, 122.62, 128.65, 139.25] (aromatic C), 164.15(C_{7a}), and 174.03($C=O$). When the reaction of 4 with phenyl isocyanate (1 eq.) was carried out in the presence of water [water/ $CHCl_3$ (1/1)], the compound (1e) was again obtained as the sole product (83 %).

A mechanistic rationalization may involve the assumption that the perchlorate

is first converted to "pseudobase"¹³ which exists in an equilibrium mixture (3), and also attains to the equilibrium involving the enamine (4) rapidly in alkali solution. Since the tautomer (3c) in the equilibrium mixture could be ascertained to be of predominant contribution under the reaction condition¹⁴, the reactions could be formally rationalized as the N-acylation of tautomeric amino-ketones(3c) (see Figure)¹⁷.

Further applications of this simple strategy for other heterocyclic systems having iminium functionality are under investigation.



Figure

Table.

Synthesis of 1-substituted 5-oxoperhydroazocines(1)

Compd.	R1	R2	Yield (%) ^{a,b}
1a	H	NHPh	77 ^c
1b	H	Ph	32 ^d
1c	H	OMe	56 ^e
1d	H	OCH ₂ Ph	63 ^f
1e	Me	NHPh	62 ^g
1f	Me	OCH ₂ Ph	63 ^e

^a Yields are based on the perchlorate (2a or 2b).

^b Phenyl isocyanate, benzoyl chloride, methyl chloroformate, and benzyl chloroformate were used as the acylating agents for the preparation of (1a) or (1e), (1b), (1c), and (1d) or (1f), respectively. ^c Mp 132-132.5° C (from EtOAc). ^d Mp 123-124° C (from Et₂O) [lit.¹⁶ mp 124-126° C]. ^e Obtained as oil^{3,4}. ^f The product purified by chromatography was solidified in a freezer, mp < 40° C [lit.⁴ mp 44-47° C]. ^g mp 123-124° C (from AcOEt).

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