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A NEW SYNTHESIS OF α,β-UNSATURATED KETONES, ALLYLIC ALKYLATION OF 1-ISOCYANO-1-TOSYLALKENES[1]

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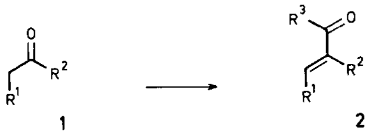
Ketones (1) are homologated to enones 2 by alkylating (introduction of R^3) the condensation products 4 (derived from 1 and tosylmethyl isocyanide), followed by acid catalyzed hydrolysis.

α,β-Unsaturated carbonyl compounds (enones) are real workhorses in organic synthesis. Among the most important areas of application are: Michael reactions,[2a] and related Robinson (ring) annulations[2b] and hydrocyanations,[3] Diels-Alder cycloadditions,[2c] and heterodiene syntheses.[4] The value of these reactions has firmly been established, particularly in the field of natural product synthesis.

Although several useful methods are available to prepare α,β-unsaturated carbonyl compounds, no general method covers all different types of enones.[5] Thus, it is not surprising that new methods are reported regularly.[6]



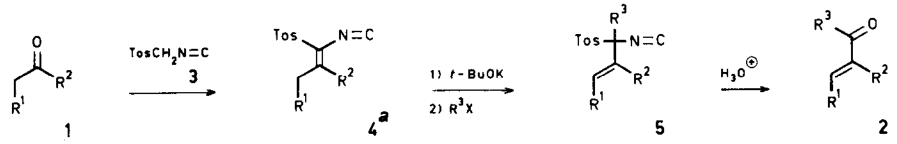
(I)

We report a new synthesis of α,β-unsaturated ketones, with the overall characteristics of Eq I. In a formal sense, this conversion of ketones can be seen as a replacement of OH of enolized 1 by an acyl group. The separate steps of this process are given in Eq II in the heading of the Table, and are described in the following.

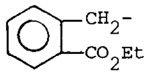
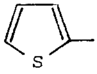
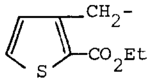
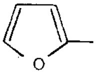
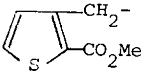
Recently, two methods have been developed in our laboratory to convert aldehydes and ketones to unsaturated isocyano sulfones 4 with the use of tosylmethyl isocyanide (TosMIC, 3).[7] So far, only Michael addition-type reactions of 4 have been investigated.[7a] However, compounds 4 — besides being Michael acceptors — can be considered also as ketene N,S-acetals of a special kind. The present enone synthesis is based on such chemistry.[8]

Allylic anions are derived from 4 quite readily by γ-deprotonation [*t*-BuOK (1 equiv), DME, -30°C, N_2]. Alkylation of these anions proved highly regiospecific, favouring α-alkyl derivatives 5 to the exclusion of any significant amounts of the γ-isomer [R^3X (1 equiv), 1 h, -30° to 20°C]. By this reaction the C,C double bond shifts position. The highest yields of 5

TABLE. 3-Isocyano-3-tosyl-1-alkenes 5 and Enones 2 Prepared from 1-Isocyano-1-tosyl-1-alkenes 4 According to:



(II)

R^1	R^2	R^3	X	Compounds 5[b]		Compounds 2[b]		
				Yield[c]	Mp(°C,with decomp.)	Yield[c] (%)	Mp or Bp (°C/Torr)	Lit. data[d]
$-(CH_2)_4-$		Me	I	81	97-98	93	93-95/0.25	(1)
		$-(CH_2)_3-$[e]	Br	76	102-103	90	49-50	
		i-Pr	I	32	107-108	90	52-53/0.25	(2)
		$PhCH_2-$	Br	61	98-99	86	44-46	(3)
			Br	83	129-130	86	66-67	
		$CH_2=CH-CH_2-$	Br	76	89-90	87	66-69/0.5	(4)
		$MeO_2C-(CH=CH)_2CH_2-$	Br	62	92-93	87[f]	140-142[f]	
		$-CH_2C(Me)=C(Me)CH_2-$[g]	Br	58	173-174	[h]		
		EtO_2CCH_2-	Br	68	90-91	[h]		
		$PhCOCH_2-$	Br	75	128-129	[h]		
$-(CH_2)_3-$		Me	I	79	87-88	91	65-68/12	(5)
		$BrCH_2CH_2-$	Br	69	106-107	90[i]	73-75/10[i]	(6)
		$MeO_2C(CH_2)_4CH_2-$	Br	59	114-115	67	142-144/0.03	(7)
		$-(CH_2)_3-$[e]	Br	59	134	89	62-63	
		i-Pr	I	29	112-113	67	68-70/18	(8)
$-(CH_2)_2-$		Me	I	82	104-105	69	36-39/60	
		$-(CH_2)_3-$[e]	Br	51	149	71	130-133/0.03	
		$p-ClC_6H_4CH_2-$	Cl	48	122	86	43-45	
H	Me	Me	I	69	75-76	51	96-103/8	(9)
		$-(CH_2)_3-$[e]	Br	59	157-158	76	88-89/0.45	
		$p-ClC_6H_4CH_2-$	Cl	81	114-115	87	53-54	
H			Br	84	100	[h]		
		$p-ClC_6H_4CH_2-$	Cl	63	138	[h]		
H			Br	83	115-116°	[h]		

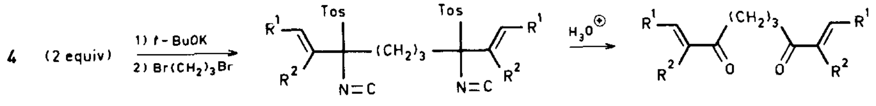
[a] The procedures for preparation of the six compounds 4 used in the present investigation are given in the following references (for R^1 and R^2, see Table): 4 derived from cyclohexanone or acetone, ref. 7a; 4 derived from cyclobutanone, ref. 7b; 4 derived from cyclopentanone, 2-acetylthiophene or 2-acetylfuran, ref. 7c.

