Tetrahedron Letters Vol. 21, pp 3723 - 3726
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0040-4039/80/0915-3723$02.00/0

USE OF DILITHIO-TOSYLMETHYL ISOCYANIDE IN THE SYNTHESIS OF OXAZOLES AND IMIDAZOLES[1]

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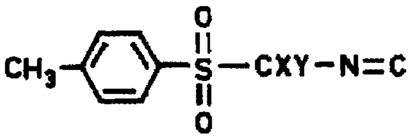
Summary. *Dilithio-tosylmethyl isocyanide (2) reacts with the carbonyl of unsaturated esters to form oxazoles, unlike tosylmethyl isocyano monoanion which gives pyrroles by reaction with the conjugated carbon-carbon double bonds. Reaction of 2 with carbon-nitrogen multiple bonds leads to imidazoles, an example of which is the one-step synthesis of imidazo[5,1-a]isoquinoline from isoquinoline. From 2 and pyridine-N-oxide or pyridazine-N-oxide unsaturated ring opened products are obtained.*

Work in our research group and by others has demonstrated the many synthetic possibilities of tosylmethyl isocyanide (TosMIC, 1). So far, all known applications of TosMIC are based on reactions initiated by mono-carbanions of TosMIC.[2] It now appears that the (di-anionic) reactivity of dilithio-TosMIC (2) extends the scope of application appreciably.



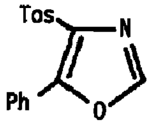
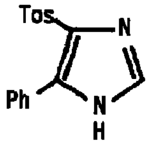
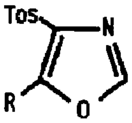
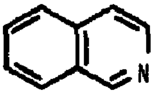
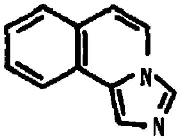
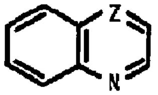
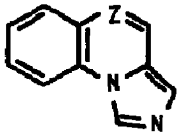
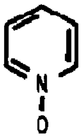
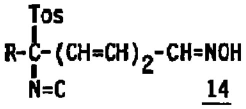
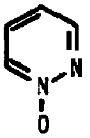
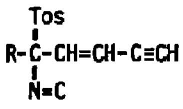
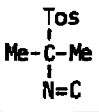
1, X = Y = H (TosMIC)
2, X = Y = Li
3, X = Li, Y = H

The dilithium derivative (2) of TosMIC is formed quite readily from TosMIC and two equivalents of n-butyllithium (BuLi) in THF at -70°C. A suspension or solution of 2 not only is more reactive than, for example, monolithio-TosMIC (3), but is considerably more stable.[3]

In the following we will discuss the results collected in the Table, all of which are obtained with dilithio-TosMIC (2). A comparison is made with the results from the same substrates and TosMIC-monoanions, in particular monolithio-TosMIC (3).

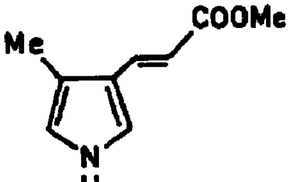
Dilithio-TosMIC (2) smoothly converts ethyl benzoate to oxazole 4 (70% yield, entry 1), whereas TosMIC monoanion, generated under a variety of conditions, does not react.[4] Similarly, imidazole 5 is formed rapidly with 2 (entry 2) but only reluctantly with TosMIC-monoanion.[5]

TABLE. Conversions Performed with Dilithio-Tosylmethyl Isocyanide (2)

Entry	Substrate	Product[8]	Yield (%)	React. time[a] (h)	M.p. (°C)
1	PhCOOEt	 4	70	0.3	142-143 (lit.[4c] 142-143
2	PhC≡N	 5	33	0.3	266-267 (rep.[5b] 267-268
3	PhCH$\overset{t}{=}$CHCOOMe	 6 R = PhCH$\overset{t}{=}$CH	53	2	139-140[b]
4	PhCH$\overset{t}{=}$CH-CH$\overset{c}{=}$CHCOOMe	7 R = PhCH$\overset{t}{=}$CH-CH$\overset{c}{=}$CH	54	2	162-164[b]
5	MeCH$\overset{t}{=}$CH-CH$\overset{t}{=}$CHCOOMe	8 R = MeCH$\overset{t}{=}$CH-CH$\overset{t}{=}$CH	25	2	114-116[b]
6		 11	44[c]	0.5	116-117 (lit.[10] 116)
7		 12 Z = CH	25	4	73-75 (lit.[12] not rep.
8		13 Z = N	30[d]	30	173-175
9		 $\mathrm{R{-}\underset{N=C}{\overset{Tos}{C}}{-}(CH{=}CH)_2{-}CH{=}NOH}$ 14 R = PhCH$_2$	64	0.3[e]	135-137
10		 $\mathrm{R{-}\underset{N=C}{\overset{Tos}{C}}{-}CH{=}CH{-}C{\equiv}CH}$ 15 R = PhCH$_2$[f]	52	0.3[g]	133-134
11	MeI (2 equiv.)	 $\mathrm{Me{-}\underset{N=C}{\overset{Tos}{C}}{-}Me}$ 16	90	0.5	88-90

