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PHASE-TRANSFER MONO-ALKYLATION OF TOSYLMETHYLISOCYANIDE.[1]

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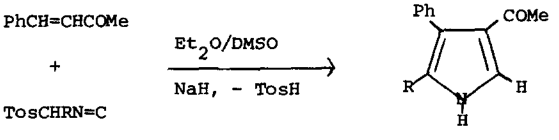
More and more, tosylmethylisocyanide (TosMIC, 1a, R = H) is emerging as a useful synthetic reagent in organic chemistry.[2] For example, TosMIC can be used to convert Michael acceptors into 3,4-disubstituted pyrroles (2, R = H) in one single operation.[3,4]

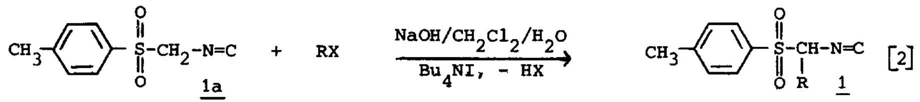


1 2 [1]

Substituents in 1 (R ≠ H) would diversify the potential reaction products considerably. As was shown previously, α-tosylbenzylisocyanide (1b, R = Ph) gives, for instance, pyrroles with an additional phenyl substituent (2, R = Ph).[3]

It, therefore, became desirable to investigate a series of mono-alkyl derivatives of TosMIC also. However, classical alkylations of TosMIC resulted at best in mixtures of non-, mono- and disubstituted products,[5] which could not be separated easily. We now wish to report that this problem can be bypassed completely when the alkylations are carried out under phase-transfer conditions.[6] Thus, the mono-alkyl derivatives 1c-i are obtained in high yields from TosMIC and primary alkyl halides, including allyl chloride and benzyl bromide (see Eq [2] and Table).[7] Introduction of a secondary alkyl group is also possible by this method, although the yield is somewhat lower (40 %, α-tosylisobutylisocyanide, 1g).

For some of the more reactive alkyl halides, i.e. methyl iodide, ethyl iodide and allyl chloride, it was necessary to run the reaction at 0°, in order to prevent a certain amount of dialkylation even under phase-transfer conditions. In the case of methyl iodide the use of benzyltriethylammonium chloride gave more satisfactory results than the more reactive[8] tetrabutylammonium iodide.


1a 1 [2]

Compd.	R	X	react. cond.[7]	m.p.	% yield
1c	$-CH_3$	I	3 h/0° [a]	oil	95
1d	$-CH_2CH_3$	I	3 h/0°	56-57°	90
	"	Br	2 h/0°	"	80
1e	$-(CH_2)_2CH_3$	I	4 h/25°	oil	85
1f	$-(CH_2)_3CH_3$	I	4 h/25°	"	75
1g	$-CH(CH_3)_2$	Cl [b]	80 h/ 5°	"	40
1h	$-CH_2-CH=CH_2$	Cl	1.5 h/0°	"	75
1i	$-CH_2Ph$	Br	1.5 h/25°	93.5-94.5°	80

[a] Benzyltriethylammonium chloride was used instead of tetrabutylammonium iodide.
[b] An excess of ten equivalents of isopropyl chloride was used instead of two equivalents as in the other reactions.

All new compounds (Table) are fully characterized by their spectra (IR, PMR and MS), together with correct elemental analyses or exact mass determinations. Furthermore, the compounds 1c and 1d were prepared by an alternate route also (Eq [3]), which parallels the original synthesis[5,9] of TosMIC itself.

$$\text{TosH} + \text{RCHO} + \text{H}_2\text{NCHO} \xrightarrow[\text{H}_2\text{O}]{\text{HCOOH}} \underset{\textstyle 3}{\text{TosCHRNHCHO}} \xrightarrow[\text{DME, }-10^{\circ}]{\text{POCl}_3/\text{Et}_3\text{N}} \underset{\textstyle 1}{\text{TosCHRN=C}} \qquad [3]$$

3c, R = Me, 75%; 3d, R = Et, 80% 1c, R = Me, 90%; 1d, R = Et, 80%

The investigation of the scope of application of the new isocyanides 1 is currently in progress.[10]

References and Notes

1. This letter is Part 10 of Chemistry of Sulfonylmethylisocyanides. For part 9, see O.H. Oldenziel and A.M. van Leusen, Tetrah. Letters 1974, 167.
2. See ref. 1 for a leading reference; Fieser and Fieser, Reagents for Organic Synthesis, Vol 4, p. 514, Wiley Interscience, New York 1974; Review: D. Hoppe, Angew. Chem. 86, 878 (1974), or Int. Ed. 13, 789 (1974); B.E. Hoogenboom, O.H. Oldenziel and A.M. van Leusen, Organic Syntheses 00, 000 (197.) (prior to publication, unchecked TosMIC-procedures are available from the Editor); Very recently, TosMIC has become commercially available also.
3. A.M. van Leusen, H. Siderius, B.E. Hoogenboom and D. van Leusen, Tetrah. Letters, 1972, 5337.
4. For other applications see ref. 1 and 2.
5. A.M. van Leusen, G.J.M. Boerma, R.B. Helmholdt, H. Siderius and J. Strating, Tetrah. Letters, 1972, 2367; Compare U. Schöllkopf, D. Hoppe and R. Jentsch, Chem. Ber. 108, 1580 (1975) for similar problems with the mono-alkylation of ethyl isocyanoacetate.
6. Reviews: J. Dockx, Synthesis 1973, 441, and E.V. Dehmlow, Angew. Chem. 86, 187 (1974).
7. The experimental conditions are as follows: A solution of TosMIC (5 mmole), alkyl halide (10 mmole) and Bu_4NI (1 mmole) in 10 ml of CH_2Cl_2 is vigorously stirred with 10 ml of 30% NaOH in H_2O. After addition of water (50 ml) the reaction mixture is extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. Extraction of the residue with cold ether, and removal of the ether *in vacuo* yielded the mono-substituted isocyanide, which was pure according to PMR.
8. A.W. Herriott and D. Picker, J. Amer. Chem. Soc. 97, 2345 (1975).
9. T. Olijnsma, J.B.F.N. Engberts and J. Strating, Recl. Trav. Chim. Pays-Bas, 91, 209 (1972).
10. The reaction of 3b with benzaldehyde and EtONa to give 4-ethyl-5-phenyloxazole (80% yield) may serve as a typical example.