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Reduction of Arylcarbonyl Using Zinc Dust in Acetic Acid

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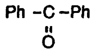
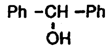
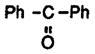
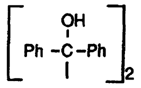
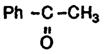
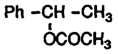
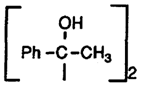
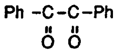
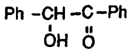
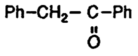
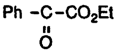
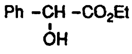
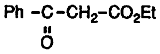
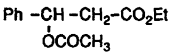
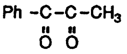
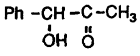
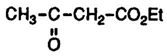
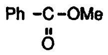
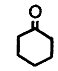
Zinc dust in acetic acid has been found to be a versatile and chemoselective reagent for the reduction of various arylcarbonyls to the corresponding alcohols or their acetates in fair yields.

There is continuing interest in functional-group selectivity in the reduction of carbonyl compounds.[1] Although lithium aluminum hydride and other metallic hydrides are the most commonly used reagents for the reduction of carbonyls to the corresponding alcohols,[2] the reaction with these reagents is broad and general and much less chemoselectivity is possible. It is often necessary to reduce aryl carbonyls without effecting the alkyl carbonyls in the organic synthesis. Reagents such as diazene[3] and lithium dihydropyridylaluminum hydride[4] are known to reduce aryl and aralkyl carbonyls preferentially in the presence of alkyl and aralkyl carbonyls, but not exclusively. In this communication, we wish to report on a chemoselective reduction of aryl carbonyls using zinc dust in acetic acid.

In our ongoing project,[5] we unexpectedly found that a carbonyl group is cleanly converted to the corresponding alcoholic acetate in the presence of zinc dust in acetic acid. Although, the reduction of various functional groups using zinc-based reagents is well known, they are not well recognized for the reduction of carbonyl groups of ketones and aldehydes.[7] A survey of the literature shows that zinc in acetic acid is usually known for the reduction of alpha halo ketones,[8] *N*-nitroso compounds,[9] arylcarbonylmethyl sulfones,[10] *N*-(2-iodoalkyl)carbamates,[11] and desulfurization of *S*-ylides.[12] To the best of our knowledge, zinc dust in acetic acid has so far not been used for the reduction of carbonyl. The only two notable zinc-based reducing agents for the carbonyl group are zinc dust in a strongly alkaline medium for the reduction of benzophenone to diphenylmethanol[13] and the reduction of α-diketones to acyloins by heating with zinc powder in aqueous dimethylformamide.[14] However the reduction with these reagents is not chemoselective, and has not been well studied for different carbonyl functional groups. Inspired by our interesting observation,[5] we explored the possibility of using zinc dust in acetic acid as a reducing agent for various carbonyl compounds. The reductions were carried out with a few different ketones to confirm the general applicability of the reagent. This paper describes the general reducing properties of zinc dust in acetic acid in the reduction of some selected carbonyl compounds.

In some of the selected systems the reagent displayed excellent activity. The results are summarized in Table 1. The reduction of aromatic aldehydes gave the corresponding arylmethyl acetates in quantitative yields (Entries 1 and 2). Benzophenone and acetophenone

Table 1.

