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TOSYLMETHYL ISOCYANIDE EMPLOYED IN A NOVEL SYNTHESIS OF KETONES.
A NEW MASKED FORMALDEHYDE REAGENT[1]

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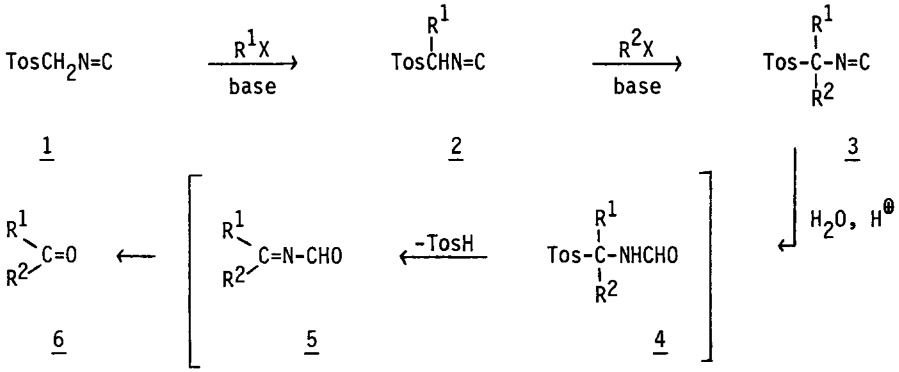
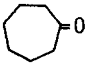
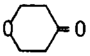
We wish to announce the use of tosylmethyl isocyanide (TosMIC, 1) as a novel tool in the synthesis of carbonyl compounds. In this letter we report a simple method for the synthesis of symmetrical and unsymmetrical ketones starting with commercially available TosMIC; the succeeding letter[2] deals with a synthesis of α-diketones based on the same principles.



(1)

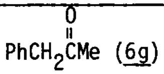
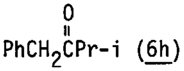
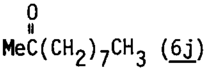
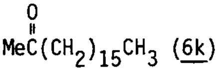
TosMIC (1) is basically a masked molecule of formaldehyde (from which TosMIC actually is prepared)[3]. The two electronegative functionalities facilitate the formation of TosMIC-anion[4], and in essence effect an umpolung[5] of carbonyl reactivity. Thus TosMIC can be alkylated efficiently, both to mono- or dialkyl derivatives.[6] Subsequently, the carbonyl is unveiled by a combination of steps as indicated in eq 1. Clearly, the overall result amounts to alkylation of formaldehyde with an electrophilic reagent.[7]

TABLE I. Symmetrical Ketones (6) Prepared through $\underline{1} \xrightarrow{2\ RX} \underline{3}$ ($R^1 = R^2 = R$) → 6

RX	Ketone (6)	% Yield [a]
$PhCH_2Br$	$(PhCH_2)_2C{=}O$ (6a)	72
$4\text{-}ClC_6H_4CH_2Cl$	$(4\text{-}ClC_6H_4CH_2)_2C{=}O$ (6b)	56
i-PrI	$i\text{-}Pr_2C{=}O$ (6c)	47
n-BuI	$n\text{-}Bu_2C{=}O$ (6d)	69
$Br(CH_2)_6Br$	 (6e)	51
$Cl(CH_2)_2O(CH_2)_2Cl$	 (6f)	16

[a] Overall yield of distilled product, calculated on TosMIC (1).

TABLE II. Unsymmetrical Ketones (6) Prepared through $\left(\underline{1} \xrightarrow{R^1X}\right) \underline{2} \xrightarrow{R^2X} \underline{3} \rightarrow \underline{6}$

R^1	R^2X	Ketone (6)	% Yield [a]
$PhCH_2$	MeI	 $PhCH_2\overset{O}{\overset{\Vert}{C}}Me$ (6g)	58
$PhCH_2$	i-PrI	 $PhCH_2\overset{O}{\overset{\Vert}{C}}Pr\text{-}i$ (6h)	65
$PhCH_2$	MeEtCHI [b]	 $PhCH_2\overset{O}{\overset{\Vert}{C}}CHMeEt$ (6i)	41
Me	$CH_3(CH_2)_7I$	 $Me\overset{O}{\overset{\Vert}{C}}(CH_2)_7CH_3$ (6j)	80
Me	$CH_3(CH_2)_{15}I$	 $Me\overset{O}{\overset{\Vert}{C}}(CH_2)_{15}CH_3$ (6k)	63

[a] Overall yield of distilled product calculated on TosMIC for 6g, and on $TosCHR^1N{=}C$ for 6h-k. [b] No alkylation was observed with 2-bromobutane instead of 2-iodobutane.

