Tetrahedron Letters No. 52, pp 5337 - 5340, 1972. Pergamon Press. Printed in Great Britain.

A NEW AND SIMPLE SYNTHESIS OF THE PYRROLE RING SYSTEM FROM MICHAEL ACCEPTORS AND TOSYLMETHYLISOCYANIDES

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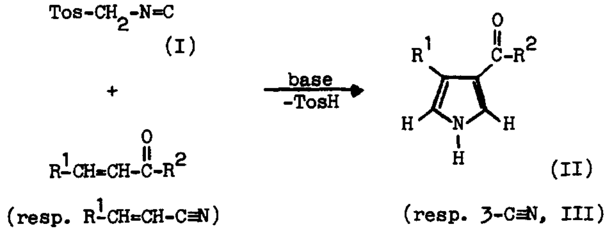
(Received in UK 8 November 1972; accepted for publication 30 November 1972)

The utility of tosylmethylisocyanide (TosMIC) (I) in heterocyclic syntheses was demonstrated in previous papers in this series.[2] We now wish to report further extension of the scope of this reagent to the synthesis of pyrroles by reaction with Michael acceptors.

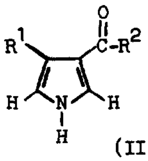
TosMIC reacts under basic conditions with α,β-unsaturated ketones, esters or nitriles to give, by concomitant loss of p-toluenesulfinic acid, 3-acylpyrroles (IIa-g), pyrrole-3-carboxylates (IIh-k) and 3-cyanopyrroles (IIIa-c), respectively.

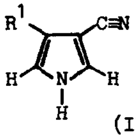


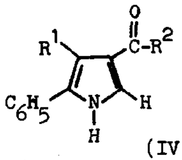
The substituent R^1 was varied from aryl and alkyl to hydrogen (see Table). Usually, the highest yields were obtained when R^1 was aryl.

It is apparent from the rationalization given below that the pyrroles prepared by this method will be perforce unsubstituted in the ring positions 1 and 2. Accordingly, Michael acceptors like mesityl oxide and 3-methyl-3-penten-2-one, devoid of at least one hydrogen at

TABLE [a]


(II)


(III)


(IV)

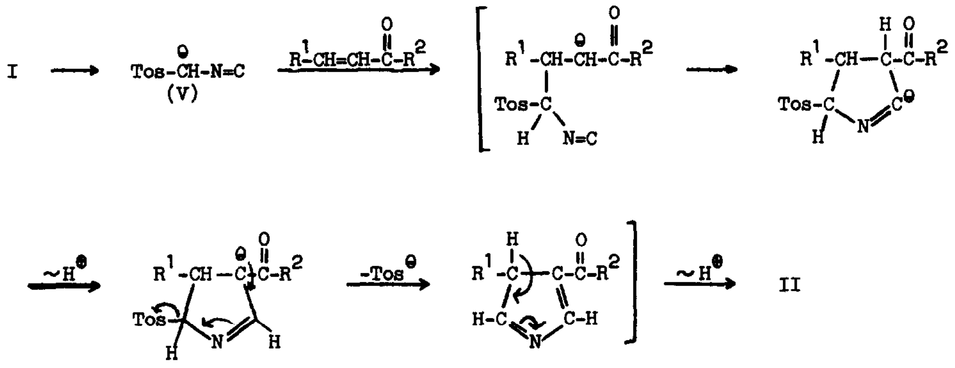
	R^1	R^2	mp. °C	yield [b]	purification
IIa	C_6H_5	CH_3	157 - 158°	70%	benzene
IIb	2-furyl	CH_3	138 - 141°	69%	Et_2O/pet. ether
IIc	2,6,6-trimethyl-hex-2-enyl	CH_3	198 - 199°	7%	Et_2O/pet. ether
IId	CH_3	CH_3	112 - 114°	45%	benzene/Et_2O alumina/CH_2Cl_2
IIe	H	CH_3	110 - 111° (rep.[6] 112-113°)	15%	alumina/CH_2Cl_2 benzene/pet. ether
IIf	C_6H_5	C_6H_5	229 - 231° (dec.)	70%	MeOH/$CHCl_3$
IIg	C_6H_5CO	C_6H_5	221 - 222°	50%	EtOH
IIh	C_6H_5	CH_3O	182 - 183°	70%	MeOH
IIi	CH_3	CH_3O	52 - 54° (rep.[8] 55-56°)	64%	alumina/CH_2Cl_2 benzene/pet. ether
IIj	H	CH_3O	86 - 87° (rep.[9] 87-88°)	33%	sublim.
IIk	$COOCH_3$	CH_3O	243 - 245° (rep.[10] 241-242°)	60%	sublim.
IIIa	C_6H_5	-	128 - 129°	35%	Et_2O/pet. ether
IIIb	CH_3	-	114 - 117°	50%	alumina/Et_2O-pet. ether [c] sublim.
IIIc	H	-	53 - 55° (rep.[6] 55-56°)	10% (33% by NMR)	sublim.
IV	C_6H_5	CH_3O	184 - 185°	23%	alumina/CH_2Cl_2 Et_2O/pet. ether