[b] Satisfactory IR, ^1H and ^{13}C NMR, MS data and combustion analyses were obtained for all new compounds.

[c] Yields refer to purified materials (after crystallization or distillation).

[d] One convenient source is given for physical data of each known compound: (1) J.C.S. 1935, 1285; (2) J.O.C. 13, 357 (1948); (3) B.S.C. France 1947, 99; (4) J.C.S. 1952, 1430; (5) Zh. Obs. Chim. 23, 47 (1953); (6) Izv. Ak. Nauk. SSR. 1958, 465; (7) J.C.S. Perkin I, 1980, 2346; (8) Tet. Lett. 1977, 1385; (9) Beilsteins Handbuch der Org. Chem., Vol. 1, EIII, 2961 (1959).

[e] In this reaction of Br-$(CH_2)_3$-Br, the second part of the general equation (Eq II) is to be read as:



(III)

5' 2'

[f] No ketone formed, but an α,β-unsaturated formamide by hydration of isocyanide and β-elimination of TosH.

[g] In this reaction of Br-$CH_2C(Me)=C(Me)CH_2$-Br, the result is analogous to Eq III except that in 5' and 2' the -$(CH_2)_3$- is replaced by -$CH_2C(Me)=C(Me)CH_2$-.

[h] Expected ketones decompose under hydrolysis conditions.

[i] 1-Cyclopentenyl vinyl ketone due to elimination of HBr.

are obtained with the more reactive halides (60 to 85%); not unexpectedly yields drop (to about 30%) with secondary halides. Acid catalyzed hydrolysis of the geminal isocyano and tosyl in 5 completes the enone synthesis [conc. HCl/Et_2O, 1:2, 20°C, shake for 1-5 min]. The Table gives ample evidence of the flexibility of this method. In nearly all cases investigated high yields have been obtained of enones (2), of which several were not previously reported. The few negative results listed in the Table are ascribed to sensitivity of the particular enones under the hydrolysis conditions.

The hydrolysis of 5 proceeds through the corresponding formamides (formed by acid catalyzed α-addition of water to the isocyano carbon), followed by elimination of *p*-toluenesulfinic acid (TosH).[9] *p*-Toluenesulfinic acid so obtained tends to add to the enone to form β-tosyl substituted ketones. This undesired consecutive reaction is impeded by carrying out the hydrolysis of 5 for a very short period of time in a two phase system as described above. Presumably, under these conditions unfavourable partition of TosH retards addition to 2 sufficiently.

References and Notes

1. Chemistry of Sulfonylmethyl Isocyanides 27; for part 26 see D. van Leusen and A.M. van Leusen, preceeding letter.
2. For leading references, see: Comprehensive Organic Chemistry, Barton & Ollis, Eds in Chief, Pergamon, Oxford 1979; (2a) A.J. Waring in Vol 1 (J.F. Stoddart, Ed.) p. 1043; (2b) see ref 2a, p. 1049; (2c) J. Newton in Vol 6 (C.J. Dayton, Ed.) p 895-897.
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5. Ref 2, Vol. I, Chapter 5, in particular ref 2a, p. 1069; Houben-Weyl, Meth. Org. Chem. 4th Ed., Band VII.
6. To illustrate the point, the following recent papers were selected: V. Reutrakul, S. Nimgriwath, S. Panichanun, and Y. Srikirin, Tetrahedron Lett. 1979, 1321; E. Friedrich and W. Lutz, Chem. Ber. 113, 1245 (1980); I. Kuwajima and M. Kato, Tetrahedron Lett. 1980, 623; J.L. Roustan, A. Guinot and P. Cardiot, J. Organomet. Chem. 194, 367 (1980); U. Hertenstein, S. Hünig and M. Öller, Chem. Ber. 113, 3783 (1980); J. Hooz and J. Oudenes, Synth. Comm. 1980, 667; J.C. Clinet and G. Linstrumelle, Tetrahedron Lett. 1980, 3987; I. Fleming and D.A. Perry, Tetrahedron 37, 4027 (1981); T. Yoshida and S. Saito, Chem. Lett. 1982, 165; E. Piers, J.R. Gierson, C.K. Lau and I. Nagakura, Can. J. Chem. 60, 210 (1982); C.L. Bumgardner, J.R. Lever and S.T. Purrington, Tetrahedron Lett. 1982, 2379.
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8. For related enone syntheses based on ketene S,S-acetals, see: D. Seebach and M. Kolb, Liebigs Ann. Chem. 1977, 811; B-T. Gröbel and D. Seebach, Synthesis 1977, 357 and references cited therein.
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