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 alkaloids[1], the methods adopted Dieckmann condensation[2], crisscross annulation[3], and hydroboration-CO insertion[4] 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^+, $C_{14}H_{19}N_2O_2$); ir($CHCl_3$) 1700 (C_5=O) and 1670 cm^{-1} (C=O on N_1); ^{1}H-nmr δ ($CDCl_3$, 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). ^{13}C-nmr δ ($CDCl_3$, TMS) 27.17 (C_3 and C_7), 40.08(C_4 and C_6), C47.45(C_2 and C_8), 120.79, 123.29, 128.65, 139.06 (aromatic carbons), 155.39(C=O on N_1),

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 (±)-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).

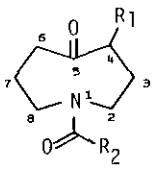
In ir spectra ($CHCl_3$), the fact that all products (**1a-1f**) showed a strong absorption of the ring carbonyl at 1700-1705 cm^{-1} indicates little contribution of a transannular effect between N_1 and C_5=O[9,10] , and also may allow one to propose that, taking the steric bulkiness of substituents on N_1 into consideration, the products require a boat-chair conformation as the sole conformation[11]. 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 (~60° 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); ^{1}H-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 %).

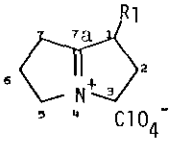
A mechanistic rationalization may involve the assumption that the perchlorate

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 condition[14], the reactions could be formally rationalized as the N-acylation of tautomeric amino-ketones(**3c**) (see Figure)[17].

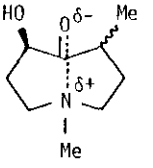
Further applications of this simple strategy for other heterocyclic systems having iminium functionality are under investigation.



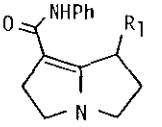
(1)



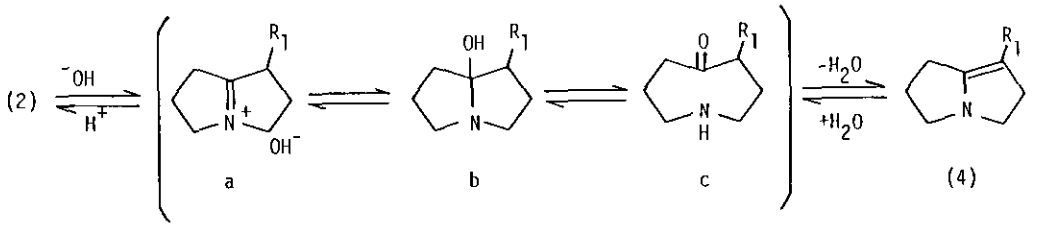
(2) a;R_1=H
b;R_1=Me



(5)



(6)



(3)

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_2Ph	63[f]
1e	Me	NHPh	62[g]
1f	Me	OCH_2Ph	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 Et_2O)[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).

REFERENCES AND NOTES

1 D. J. Robins, ' The Pyrrolizidine Alkaloids' in ' Progress in The Chemistry of Organic Natural Products. Vol. 41' , W. Herz, H. Grisebach, and G. W. Kirby, Ed., Springer-Verlag Wien New York, 1982 and related references cited therein.

2 J. P.Schaefer and J. J. Bloomfield, Org. React. 1967, 15, 1.

3 T. Ohnuma, M. Nagasaki, M. Tabe, and Y. Ban, Tetrahedron Lett., 1983, 4253.

4 M. E. Garst, J. N. Bonfiglio, and J. Marks, J. Org. Chem., 1982, **47**, 1494.

5 S. Miyano, T. Somehara, M. Nakao, and K. Sumoto, Synthesis, 1978, 701; K. Sumoto, S. Fujii, O. Yamashita, T. Somehara, and S. Miyano, J. Heterocycl. Chem., 1981, **18**, 413 , and related references cited therein.

6 S. Miyano, S. Fujii, O. Yamashita, N. Toraishi, K. Sumoto, F. Satoh, and T.

Masuda, J. Org. Chem., 1981, **46**, 1737.

7 All products were purified by column chromatography or recrystallization and adequately characterized by elemental analysis and spectroscopic methods.

8 For example, see M. Hikichi and T. Furuya, Chem Pharm. Bull., 1976, **24**, 3178; T. Furuya, M. Hikichi, and Y. Iitaka, Chem. Pharm. Bull., 1976, **24**, 1120; M. Hikichi and T. Furuya, Tetrahedron Lett., 1974, 3657; C. C. J. Culvenor, G. M. O'Donovan, and L. W. Smith, Aust. J. Chem., 1967, **20**, 801.

9 N. J. Leonard and M. Oki, J. Am. Chem. Soc.,1954, **76**, 3463; N. J. Leonard and M. Oki, J. Am. Chem. Soc., 1955, **77**, 6241, 6245.

10 W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds, Part 1 (chapter 4)', E. C. Tayer and A. Weissberger Ed., John Wiley & Sons. Inc. 1977.

11 Taking steric bulkiness of an acyl group (COR_2) on N_1 into consideration, among many possible boat-chair(BC) conformations, BC-5 conforamtion seems to be the most probable one for the products (1) [see, F. A. Anet, Topics in Current Chemistry, 1974, **45**, 169].

12 For these products, the estimated $\Delta G^{\ddagger}$ values of barriers to amide rotation were in the range of ca. 16 - 17.5 kcal/mol. [see, J. A. Hirsch, R. L. Augustine, G. Koletar, and H. G. Wolf, J. Org. Chem., 1975, **40**, 3547].

13 For example see, K. Bláha and O. Červinka, Adv. Heterocycl. Chem., 1966, **6**, 147.

14 The ^{13}C-nmr spectra of 2a apparently depended on the acidity of the media. The spectrum under basic media [H_2O + NaOH (3 molar amounts), dioxane-D_8 as an internal reference (66.50 ppm)] showed only four ^{13}C resonances [δ 26.25 (C3 and C7), 39.43 (C4 and C6), 54.85 (C2 and C8), and 195.11 (C5) ppm] ascribable to the tautomer (**3c**, R_1=H)[15].

15 T. T. Nakashima and G. E. Maciel, Org. Magn. Reson., 1972, **4**, 321.

16 R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, J. Org. Chem., 1968, **33**, 3187.

17 In the recent study on total synthesis of (±)-otonecine, the N-alkylation of the tautomer (**3b**) with MeI has been applied [see, H. Niwa, Y. Uosaki, and K. Yamada, Tetrahedron Lett., 1983, 5731].

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