Tetrahedron Letters, Vol.22, No.38, pp 3769 - 3772, 1981
Printed in Great Britain

0040-4039/81/833769-04$02.00/0

NEW SYNTHESIS OF PYRIDONE DERIVATIVE FROM 1-AZADIENE

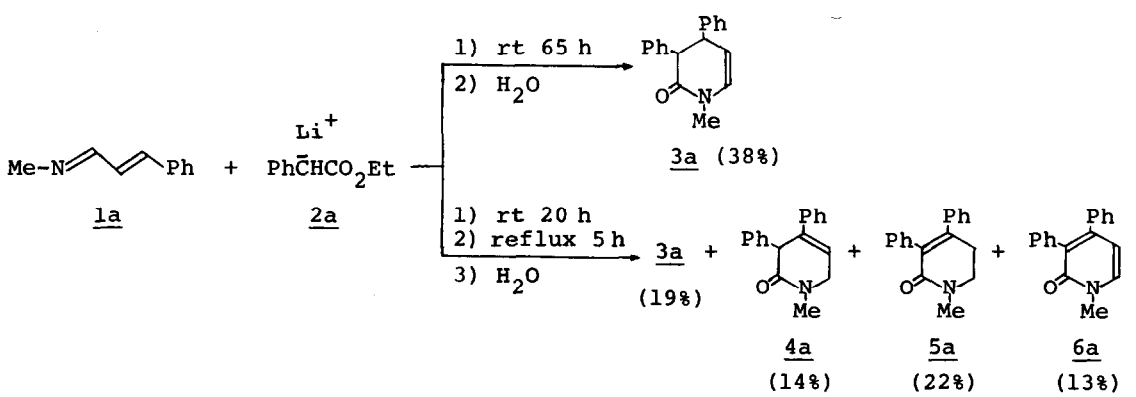
Mitsuo KOMATSU,* Shinji YAMAMOTO, Yoshiki OHSHIRO,* and Toshio AGAWA
Department of Petroleum Chemistry, Faculty of Engineering, Osaka University
Yamada-oka, Suita, Osaka 565, Japan

Summary: The reaction of 1-azabutadienes with enolates of substituted acetates gave 3,4-dihydro-2-pyridones which rearrange or dehydrogenate to other isomeric dihydropyridones or pyridones. Thus 1-azabutadienes were found to be good building blocks for pyridone derivatives.

1-Azabutadienes are expected to be useful building blocks for pyridone derivatives whose ring is an important feature of many natural alkaloids and physiologically active subsatnces.[1] Pfleger first reported the formation of a dihydropyridone from N-cinnamilideneaniline and phenylketene,[2] but later the product was proved to be a [2 + 2] cycloadduct, an azetidinone derivative.[3] Afterwards not so many [4 + 2] cycloaddition reactions of 1-azabutadienes including formation of pyridone ring have been reported.[4] These examples of pyridone formation were, however, rather special ones that have many limitations.[5]

We now wish to report the reaction of 1-azabutadienes with ester enolates as a novel and more general entry into pyridone derivatives.

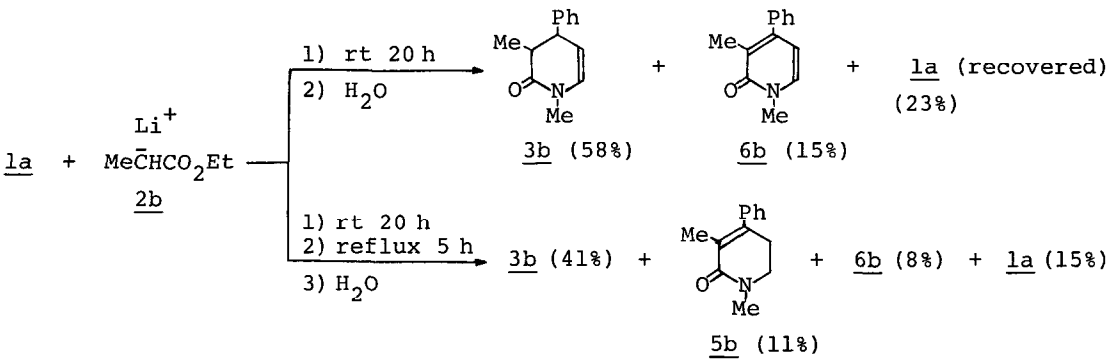
To a solution of lithium diisopropylamide prepared from n-butyllithium (18 mmol) and diisopropylamine (18 mmol) in 23 ml of THF was added dropwise a solution of ethyl phenylacetate (2.95 g, 18 mmol) in THF (3 ml) over 1 h at -15°C. Then a solution of 1-methyl-4-phenyl-1-azabuta-1,3-diene (1a, 2.18 g, 15 mmol) in THF (3 ml) was added and stirred for 1 h at the same temperature. The reaction mixture was allowed to react at room temperature for 65 h in one



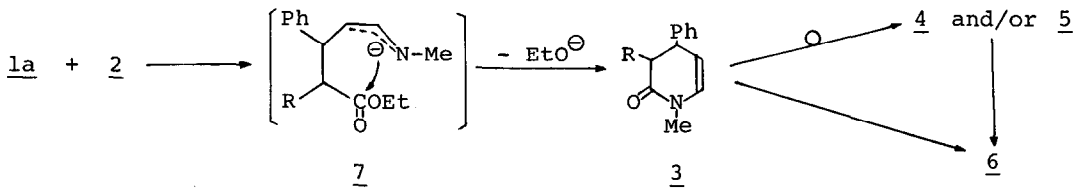
case and was allowed to stand at room temperature for 20 h followed by refluxing for 5 h in the other. After quenching with water and the usual workup, the 3,4-dihydro-2-pyridone 3a, the 3,6-dihydro-2-pyridone 4a, the 5,6-dihydro-2-pyridone 5a, and the 2-pyridone 6a were obtained. The unreacted 1a was recovered (13%) in the latter case. The products were separated by silica gel chromatography and characterized by spectral and elemental analyses.[6]

When the reaction was performed at room temperautre, the 3,4-dihydropyridone 3a was obtained as the sole product. On the other hand, the total yield became higher when the reaction mixture was refluxed in THF, but the product was a mixture of three isomeric dihydropyridones 3a-5a and the 2-pyridone 6a.

The reaction of the 1-azabutadiene 1a with ethyl α-lithiopropionate was carried out in a similar manner except for the reaction temperature: lithiation of the ester and addition of the azadiene at -70°C.



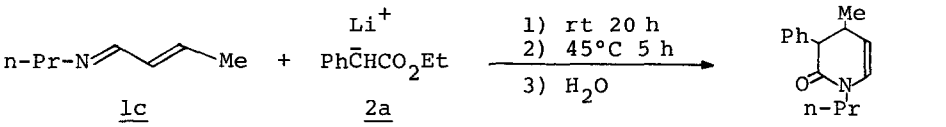
The above results imply that the initial product of the reaction is the 3,4-dihydropyridone 3 which rearranges or dehydrogenates to the others during the course of the reaction. Thus the reaction path is considered to be as follows.



In fact 3a was converted directly to 6a when treated with sodium hydride in refluxing THF. Similarly 3b was converted to a mixture of 5b and 6b and a mixture of 4a and 5a was converted to 6a. These results are consistent with the above reaction scheme and indicate that the products can ultimately be converted to the pyridone 6. Dehydrogenation of 5a to 6a was also successful with DDQ in refluxing dioxane. The lower yield of 6b under refluxing condition may be attributed to further transformation of the compound in the reaction

system.

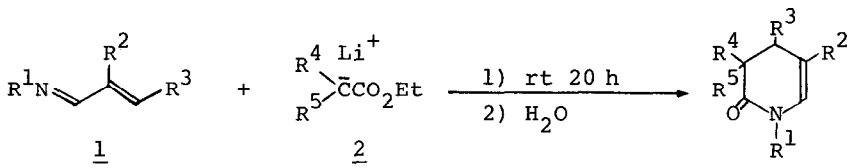
Intramolecular cyclization of the Michael-type adduct 7 is strongly hindered by a bulky N-substituent; the reaction of 1-tert-butyl-4-phenyl-1-aza-buta-1,3-diene with enolate of ethyl phenylacetate gave only a few percent of 5,6-dihydro-2-pyridone and 2-pyridone derivatives. On the other hand, 1-n-propyl-1-azapenta-1,3-diene (1c) afforded a single product, 3,4-dihydro-2-pyridone 3c, in 70% yield with recovery of the unreacted 1c (30%) when treated with the enolate 2a under similar conditions.



1c 2a 3c (70%)

The extension of this reaction was done by employing enolate of dialkyl substituted acetate which gave 3,4-dihydro-2-pyridones. Reactions and workup were carried out in the same manner as the previous runs except for lack of refluxing, since they would form neither 5,6-dihydropyridones nor pyridones. The results are summarized in Table 1.

