Regeneration of Ketones from Tosylhydrazones, Arylhydrazones, and Oximes by Exchange with Acetone

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Derivatives of carbonyl compounds such as tosylhydrazones serve as important synthetic intermediates and are at the same time very useful for purification and characterization. However, their utility is limited to some extent because of resistance to hydrolytic cleavage to the parent carbonyl compounds. Most of the known methods of regenerating carbonyl compounds from their nitrogenous derivatives require strongly oxidative or reducing, acidic, or basic media, or tedious procedures and/or expensive reagents.[1]

Among the earliest reported regeneration methods are the exchange reactions with other carbonyl compounds such as pyruvic[2] or levulinic acid.[3] We report here that a wide variety of ketones can be regenerated from their tosylhydrazones (Table I) by simply allowing them to react with an excess of acetone at temperatures between 20 and 80° (eq 1).

Table I
Carbonyl Compounds Regenerated from Their Tosylhydrazones and Other Derivatives by Exchange with Acetone

Carbonyl compd	Registry no.	Derivative	Registry no.	Reaction time, hr	Reaction temp °C	Yield, %
Cyclopentanone	120-92-3	*a*	17529-98-5	18	50	75
		d	2057-87-6	20	75	79
Cyclohexanone	108-94-1	*a*	4545-18-0	24	65	78
		b	100-64-1	100	80	72
		c	946-82-7	100	80	60
		d	1589-62-4	20	75	84
Pentan-3-one	96-22-0	*a*	28495-72-9	48	75	83
		d	1636-83-5	20	75	80
Phenyl *tert*-butyl ketone	938-16-9	*a*	24379-40-6	70	60	68
7,7-Dimethylbicyclo-[3.2.0]hept-2-en-6-one	767-85-1	*a*	56454-20-7	18	60	87
Pentacyclo[$4.3.0.0^{2,5}.0^{3,8}0^{4,7}$]-nonan-9-one (homocubanone)	15291-18-6	*a*	56454-21-8	48	25	84
Carvone	99-49-0	*a*	21195-60-8	24	65	69
6, 6-Dimethylcyclohex-1-en-3-one	1073-13-8	*a*	21195-63-1	48	80	52
6,6-Dimethylcyclohexa-1,4-dien-3-one	1073-14-9	*a*	24832-83-5	48	80	27
Benzaldehyde	100-52-7	*a*	1666-17-7	16	75	5

[a] Tosylhydrazone. [b] Oxime. [c] Phenylhydrazone. [d] 2,4-Dinitrophenylhydrazone.

$$R_1R_2C{=}N{-}NHTS + Me_2C{=}O \rightleftharpoons R_1R_2C{=}O + Me_2C{=}N{-}NHTS \quad (1)$$

Using acetone as the exchange reagent offers some advantages over the reported exchange procedures as it involves a nonacidic reaction medium, simple work-up, and inexpensive reagents. The reaction is most easy to perform. After equilibrium is reached, the excess acetone is removed by distillation and the acetone tosylhydrazone formed is precipitated from the reaction mixture with pentane. The carbonyl compound is recovered from the concentrated pentane solution by crystallization, distillation, or, when the reaction has been performed on a very small scale, VPC separation.

This procedure is not limited in its applicability to tosylhydrazones but works also for regenerating ketones from other derivatives such as oximes, phenylhydrazones, or 2,4-dinitrophenylhydrazones. The yields are normally acceptable. The preparative applicability of this method is limited to the regeneration of ketones, as aldehydes can be recovered only in low yields. It appears that a certain thermal stability of the carbonyl compound is required.

This method is very useful for the incorporation of deuterium into carbonyl compounds during their regeneration. We observed that the reaction of tosylhydrazones of enolizable ketones with acetone-d_6 produced ketones which are perdeuterated in the α positions (Table II). The enolizable ketone when heated with acetone-d_6 alone under the same conditions does not exchange its α hydrogens. However, when a 1:1 mixture of the ketone and its tosylhydrazone is heated in acetone-d_6, all of the isolated carbonyl compound is perdeuterated in the α positions. This implies that the tosylhydrazone or free tosylhydrazide serves as base in this efficient deuterium exchange.[4]

Experimental Section

Tosylhydrazones were prepared in the usual way by reaction of the carbonyl compounds with equimolar amounts of tosylhydrazide in methanol. They were recrystallized from methanol.

General Procedure for the Regeneration of Ketones from Tosylhydrazones. The tosylhydrazone (1.0 g) was dissolved in 5

Table II
α-Perdeuterated Ketones from Nitrogenous Derivatives by Exchange with Acetone-d_6

Ketone	Registry no.	Derivative	Yield, %[d]	Deuterium incorporation in the α positions
Cyclopentanone	3994-89-5	*a*	62	*e*
		c	58	
Cyclohexanone	1006-03-7	*a*	59	*e*
		b	55	*e*
		c	50	
Pentan-3-one	6400-97-1	*a*	66	*e*
		c	52	

[a] Tosylhydrazone. [b] Oxime. [c] 2,4-Dinitrophenylhydrazone. [d] Ketones were isolated by preparative VPC. [e] >95%; no α-hydrogen atoms could be detected by NMR.

ml of reagent grade acetone. The solution was heated in a sealed glass tube until equilibrium had been established (analysis by TLC or VPC). The excess acetone then was removed under reduced pressure and 30 ml of pentane added. The precipitate of acetone tosylhydrazone was removed by filtration and the remaining solution concentrated in vacuo. The carbonyl compound was isolated either by recrystallization or distillation from the residue.

