[Chem. Pharm. Bull. 24(12)3205—3207(1976)]

UDC 547.781.1.04: 542.942.4.04

Synthesis of N-Alkylimidazoles from N-Alkyloxazolium Salts

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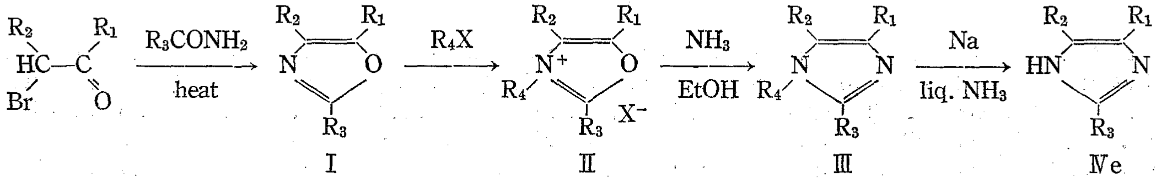
(Received March 31, 1976)

N-Methyloxazolium salts were converted to the corresponding N-methylimidazoles in ethanol–ammonia. N-Benzyl-4-methyl-5-phenyloxazolium salt (IIe) was also converted to the N-benzylimidazole (IVe) which was debenzylated by the known method.

One of the most generally useful methods for the preparation of substituted imidazoles involves the reaction of α-bromoketone (often generated by bromination of the ketone *in situ*) with solvent formamide at 170—190°.[2] Nevertheless, yields may vary widely from one case to another, and difficulties are sometimes encountered in removal of residual formamide or in isolation of product from the deeply colored reaction mixtures. When the same reaction is performed below 150°, the product is usually an oxazole, which has been postulated to be an intermediate in the imidazole synthesis.[3a] Some oxazoles, at least, can be converted into imidazoles when their solutions in formamide are maintained at the higher temperature for several hours, or when they are exposed to aqueous or ethanolic ammonia at 180° or above. If the oxazole carries alkyl groups larger than methyl at either C-2 or C-5 (or both), conversion to the imidazole fails by either method.[3] For some oxazoles, this lack of reactivity has been overcome by passage of a stream of ammonia through the refluxing formamide solution for several hours.[3a,4] Synthesis of imidazoles with additional functional groups is rarely achieved by any of these methods, the use of such high temperatures leading to extensive decomposition or to the formation of significant side products.

In the course of synthesis of a variety of functionalized imidazoles with bulky substituents, we encountered all of these difficulties; finally, we explored an alternative approach, involving activation of the oxazole by quaternization of the ring nitrogen and reaction of the product with ethanolic ammonia.[5] Since oxazoles are very weak bases, forcing conditions have



a: $R_1=R_4=CH_3$, $R_2=Ph$, $R_3=H$
b: $R_1=Ph$, $R_2=R_4=CH_3$, $R_3=H$
c: $R_1=R_3=R_4=CH_3$, $R_2=Ph$
d: $R_1=R_3=C_2H_5$, $R_2=Ph$, $R_4=CH_3$
e: $R_1=Ph$, $R_2=CH_3$, $R_3=H$, $R_4=PhCH_2$

Chart 1

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[1] Location: *a) 1-1 Keyakidai, Sakadomachi, Saitama, 350-02 Japan*; *b) Bethesda, Maryland 20014, U.S.A.*
[2] *a)* H. Brederick, R. Gompper, H.G. Schuh, and G. Theilig, *New Methods of Preparative Organic Chemistry*, 3, 241 (1964); *b)* H. Brederick, F. Effenberger, F. Marquez, and K. Ockewitz, *Chem. Ber.*, **93**, 2083 (1960).
[3] *a)* G. Theilig, *Chem. Ber.*, **86**, 96 (1953); *b)* J.W. Cornforth and H.T. Huang, *J. Chem. Soc.*, **1960** (1948).
[4] F. Marquez, *Anales Real Soc. Espan. Fis. Quim.* (*Madrid*) *Ser. B*, **57**, 723 (1961) [*C.A.*, **57**, 12467 (1962)].
[5] Several N-phenyloxazolium salts have been converted into N-phenylimidazoles in a refluxing mixture of ammonium acetate, acetic anhydride, and acetic acid: R. Gompper, *Chem. Ber.*, **90**, 374 (1957).