Entry	Carbonyl compound	Product	Yield (%)
1	$\mathrm{Ph{-}CHO}$	$\mathrm{Ph{-}CH_2OCOCH_3}$	92
2	$\mathrm{p{-}MeOC_6H_4CHO}$	$\mathrm{p{-}MeOC_6H_4CH_2OCOCH_3}$	95
3	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}Ph}$	 $\mathrm{Ph{-}\underset{OH}{\underset{\mid}{C}H}{-}Ph}$	40
	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}Ph}$	 $\left[\mathrm{Ph{-}\underset{\mid}{\overset{OH}{\overset{\mid}{C}}}{-}Ph}\right]_2$	55
4	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}CH_3}$	 $\mathrm{Ph{-}\underset{OCOCH_3}{\underset{\mid}{C}H}{-}CH_3}$	30
		 $\left[\mathrm{Ph{-}\underset{\mid}{\overset{OH}{\overset{\mid}{C}}}{-}CH_3}\right]_2$	40
5	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}Ph}$	 $\mathrm{Ph{-}\underset{OH}{\underset{\mid}{C}H}{-}\underset{O}{\underset{\|}{C}}{-}Ph}$	60
		 $\mathrm{Ph{-}CH_2{-}\underset{O}{\underset{\|}{C}}{-}Ph}$	20
6	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}CO_2Et}$	 $\mathrm{Ph{-}\underset{OH}{\underset{\mid}{C}H}{-}CO_2Et}$	80
		$\mathrm{Ph{-}CH_2{-}CO_2Et}$	5
7	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}CH_2{-}CO_2Et}$	 $\mathrm{Ph{-}\underset{OCOCH_3}{\underset{\mid}{C}H}{-}CH_2{-}CO_2Et}$	60
8	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}CH_3}$	 $\mathrm{Ph{-}\underset{OH}{\underset{\mid}{C}H}{-}\underset{O}{\underset{\|}{C}}{-}CH_3}$	65
9	$\mathrm{Ph{-}CH_2{-}CH_2{-}CHO}$	—	
10	 $\mathrm{CH_3{-}\underset{O}{\underset{\|}{C}}{-}CH_2{-}CO_2Et}$	—	
11	 $\mathrm{Ph{-}\underset{O}{\underset{\|}{C}}{-}OMe}$	—	
12		—	

considerably underwent reductive dimerization to give pinacols along with the corresponding alcohols (Entries 3 and 4). The reduction of diphenyl diketones gave not only a simple reduction product, but also a partially deoxygenated product in 20% yield (Entry 5). The reduction of α-keto ester and β-keto ester gave the corresponding reduction products (alcohol as acetate in latter case) in good yields (Entries 6 and 7). The inability of 3-phenylpropionaldehyde and ethyl acetoacetate (Entries 9 and 10) to undergo reduction has confirmed its chemoselective nature towards aryl carbonyls. The reduction of 1-phenyl-1,2-propanedione (Entry 8) further confirms its intramolecular chemoselective behavior by reducing only arylcarbonyl, while not touching the aliphatic carbonyl group.

In summary, the reagent reduces arylcarbonyl to the corresponding alcohols as acetates (Entries 1,2, and 7), whereas it gives alcohols in case of 1,2-dicarbonyls (Entries 5,6, and 8). The reagent is not only chemoselective towards arylcarbonyls, but is also selective over both the aliphatic and aromatic ester carbonyl groups (Entries 10 and 11). In conclusion, we have developed a convenient method using zinc dust in acetic acid for the reduction of the arylcarbonyl group under mild and simple experimental conditions; we consider our observations to be important due to the large scale use of zinc in organic synthesis.

Experimental

The known products were characterized by a comparison with authentic samples or with their mass and ^{1}H NMR spectral data. ^{1}H NMR spectra were measured in $CDCl_3$ on a JEOL (JNM-EX 270 MHz) instrument. The chemical shifts are referred to Me_4Si (0 ppm) or $CHCl_3$ (7.25 ppm) for ^{1}H NMR, $CDCl_3$ (77.0 ppm) for ^{13}C NMR. The mass spectra were run on a Hitachi M80. All of the reductions were carried out at room temperature (20 °C) and stirred for 12—14 h. Removal of the acetic acid was carried out under reduced pressure. The products were purified by column chromatography on silica gel 60 (230—400 mesh ASTM) of Merck. All of the yields refer to the isolated products. All of the chemicals were purchased from commercial sources and were used without further purification.

