SYNTHESIS OF OXAZOLES, IMIDAZOLES AND PYRROLES WITH THE USE OF MONO-SUBSTITUTED TOSYLMETHYL ISOCYANIDES[1]

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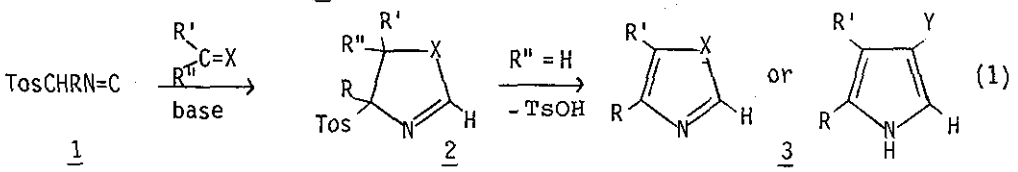
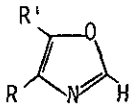
Oxazoles, pyrroles and imidazoles are synthesized from mono-alkylated tosylmethyl isocyanides (TosCHRN=C) and aldehydes, Michael-acceptors or aldimines.

Tosylmethyl isocyanide (TosMIC, 1, R = H) has been found a useful synthon in organic chemistry.[2] Base-induced reactions of TosMIC with unsaturated substrates such as ketones, aldehydes, imines and Michael acceptors lead to heterocyclic compounds (Eq 1). Elimination of p-toluenesulfinic acid (TsOH, possible for R" = H) converts the initially formed azolines 2 to oxazoles, imidazoles or pyrroles (3).[3,4,5]



(1)

X = O, NR, CHY (for Y see Table II)

TABLE I. TosCHRN=C + R'-C(=O)-H $\xrightarrow{-TsOH}$ 

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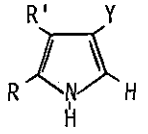
R	R'	Yield (%)	Conditions	bp or mp (^{o}C)
Me	Ph	75	t-BuOK, MeOH, 40^{o}	70-71 (0.7 mm)[a]
Me	p-ClC_6H_4	74	K_2CO_3, MeOH, reflux	78-80 (0.2 mm)
Me	2-furyl	64	t-BuOK, MeOH, 40^{o}	57-58 (0.15 mm)
Et	Ph	82	K_2CO_3, MeOH, reflux	72-74 (0.6 mm)[b]
Et	p-ClC_6H_4	73	t-BuOK, MeOH, 40^{o}	97-98 (0.35 mm)
$PhCH_2$	p-ClC_6H_4	81	K_2CO_3, MeOH, reflux	76.5-77.5
$PhCH_2$	2-furyl	62	t-BuOK, MeOH, 40^{o}	123-124 (0.2 mm)
$PhCH_2$	2-thienyl	71	K_2CO_3, MeOH, reflux	162-165 (0.04 mm)

a. Lit.[8] bp 120-125^{o}C (15 mm); b. Lit.[8] bp 124-128^{o}C (11 mm).

TABLE II. TosCHRN=C + R'-CH=CH-Y $\xrightarrow{-TsOH}$ 

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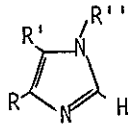
R	R'	Y	Yield (%)	Mp(^{o}C)
Me	Me	COOMe	71	146.5-148
Me	Ph	PhCO	83	206-207.5
$PhCH_2$	Ph	PhCO	83	168-169
$PhCH_2$	Me	COOMe	81	134.5-135.5
$PhCH_2$	Ph	C≡N	80	121-123
CH_2=CH-CH_2	Ph	PhCO	78	209-210.5

Since the recent phase-transfer alkylation of TosMIC has made available a series of mono-substituted TosMIC-derivatives (1, R = alkyl, benzyl, allyl),[6] we were able now to synthesize a host of new azoles[7] (Table I, II, III). For instance, 4-ethyl-5-phenyloxazole (3, R = Et, R' = Ph, X = O) was prepared in 82% yield by refluxing equimolar quantities of α-tosylpropyl isocyanide[6] (1, R = Et) and benzaldehyde for 1 hr with 1.5 equivalent of K_2CO_3 in MeOH. Other base-solvent systems such as sodium ethoxide in ethanol, or potassium t-butoxide in methanol or t-butanol were used with success also. Further examples are collected in Table I.

Occasionally, the intermediate 2-oxazolines (2, X = O) were isolated by carrying out the reaction at room temperature (K_2CO_3 in MeOH), which means that the elimination of TsOH is slow compared to the cycloaddition [2, X = O, R = $PhCH_2$: R' = Ph, 83%, mp 106-107°; R' = p-ClC_6H_4, 74%, mp 106.5-108°; R' = p-$MeOC_6H_4$, 36%, mp 106-107°]. These oxazolines were readily converted to the corresponding oxazoles 3 with K_2CO_3 in refluxing MeOH. Alternatively, 2-oxazolines were obtained under phase-transfer conditions (CH_2Cl_2, 30% NaOH, Bu_4NI), or with KOH and 18-Crown-6 in benzene.

2,3,4-Trisubstituted pyrroles (Table II) were synthesized in high yields from 1 and Michael acceptors with NaH in DMSO-Et_2O at room temperature. These pyrroles are stable crystalline compounds. As an exception, no pyrrole was obtained from 1 (R = Me) and methyl acrylate, which polymerized under the conditions of the reaction.

Table III collects the results of the reaction of 1 with aldimines to 1,4,5-trisubstituted imidazoles. Here, a successful reaction appears to demand at least one electronegatively substituted (NO_2 or Cl) group in the aldimine, which is consistent with similar observations made with TosMIC itself.[5]

TABLE III. TosCHRN=C + R'-CH=N-R'' $\xrightarrow{-TsOH}$ 

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R	R'	R''	Yield (%)	Conditions
Me	Ph	p-$O_2NC_6H_4$	75	NaH/DME
Me	p-$O_2NC_6H_4$	Ph	78	t-BuOK/DMSO
Me	Ph	Ph	-[a]	"
$PhCH_2$	p-$O_2NC_6H_4$	Ph	62	"
$PhCH_2$	p-ClC_6H_4	Ph	68	NaH/DMSO
$PhCH_2$	p-$MeOC_6H_4$	Ph	-[a]	t-BuOK/DMSO
$PhCH_2$	Ph	Me	-[a]	"

a. In the reaction mixture variable amounts of R'C(CH_3)=NR'' were found.

REFERENCES

1 This letter is part 15 of Chemistry of Sulfonylmethyl Isocyanides. Part 14, see A.M. van Leusen and J. Wildeman, Synthesis, submitted.

2 See, e.g. Fieser and Fieser, "Reagents for Organic Synthesis", Wiley Interscience, New York, 1974-5, Vol. 4, 514, 272; 5, 684.

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7 All new compounds are fully characterized by correct elemental analyses, and IR and NMR spectra.

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