Table 1. 3,4-Dihydro-2-pyridones from 1-Azadienes and Enolates



1 2 3

R^1	R^2	R^3	R^4	R^5	Solvent	Yield (%)[a] of 3	Recovery (%)[a] of 1
Me	H	Ph	$-(CH_2)_5-$		THF	78	—
"	"	"	Me	Me	"	63	13
n-Pr	"	Me	"	"	"	49	—
t-Bu	"	Ph	"	"	"	24	44
"	"	"	"	"	diglyme	33	52
"	"	"	"	"	THF-HMPA[b]	50	16
Me	Me	"	"	"	"	27 (16)	56 (59)
t-Bu	Et	H	"	"	"	61 (29)	— (40)

a: The yields have not been optimized in any case and yields and recoveries in parentheses are those obtained when HMPA was not added.

b: 2.4 Equiv of HMPA was added per 1 equiv of 1 and 1.2 equiv of 2.

The results show that not only a bulky substituent on the nitrogen atom (R^1) but an alkyl substituent, even a methyl group, on 3-position (R^2) hindered the reaction. However, the addition of HMPA improved the yields, which were approximately doubled by changing the solvent system.

Thus 1-azabutadienes are found to be a good synthon for dihydropyridone and pyridone derivatives and our current investigation is directed to the generalization of this reaction to other carbanions and dienes.

Acknowledgment: We thank the Watanabe Foundation for their generous financial support.

References and Notes

1) J. S. Glasby, "Encyclopedia of the Alkaloids", Plenum Press, New York, N. Y., 1975; A. Weissberger Ed., "Pyridine and Its Derivatives", Wiley, New York, N. Y., 1960; A. Abramovitch Ed., "Pyridine and Its Derivatives" Supplement Part 3, Wiley, New York, N. Y., 1975.

2) R. Pfleger and A. Jäger, Chem. Ber., 90, 2460 (1957).

3) M. Sakamoto and Y. Tomimatsu, Yakugaku Zasshi, 90, 1386 (1970).

4) Y. Tomimatsu, ibid., 77, 186 (1957); T. Kato and T. Chiba, ibid., 89, 1464 (1969); O. Tsuge and S. Iwanami, Bull. Chem. Soc. Jpn., 44, 2750 (1971); C. M. Gladstone, P. H. Daniels, and J. L. Wong, J. Org. Chem., 42, 1375 (1977).

5) R. Gompper, Angew. Chem., 81, 348 (1969); F. Duran and Léon Ghosez, Tetrahedron Lett., 245 (1970); S. Mohan, B. Kumar, and J. S. Sandhu, Chem. and Ind. (London), 671 (1971); T. Kato, T. Chiba, and S. Tanaka, Chem. Pharm. Bull. (Tokyo), 22, 744 (1974); M. Sakamoto, K. Miyazawa, K. Kuwabara, and Y. Tomimatsu, Heterocycles, 12, 231 (1979).

6) Spectral data of the dihydropyridones 3a-5a and the pyridone 6a are given below. The other products in this communication also showed satisfactory spectral data.

3a (a mixture of cis- and trans-isomers): ir ($CHCl_3$) 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.10 (s, 2.1H, Me), 3.15 (s, 0.9H, Me); 3.77 (d) and 4.0 (m) (2H, methine protons), 5.2 (m) and 5.3 (m) (1H, NC=CH), 6.10 (d) and 6.20 (d) (1H, NCH=), 6.9-7.2 (m, 10H, 2 Ph); mass spectrum (m/e) 263 (M^+).

4a: ir (neat) 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.97 (s, 3H, Me), 4.0-4.2 (m, 2H, NCH_2), 4.61 (dd, 1H, PhCH), 6.32 (dd, 1H, =CH), 6.9-7.4 (m, 10H, 2 Ph); mass spectrum (m/e) 263 (M^+).

5a: ir (Nujol) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.87 (t, 2H, CH_2), 3.10 (s, 3H, Me), 3.60 (t, 2H, NCH_2), 6.9-7.2 (m, 10H, 2 Ph); mass spectrum (m/e) 263 (M^+).

6a: ir (Nujol) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.50 (s, 3H, Me), 6.18 (d, 1H, =CH), 7.0-7.3 (m, 11H, 2 Ph and NCH=); mass spectrum (m/e) 261 (M^+).

(Received in Japan 6 July 1981)