As a typical example of the synthesis of symmetrical ketones (Table I) the dialkylation of TosMIC was carried out with 2 equiv of $PhCH_2Br$ (using NaH in Me_2SO - Et_2O, 20°C, 1 h) to give 3a ($R^1 = R^2 = PhCH_2$).[6b] To effect the conversion to 6a, a suspension of crude 3a (ca. 10 mmol) in a mixture of Et_2O (15 ml) and CH_2Cl_2 (5 ml) was rapidly stirred for 5 min at 20°C with 38% aqueous HCl (1 ml), followed by treatment with NaOH to remove p-toluenesulfinic acid. The yield of dibenzyl keton (6a) was 72% overall.

As an example of unsymmetrical ketones (Table II), benzyl methyl ketone (6g) was prepared by a one-pot phase-transfer alkylation of TosMIC (CH_2Cl_2/40% aqueous NaOH; 5% $n\text{-}Bu_4NI$; 25°C), first with 1 equiv of $PhCH_2Br$, after 30 min followed by 1.1 eq of MeI to give 3g [71% overall yield, mp 133.5-134.0°C; $\gamma_{N=C}$ 2130 cm^{-1}; δ 3.26 (s, CH_2), 1.52 ppm (s, $\alpha\text{-}CH_3$)]. Conversion of 3g, analoguously to the symmetrical ketones, gave 6g in 58% yield calculated on TosMIC. The other ketones of Table II were prepared from isolated phase-transfer reaction products 2 ($R^1 = PhCH_2$ or Me)[6a] by introducing R^2 with NaH in Me_2SO-Et_2O as described above.

We assume that the reaction of 3 to 6 is initiated by acid catalyzed hydration[8] to 4, followed by a rapid elimination of p-toluenesulfinic acid and hydrolysis (eq 1). Attempts to interrupt the reaction at the stage of formamide 4a ($R^1 = R^2 = PhCH_2$) were unsuccessful, but the proposed mechanism gains support by the hydration of TosCHRN=C (R = H, Me, $PhCH_2$) to the corresponding formamides[9] and the observations discussed in the succeeding letter.[2]

References and Notes

1. Chemistry of Sulfonylmethyl Isocyanides 16; for part 15 see O. Possel and A.M. van Leusen, Heterocycles, in print (1977).
2. D. van Leusen and A.M. van Leusen, Tetrahedron Lett., succeeding letter.
3. B.E. Hoogenboom, O.H. Oldenziel, and A.M. van Leusen, Org. Synth., 57, 84 (1978); ref. 4a.
4. TosMIC-anion has been exploited thus far mainly in the synthesis of azoles and azolines, and in the conversion of ketones to nitriles or α-hydroxy aldehydes; for leading references see: (a) A.M. van Leusen, J. Wildeman and O.H. Oldenziel, J. Org. Chem., 42, 1153 (1977); (b) O.H. Oldenziel, D. van Leusen, and A.M. van Leusen, J. Org. Chem., 42, October issue (1977).
5. Reviews: D. Seebach and M. Kolb, Chem. Ind. (London), 1974, 687; O.W. Lever, Tetrahedron 32, 1943 (1976); B.-T. Gröbel and D. Seebach, Synthesis, 1977, 357.

6. (a) A.M. van Leusen, R.J. Bouma, and O. Possel, Tetrahedron Lett., 1975, 3487; (b) A.M. van Leusen, G.J.M. Boerma, R.B. Helholdt, H. Siderius, and J. Strating, ibid., 1972, 2367.
7. A reaction sequence similar to 3 → →6 when applied to 2 (R^1 = $PhCH_2$) was shown to provide phenylacetaldehyde in 50% overall yield, O. Possel.
8. See: T. Saegusa and Y. Ito in "Isonitrile Chemistry", I. Ugi, Ed., Academic Press, New York, N.Y., 1971, p. 65.
9. O. Possel, unpublished.