usually been found necessary to effect quaternization;6) with methyl fluorosulfonate (Magic Methyl), however, reaction occurrs rapidly and completely at room temperature or below. Without purification, the oxazolium salt (II) is subjected to refluxing ethanolic ammonia for 2 hr, and the corresponding N-methylimidazole (III) is isolated in high yield. Multiple, or bulky, substitution does not appear to offer any obstacle to either step; thus, 2,5-diethyl-4-phenyloxazole (Id), which could not be converted into the imidazole *via* the usual procedure,3a) produced 1-methyl-2,4-diethyl-5-phenylimidazole (IIId) in 72% overall yield. Since direct N-alkylation of imidazoles often leads to mixtures of the N-1 and N-3 isomers (or to the undesired isomer), this method has the further advantage of producing a single product of known structure.7)

Table I. N-Alkylimidazoles

Compd. III	Yield (%)	Picrate[a] mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	61	179—180	$C_{17}H_{15}O_7N_5$	50.87	3.74	17.46	50.79	3.66	17.58
b	87	205—207	$C_{17}H_{15}O_7N_5$	50.87	3.74	17.46	50.88	3.58	17.62
c	84	144—146	$C_{18}H_{17}O_7N_5$	52.05	4.10	16.87	51.93	4.15	17.09
d	72	129—130	$C_{20}H_{21}O_7N_5$	54.33	5.09	15.86	54.18	4.74	15.80
e	97	169—170	$C_{23}H_{19}O_7N_5$	57.86	3.98	14.68	57.74	4.22	14.75

a) All picrates were crystallized from ethanol.

Dealkylation of an N-methylimidazole is not achieved readily, while N-benzylimidazoles can be debenzylated by sodium in liq. ammonia8); it was appropriate, therefore, to attempt the same conversion with an N-benzyloxazolium salt. Benzyl chloride or bromide was found unreactive toward oxazoles under moderate conditions,9) but benzyl benzenesulfonate, although not as reactive as methyl fluorosulfonate, was effective in forming the desired quaternary salts. As before, ammonolysis of the oxazolium ion was achieved under mild conditions. This report describes the general synthetic procedures, using simple imidazoles as models. The methods have been applied to more complex cases, and the results will be reported in connection with other studies.10)

Experimental

Materials——Oxazoles were prepared from the corresponding α-bromoketones according to literature methods: Ia (bp 105—106°/6 Torr, reported3a) bp 115—116°/15 Torr), Ib (bp 100—104°/5 Torr, reported3a) bp 120—125°/15 Torr), Ic (bp 129—131°/11 Torr),11) Id (bp 128—131°/5 Torr, reported12) bp 139—144°/10 Torr). Methyl fluorosulfonate (Magic Methyl) was obtained from the Aldrich Chemical CO. Benzyl benzenesulfonate was prepared according to the published procedure,13) the product being stored at 0° with protection from light and moisture.

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6) *e.g.*, H.A. Staab, H. Irngartinger, A. Mannschreck, and M.-Th. Wu, *Ann. Chem.*, **695**, 55 (1966); P. Haake, L.P. Bausher, and W.B. Miller, *J. Am. Chem. Soc.*, **91**, 1113 (1969).

7) The pattern of 4,5-substitution in an oxazole is generally assumed to correspond to that of its α-bromoketone precursor. Although pathways can be formulated for rearrangement prior to ring closure (*via* acyl shifts), we are unaware of any observation of such rearrangement.

8) R.G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).

9) N-Benzyloxazolium salts do not appear to have been reported in the literature.

10) Studies on the facile conversion of N-alkyloxazolium ions to N-alkylthiazolium ions will be reported separately.