[a] All new compounds gave microanalyses for C, H and N within 0.3% of the calculated values. IR and NMR spectra support the structures.

[b] Yield of isolated compounds after one purification (crystallization, chromatography or sublimation, see last column).

[c] Chromatography gave a second product (in 9% yield): 1-(1-cyanoisopropyl)-3-cyano-4-methylpyrrole.

both C_α and C_β, provide no pyrroles at all. Ring position 5 in II and III remains also unsubstituted, as a consequence of the choice of TosMIC (I). However, by use of α-tosylbenzylisocyanide[3], instead of TosMIC, a 5-phenyl substituted pyrrole IV is obtained (see Table).



The vinylic carbon atoms of the Michael acceptors become C_3 and C_4 of the pyrrole ring. This is an essential feature of our synthetic method as is illustrated, for example, by the conversion of methyl crotonate. Reaction with TosMIC gives in one shot methyl 4-methylpyrrole-3-carboxylate (IIi) in 64% yield. It is worthwhile to compare this result with the previously reported preparation of the isomeric methyl 2-methylpyrrole-3-carboxylate also employing methyl crotonate. This synthesis, for which ethyl N-ethoxycarbonylglycinate is used, requires four separate reaction steps (overall yield 35%).[4]

Another characteristic of our method is the construction of the pyrrole ring by formation of both the C_2-C_3 and the C_4-C_5 bonds. This is a rather new and scarcely applied approach in pyrrole synthesis.[5] It has been used for the first time by Dimroth et.al.[5a] for the synthesis of penta-substituted pyrroles by an adaptation of the Hinsberg thiophene synthesis to the pyrrole problem.

Our new pyrrole synthesis provides a simple method for preparing various 3-acylpyrroles with free 1 and 2 positions. Such compounds are relatively inaccessable otherwise. They have been obtained previously by multi-step syntheses involving decarboxylation at N and/or C_2 in the final stage of the reaction.[6]

It should be noted that our method does not apply, however, to the synthesis of 3-formylpyrroles. TosMIC anion (V) attacks acrolein on the carbonyl carbon rather than on C_β. Thus, a 2-oxazoline is formed instead of a pyrrole.[7]

General procedure. A solution of a mixture of 5 mmole of TosMIC and 5 mmole of substrate in 25 ml of Et_2O/DMSO (2:1) is added dropwise to a stirred suspension of *ca*. 1.2 equiv. of NaH in Et_2O (10 ml).

The mixture, which starts to reflux from the exothermic reaction, is after 15 min diluted with water and extracted with Et_2O, followed by purification as indicated in the Table. Bases other than NaH were used with similar results: t-BuOK in THF for II,d,f,j, and K_2CO_3 in refluxing CH_3OH (2 hr) for IIf.

Notes and references.

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2. This letter is considered Chemistry of Sulfonylmethylisocyanides Part 6. For Part 5 see O.H. Oldenziel and A.M. van Leusen, *Synth. Comm.*, **1972**, 281.
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