General Reaction Procedure for the Reduction of Arylcarbonyl Using Zinc Dust in Acetic Acid: A representative procedure is illustrated for benzaldehyde (Entry 1), as follows: A solution of 2.12 g (0.02 mol) of benzaldehyde in 6 ml of glacial acetic acid was added to a well-stirred mixture of 6.5 g (0.1 mol) of zinc dust in 20 ml of acetic acid. After the mixture has been stirred at room temperature for 12 h, the zinc acetate and excess zinc dust were removed by filtration and thoroughly washed with glacial acetic acid. The combined filtrate was concentrated under reduced pressure to remove acetic acid, and the residual oil was purified by column chromatography to obtain a pure product. Selected spectral data of new compounds are as follows:

p-MeO-$C_6H_4CH_2OCOCH_3$ (Entry 2): ^{1}H NMR δ=2.02 (3H, s, $COCH_3$), 3.7 (3H, s, OCH_3), 5.02 (2H, s, $Ph\underline{CH_2}$), 6.84—6.88 (2H, m, *ortho* to OCH_3), 7.24—7.29 (2H, m, *meta* to OCH_3); ^{13}C NMR δ=21.0 ($CO\underline{CH_3}$), 55.2 (OCH_3), 66.1 ($Ph\underline{CH_3}$), 113.9 (aromatic carbons ortho to OCH_3), 130.1 (aromatic carbons *meta* to OCH_3), 128.1 ($\underline{C}CH_2$), 159.6 ($OCH_3\underline{C}$), 170.8 (CO); IR (neat) 1735 (CO), 1240 cm^{-1} (C–O–C); MS m/z (rel intensity) 180 (M^+ ; 64), 148 (38), 138 (22), 121 (100), 91 (16). Found: C, 66.30; H, 6.71%. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

$PhCH(CH_3)OCOCH_3$ (Entry 4): ^{1}H NMR δ=1.5 (3H, d, J=8.6 Hz, $CH\underline{CH_3}$,), 2.0 (3H, s, $COCH_3$), 5.8 (1H, q, J=6.6 Hz, $Ph\underline{CH}$), 7.35 (5H, m, phenyl); ^{13}C NMR δ= 21.3 ($CO\underline{CH_3}$), 22.2 ($CH\underline{CH_3}$), 72.2 ($Ph\underline{CH}$) 126.0, 127.8, 128.5 (phenyl), 141.6 (aromatic quaternary carbon), 170.2 (CO); IR (neat) 1740 (CO), 1240 cm^{-1} (C–O–C); MS m/z (rel intensity) 164 (M^+, 72), 121 (100), 105 (65), 77 (33). Found: C, 72.92; H, 7.32%. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37%.

$PhCH(OCOCH_3)CH_2COOCH_2CH_3$ (Entry 7): ^{1}H NMR δ=1.21 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 2.07 (3H, s, $COCH_3$), 2.75 (1H, dd, J=5.28 & 15.84 Hz, CH_2), 2.95 (1H, dd, J=8.91 & 15.83 Hz, CH_2), 4.14 (2H, q, J=7.11 Hz, OCH_2), 6.17 (1H, dd, J=5.56 & 8.91 Hz, $Ph\underline{CH}$), 7.29—7.38 (5H, m, phenyl); ^{13}C NMR δ=14.1 (CH_3), 21.0 ($CO\underline{CH_3}$), 41.5 (OCH_2), 60.7 ($CH\underline{CH_2}$), 72.1 ($Ph\underline{CH}$), 126.4, 128.3, 128.5 (phenyl), 139.2 (aromatic quaternary carbon), 169.7 (CO); IR (neat) 1740 (CO), 1230 cm^{-1} (C–O–C); MS m/z (rel intensity) 236 (M^+, 8), 193 (100), 131 (32), 120 (24), 105 (90). Found: C, 66.12; H, 6.84%. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%.

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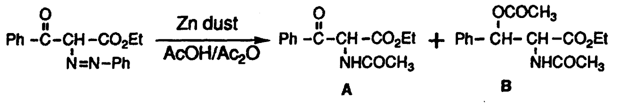
5) When the reported procedure$^{6)}$ was repeated for the preparation of **A** with 6.6 molar amounts of zinc dust in acetic acid and acetic anhydride for overnight in our laboratory, we observed the formation of **B** in 21% yield. When 12 molar amounts of zinc was used, only **B** formed quantitatively.



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