[a] Reaction temp. -70 to 0°C, except for entry 11 at 20°C. [b] Compds. 6-8 are isomerically pure b ^{13}C NMR, suggesting no *cis-trans* isomerization during reaction; cf. 9 and 10 in text. [c] 6 Equiv. of LiBr added to reaction mixture. [d] Reaction carried out in presence of 2 equiv. of [CuI·nBu$_3$P]ₗ [e] Followed by addition of PhCH$_2$Br (1h, 0°C). [f] Primary product converted with PhCH$_2$Br to PhCH$_2$C(Tos)(N=C)-(CH=CH)$_2$-N=NOH, which spontaneously lost N$_2$ and H$_2$O to give 15. [g] As e) (2 h, 0°C

Of greater importance, however, are the results of entries 3-8. Conjugatively unsaturated esters react with 2 to give the oxazoles 6, 7 and 8, exclusively, through reaction with the ester carbonyl. Conversely, the softer TosMIC-monoanions are known to react only with the carbon-carbon double bonds of Michael acceptors to form pyrroles instead of oxazoles.[6] Accordingly, we now find it possible to transform methyl sorbate selectively into oxazole 8 with 2 (entry 5), or in either of the pyrroles 9 or 10 using TosMIC-monoanion. Pyrrole 9 is formed in 60% (in addition to 2% of 10 and no 8)[7] from equimolar quantities of methyl sorbate and TosMIC using 1 equivalent of NaH in DMSO-Et_2O at 20°C (1 h), and is pure after one crystallization (56% yield, m.p. 93-94°C, Jtrans = 16 Hz).[8] Conversely, pyrrole 10 (m.p. 113-115°C, Jtrans = 16 Hz) is formed in 34% yield (without 9 or 8)[7] by using one equivalent of BuLi in THF (2 h, -70 to 0°C).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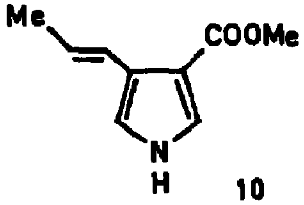
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Entries 6-8 give examples of the use of dilithio-TosMIC (2) to form in one-step the imidazo compounds 11, 12 and 13, respectively, in a reaction reminiscent of the synthesis of imidazoles from TosMIC-monoanion and the more reactive aldimines.[9] The same products 11-13 are not formed when monolithio-TosMIC (3) is used instead of 2. Furthermore, no reaction is observed between 2 and pyridine or pyridazine. Apparently, the weakly electrophilic C-N bonds of azaaromatics form a borderline case for a reaction with TosMIC (dianion), as may be reflected also in the moderate yields of 11-13. Nevertheless, the present one-step conversion of isoquinoline to imidazo[5,1-a]isoquinoline (11) (using commercially available starting materials only) is an improvement compared to the literature procedure, which requires 5 steps (14% overall yield).[10]

The enhanced electrophilicity of pyridine-N-oxide does permit reaction of 2 with the C-N bond but an unstable ring opened product 14 (R = H) was formed rather than an imidazo derivative. This compound was converted to a benzyl derivative 14 (R = $PhCH_2$, entry 9). A similar result was obtained from pyridazine-N-oxide (entry 10). Comparable ring opening reactions of the same N-oxides with Grignard reagents have been reported.[11]

REFERENCES and NOTES

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2. For a brief review, see: A.M. van Leusen , in Lectures in Heterocyclic Chemistry, Vol. 5, in press, Hetero Corporation, Provo, 1980.
3. (a) The half-life of a solution of monolithio-TosMIC (3) in THF-hexane is ca. 3 h at 20°C under nitrogen, whereas from a solution of dilithio-TosMIC (2) under the same conditions 80% of TosMIC is recovered after 24 h; (b) S.P.J.M. van Nispen. Ph.D. thesis, Groningen, 1980.
4. (a) For example, no reaction is observed with PhCOOEt using 1 equiv. of BuLi in THF (-60 to 20°C, 1.5 h), with t-BuOK in DMSO (60°C, 72 h), or with NaH in DME;[4d] (b) On the other hand, oxazole 4 is formed from benzoyl chloride or phenyl benzoate and TosMIC-monoanion,[4c,d] as well as 2[3b]; (c) A.M. van Leusen, B.E. Hoogenboom and H. Siderius, Tetrahedron Lett., 1972, 2369; (d) H. Siderius and D. Lok, unpublished results.
5. (a) With TosMIC and t-BuOK 48% of 5 is obtained after 6 days at 20°C in HMPT; (b) D. van Leusen, unpublished results.
6. (a) O. Possel and A.M. van Leusen, Heterocycles, 7, 77 (1977); (b) Methyl cinnamate and TosMI with NaH in DMSO-Et$_2$O give methyl 4-phenylpyrrole-3-carboxylate in 70% yield: A.M. van Leusen, H. Siderius, B.E. Hoogenboom and D. van Leusen, Tetrahedron Lett., 1972, 5337.
7. As determined by GLC and NMR, respectively.
8. All new compounds gave satisfactory C, H, N, (S) elemental microanalyses.
9. (a) A.M. van Leusen, J. Wildeman and O.H. Oldenziel, J. Org. Chem., 42, 1153 (1977); (b) ref.
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12. D.E. Kula, U.S. Patent 4.044.015 (1977); Chem Abstr., 88 50828p (1978).

(Received in UK 14 July 1980)