11) Ic was prepared by the same synthetic procedure described in lit. 3*a*.

12) H. Bredereck and R. Gompper, *Chem. Ber.*, **87**, 706 (1954).

13) Z. Földi, *Ber.*, **60**, 656 (1927).

Conversion of Oxazoles into N-Methylimidazoles——To a chilled solution of the oxazole (0.5 g) in 10—20 ml of dichloromethane was added 0.3—0.4 ml of methyl fluorosulfonate. After 0.5—1 hr, the solvent was evaporated under reduced pressure. The residual oil was dissolved in 10 ml of ammonia-saturated ethanol and the solution was heated at reflux for 2 hr.[14] After evaporation of the solvent, 10% sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic layer was dried and evaporated to give a colorless residue. Purification was effected most readily by chromatography on a short silica gel column, using 3% methanol–ethyl acetate for elution. Yields are given in Table I.

3-Benzyl-4-methyl-5-phenyloxazolium Benzenesulfonate (IIe)——A mixture of 4-methyl-5-phenyloxazole (Ie, 100 mg) and benzyl benzenesulfonate (500 mg) was heated at 90° for 5—10 min. The reaction mixture was diluted with dry ether and the resulting precipitate was filtered and recrystallized from ethanol–ether, mp 133—136°.

1-Benzyl-5-methyl-4-phenylimidazole (IIIe)——The N-benzyloxazolium salt (IIe, 0.41 g, 1 mmol) was added to 10 ml of ammonia-saturated ethanol and the solution was refluxed for 2 hr. The product was isolated as described above. Silica gel chromatography provided 0.23 g (97%) of an oil which solidified, mp 76—78°. The picrate was crystallized from ethanol, mp 169—170°.

4-Methyl-5-phenylimidazole (IVe)——Debenzylation of IIIe (248 mg, 1 mmol) was carried out by Na in liq. NH_3[8] to give IVe (109 mg, 69%, mp 184—187°, from benzene, reported[15] mp 192°).

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[14] Conversion can also be effected at room temperature in a few days.

[15] H. Bredereck, R. Gompper, and F. Reich, *Chem. Ber.*, 93, 733 (1960).

Chem. Pharm. Bull. 24(12)3207—3211(1976)

UDC 615.356 : 577.161.1.032.033

The Effect of Dosage Form on Absorption of Vitamin A into Lymph

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(Received April 7, 1976)

Some effects of dosage form on absorption of vitamin A into thoracic duct were studied in rats fed vitamin A. Forty-five % of administered vitamin A was recovered in lymph when vitamin A was given in micellar solution form, while 29% of administered vitamin A was recovered when vitamin A was given in triolein solution form. The time courses of appearance of vitamin A in lymph of these two kinds of preparation were very different one another. Vitamin A appearance in lymph showed a sharp peak between 1 and 2 hr after the administration in micellar solution form and indicated the almost complete absorption of vitamin A, while it showed a broad band over 4 hr after the administration in oily solution form. The time courses of vitamin A in serum did not exactly reflect those in lymph.

Most of compounds orally administered are absorbed *via* portal vein system but some fat soluble compounds are absorbed *via* thoracic duct. Some biologically important compounds such as triglyceride, cholesterol, fat soluble vitamins and DDT are known to be absorbed into lymph.[2] The mechanism of lymphatic transport was investigated much about triglyceride and cholesterol, and some about vitamin A (VA). Orally administered VA esters are partially hydrolysed by the pancreatic hydrolase with resultant appearance of VA alcohol and its esters in micellar solution from which the brush border rapidly picks up both ingredients. VA alcohol is directly admitted into the cell, while its esters are hydrolysed by the hydrolase situated on the outer surface of the brush border, and then VA alcohol is

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[1] Location: *a) Hongo, Bunkyo-ku, Tokyo*; *b) Kohda-cho, Takada-gun, Hiroshima.*

[2] H. Kilian, *Pharmaceutisch Week Blad*, 108, 1153 (1973).