α-Perdeuterated Ketones from Tosylhydrazones by Exchange with Acetone-d_6. The tosylhydrazone (150 mg) was dissolved in 0.6 ml of acetone-d_6 and heated in a sealed NMR tube until equilibrium was reached (analysis by NMR). The excess acetone-d_6 then was removed by distillation in vacuo and 5 ml of pentane was added to the residue. The solution was filtered from the precipitate and concentrated. The α-perdeuterated ketone was recovered by preparative VPC.

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Registry No.—Acetone, 67-64-1; acetone-d_6, 666-52-4.

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Solvent Effects in the Solvolysis of Aryldi-*tert*-butylcarbinyl *p*-Nitrobenzoates in Aqueous Acetic Acid. Substituent Effects on Transition State Charge Separation

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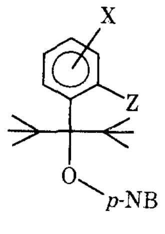
The Grunwald–Winstein equation,[1] log $k/k_0 = mY$, has proved invaluable in solvolysis studies because of the possibility of using m as an empirical criterion of reaction mechanism. However, recent data[2] on the solvolysis of phenyldi-*tert*-butylcarbinyl *p*-nitrobenzoate (**1d**) in aqueous acetone indicate an m value of 0.32 at 100°, substantially lower than is usual for limiting solvolysis without nucleophilic solvent assistance[3] or anchimeric assistance.[4,5]



1, Z = H
2, Z = Me

Table I
Grunwald–Winstein *m* Values for the Solvolysis of Aryldi-*tert*-butylcarbinyl *p*-Nitrobenzoates in Aqueous Acetic Acid at 85°

Compd	Substituent X	$10^4 k_{\text{HOAc, 100\%}}$, sec^{-1}	m[a]
1a	*p*-MeO	6.18	0.316
1b	*p*-Me	1.74	0.384
1c	*m*-Me	1.26	0.383
1d	H	0.805	0.370
1e	*p*-Cl	0.220	0.370
1f	*m*-Cl	0.100	0.402
1g	*m*-CF_3	0.0364	0.425
2b[b]	*p*-Me	393 (9.67)[c]	0.259
2c[b]	*m*-Me	332 (7.78)[c]	0.265
2d[b]	H	220 (4.93)[c]	0.274

[a] Standard deviation on k, 1–4%; standard deviation on m, less than 0.01 (**1**) or 0.02 (**2**). [b] Values at 85° were estimated from data at 30–60°; values in parentheses are at 50.5°. [c] Corresponding rate constants in 97.7% aqueous ethanol follow: **2b**, 2.74×10^{-4}; **2c**, 2.30×10^{-4}; **2d**, 1.56×10^{-4} sec^{-1}.

We have now determined the solvolysis rates of some aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates **1** and **2** in aqueous acetic acid (0–8 M in water, 0.01 M in sodium acetate) by the uv spectroscopic method.[6] The m values range from 0.26 (**2b**) to 0.42 (**1g**) at 85° (Table I). The calculated value[7] for *tert*-butyl chloride under these conditions being 0.75, these values are indeed abnormally low. However, these molecules contain several features which are known to reduce m. Firstly, low solvent sensitivity is associated with leaving groups which are able to disperse the developing negative charge; m decreases in the order Cl > Br > OTs[8] and, more pertinently, Cl > *p*-NB > thionbenzoate.[9] Secondly, relief of steric strain in the solvolysis of congested tertiary derivatives leads to an early transition state with little charge separation.[3,10] The unusually small ρ value reported for **1** in 70% aqueous acetone at 100° (−1.79)[2a] is approximately confirmed in the present work[11] and is consistent with an early transition state. A further factor which could reduce m is steric inhibition of solvation of the incipient cation,[12] but its role has not yet been clearly demonstrated.

Notwithstanding some scatter, there is a well-defined trend in the relationship between solvent sensitivity and reactivity: as the reactivity (log k) of these aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates increases, m tends to decrease linearly (Figure 1). The substituent dependence of m[13] raises an interesting point regarding the Hammett and

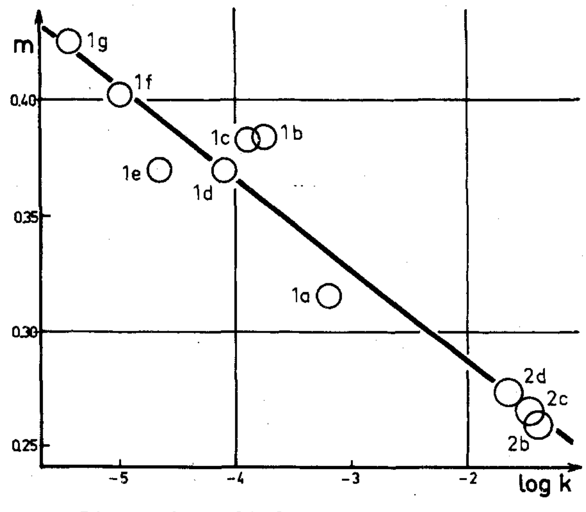


Figure 1. Linear relationship between reactivity (log k) and solvent effect (m) in the solvolysis of aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates.