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A NOVEL AND EFFICIENT SYNTHESIS OF OXAZOLES FROM TOSYLMETHYLISOCYANIDE AND CARBONYL COMPOUNDS

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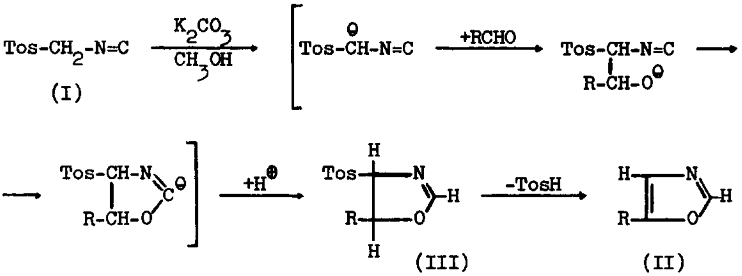
We wish to report a new chemical tool for the construction of heterocyclic ring-systems. The reagent of vital importance in these syntheses is tosylmethylisocyanide (TosMIC) (I). It is an easily prepared, stable, crystalline, and odourless isocyanide (see preceding paper[2]).

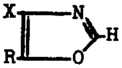
As will be shown here and in future papers in this series[3], TosMIC combines a number of chemical properties that make it a highly valuable reagent. In particular, it can be used to add a C-N=C unit to unsaturated systems.

Aldehydes, for instance, are converted efficiently in a one-pot reaction into 5-substituted oxazoles. Thus, 5-phenyloxazole (IIa) is prepared in 91% yield simply by reacting equimolar quantities of TosMIC and benzaldehyde with K_2CO_3 in refluxing methanol (2 hrs.).[4] The propensity of isocyanides to undergo nucleophilic α-additions at the terminal carbon, together with the presence of an activated methylene and a potential leaving group (i.e. tosyl), suggest the following reaction path:



Other examples of analogous reactions are collected in Table I, (compounds IIa-c).

TABLE I



	from TosMIC and	X	R	m.p. °C	% yield	δ C_2-H	δ C_4-H
IIa	benzaldehyde	H	C_6H_5	36-8° (rep.[8] 40-42°)	91	8.13	7.52
IIb	p-nitrobenzaldehyde	H	p-$O_2NC_6H_4$	136-8.5° (rep.[8] 136-7°)	91	8.30	7.88
IIc	p-chlorobenzaldehyde	H	p-ClC_6H_4	66-7° (rep.[8] 68-70°)	57	8.16	7.54
Va	benzoylchloride	Tos	C_6H_5	142-3°	57[a],65[b]	7.85	-
Vb	acetic anhydride	Tos	CH_3	136-7°	66[a],73[b]	7.70	-
Vc	phthalic anhydride	Tos	o-$HOOCC_6H_4$	224-5°	47[a]	-	-

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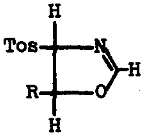
[a] With KOH in dimethoxyethane at 20° (3 hrs.), followed by dilution with water.

[b] With n-Buli in THF from -60° to 20° (2 hrs.), followed by addition of water.

Under the same conditions, but at lower reaction temperature (20°), the elimination of toluenesulfinic acid (III $\longrightarrow$ II) can be avoided. Therefore, TosMIC can be used equally well for the synthesis of 4-tosyl-Δ^2-oxazolines[5], as indicated from the results given in Table II.

TABLE II

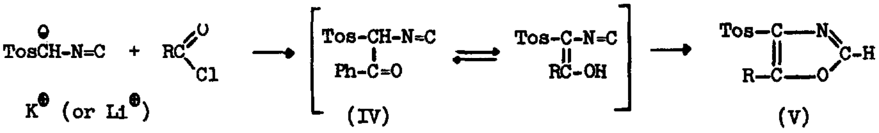


R	m.p. °C	% yield	δ C_2-H
p-$O_2NC_6H_4$	128 - 129°	80[a]	7.45 (d)
CH_2=CH-	100 - 101°	53[a]	7.08 (d)
n-C_7H_{15}	116 - 117°	78[b]	7.02 (br. s)
CH_3	134 - 134.5°	77[b]	6.98 (br. s)

[a] With K_2CO_3 in methanol at 20° for 2.5 hrs.

[b] as a) except reaction time 10 min.

Oxazoles are also obtained from TosMIC and acid chlorides or anhydrides. In these cases the oxazoles V (Table I) carry a tosyl substituent in the 4-position. Presumably the reactions occur *via* the acyl derivatives IV which, however, have not been isolated.[6]



Ethyl benzoate is not sufficiently reactive to undergo a similar acylation reaction.

The oxazoles in Table I, whether prepared from aldehydes, acylchlorides or anhydrides, all are unsubstituted in the 2-position. This is a valuable characteristic of our method, since most of the oxazole syntheses thus far available[7,8] lead to 2-substituted derivatives.

NOTES AND REFERENCES

1. On leave of absence of Gustavus Adolphus College, St. Peter, Minnesota (1970-1971).
2. This letter is considered Chemistry of Sulfonylmethylisocyanides Part 2; Part 1 is the preceding paper.
3. For the synthesis of 4-tosylimidazoles, see succeeding paper.
4. The product is isolated by removal of the methanol, and triturating the residual oil with water.
5. The Δ^2-oxazolines separate directly from the reaction mixture (after about 10 min.) due to protonation of anionic III in the protic medium.
6. β-Oxoisocyanides are known to cyclise readily to oxazoles: I. Hagedorn, U. Eholzer and H. Etling, Chem. Ber. **98**, 193 (1965).
7. Review: J.W. Cornforth in Heterocyclic Compounds (Elderfield), Wiley, New York 1957, Vol. 5, p. 298.
8. C. Tanaka, Yakugaku Zasshi **85**, 186 (1965); Chem. Abstr. **62**, 16222c (1965). II is obtained by decarboxylation of the corresponding 2-COOH derivatives.