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

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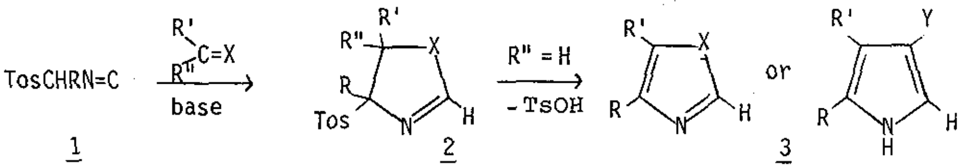
Oxazoles, pyrroles and imidazoles are synthesized from mono-alkylated tosylmethyl isocyanides (TosCHRN=C) and aldehydes, Michael-acceptors or aldimines.

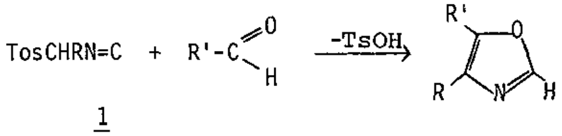
Tosylmethyl isocyanide (TosMIC, 1, R = H) has been found a useful synthon in organic chemistry.[2] Base-induced reactions of TosMIC with unsaturated substrates such as ketones, aldehydes, imines and Michael acceptors lead to heterocyclic compounds (Eq 1). Elimination of p-toluenesulfinic acid (TsOH, 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)

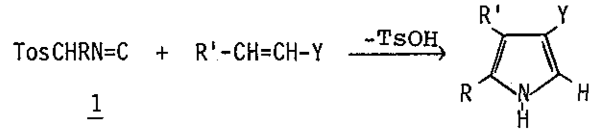
TABLE I.



| R | R' | Yield (%) | Conditions | bp or mp (°C) |
|---|---|---|---|---|
| Me | Ph | 75 | t-BuOK, MeOH, 40° | 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° | 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° | 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° | 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°C (15 mm); b. Lit.[8] bp 124-128°C (11 mm).

TABLE II.



| R | R' | Y | Yield (%) | Mp(°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. $TosCHRN{=}C$ + $R'\text{-}CH{=}N\text{-}R''$ $\xrightarrow{-TsOH}$

1

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

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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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