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Zinc mediated reductive dimerization and cyclization of α,β-unsaturated ketones in the presence of a catalytic amount of mercury(II) chloride

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Abstract—The zinc mediated reductive dimerization and cyclization of α,β-unsaturated ketones gives functionalized cyclopentanols in good yield in the presence of a catalytic amount of mercury(II) chloride in *N*,*N*-dimethylformamide as solvent at room temperature. The reaction is regio- and stereo-selective producing 3,4-*trans*-diarylcyclopentanols selectively.

Carbon–carbon bond formation is the backbone of organic synthesis and the reductive dimerization of carbonyl compounds by active metals is valuable for forming carbon–carbon bonds. Among the principle procedures are the pinacol reduction and the acyloin condensation using alkali or alkaline earth metals[1–4] and the reductive cyclodimerization of α,β-unsaturated esters and amides catalyzed by samarium(II) iodide.[5,6] Zhou and Zhang[7] reported the SmI_2 catalyzed cyclodimerization of α,β-unsaturated ketones initiated by single electron transfer (SET) from Sm^{2+} to the α,β-unsaturated ketones and that the reaction is regioselective and stereocontrolled.

SmI_2 is generated in situ from expensive samarium metal and iodine in dry tetrahydrofuran. The reaction requires strictly inert conditions, sophisticated techniques and the work-up involves the use of hydrochloric acid. We wished to develop a cheaper and more versatile alternative of this reagent and planned to employ zinc powder, which is easily and cheaply available, to initiate the reaction via a SET.[8,9] Zinc dust in combination with other reagents has been employed for cyclization and cyclodimerization of different substrates, for example, ketonitriles[10] and arylidenemalononitriles.[11]

Benzylideneacetophenone **1a** was reacted with zinc powder in distilled THF, THF/DMF (9:1) mixture and DMF but, to our chagrin, no reaction was observed and the starting material was recovered intact. However, addition of 2.5 mol % mercury(II) chloride to the reactions in the THF/DMF (9:1) mixture, and in DMF, resulted in smooth conversion of the starting α,β-unsaturated ketone into a slightly more polar product (TLC). This product was isolated by column chromatography by eluting with 10% EtOAc/hexane and its structure was established by spectral means and found to be identical with the earlier reported 2-benzoyl-1,3,4-triphenylcyclopentanol **2a**.[7] The ^{13}C NMR spectrum of **2a** displayed 22 resonances at δ ($CDCl_3$): 204.94 (C=O), 145.2, 143.9, 139.8, 137.5, 133.2, 128.4, 128.34, 128.29, 128.11, 128.04, 127.87, 127.58, 126.95, 126.87, 126.30, 124.83 (aromatic Cs), 84.24 (C-1), 76.34 (C-2), 63.52 (C-3), 59.53 (C-4) and 51.34 (C-5).

The reaction was extended to a variety of other substrates and the results are shown in Table 1. The role of mercury(II) chloride in this reaction seems to be that of a Lewis acid facilitating the SET. The following mechanism is proposed.

Another minor spot, more polar and overlapping with compound **2a** was also seen by TLC. Attempts to purify this compound via column chromatography resulted in its decomposition to unidentifiable products. Replacement of the $HgCl_2$ with $ZnCl_2$ gave the desired product but the yield was low (less than 35%).

Keywords: Zinc; Mercury(II) chloride; α,β-Unsaturated ketones; Cyclodimerization; Cyclopentanols.

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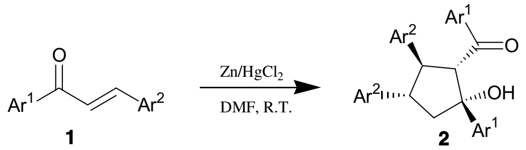
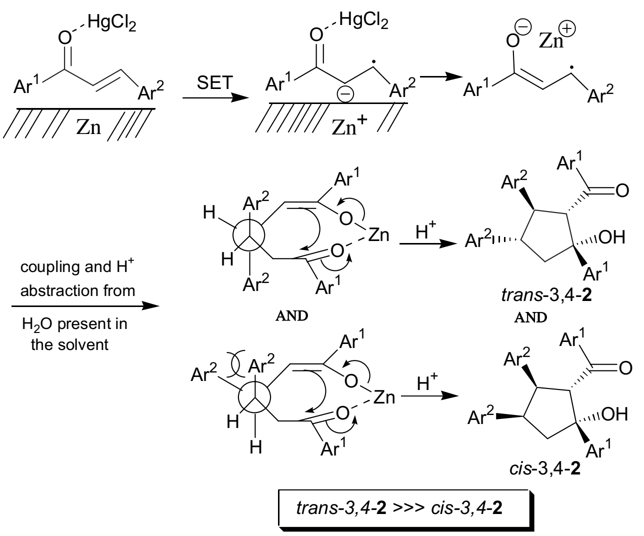
Table 1. Zn/$HgCl_2$ mediated reductive dimerization and cyclization of α,β-unsaturated ketones



Entry	Ar^1	Ar^2	Product **2**	Time (h)	Yield (%)	Melting point (°C)	
						Observed	Literature[7]
1	C_6H_5	C_6H_5	**a**	5.0	85	195	192–194
2	C_6H_5	4-Cl–C_6H_4	**b**	5.5	80	193–195	192–194
3	C_6H_5	2-Cl–C_6H_4	**c**	5.0	78	190–192	191–193
4	4-Me–C_6H_4	C_6H_5	**d**	4.5	74	172–173	172–174
5	C_6H_5	4-Me–C_6H_4	**e**	4.5	76	185	186–188
6	C_6H_5	3,4-OCH_2O–C_6H_3	**f**	6.5	72	182–183	182–184
7	4-Me–C_6H_4	3,4-OCH_2O–C_6H_3	**g**	6.0	70	171–173	170–171
8	Me	H	**h**	7.0	—	—	—
9	Me	C_6H_5	**i**	8.0	—	—	—
10	C_6H_5–CH=CH	C_6H_5	**j**	3.0	55	149–151	



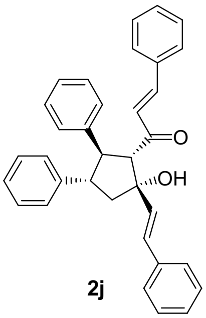
Replacement of the $HgCl_2$ with other Lewis acids such as $NiCl_2$, $CoCl_2$, $FeCl_3$ and $SnCl_2$ either failed completely or resulted in the formation of only trace amounts of products.

As is apparent from Table 1, the ketonic part of the α,β-unsaturated ketone must be aromatic for the reaction to be successful since methyl vinyl ketone (entry 8) and benzylideneacetone (entry 9) did not lead to any product formation. However, with dibenzylideneacetone (entry 10), which has the ketone conjugated to an aromatic moiety, the cyclodimerzation was successful.

Thus, the reaction of benzylideneacetophenone using zinc dust and mercury(II) chloride provides an easy, cheap and versatile method for the formation of substituted cyclopentanols. This is the first reported example of the use of the Zn–$HgCl_2$ combination for reductive dimerization and cyclization of α,β-unsaturated ketones.

General procedure: To the benzylideneacetophenone (10 mmol) in a THF/DMF (9:1) mixture (10 ml) were added zinc powder (15 mmol) and mercury(II) chloride (2.5 mol %) and the mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), ether (50 ml) was added to the reaction mixture, which was filtered through Celite. The filtrate was washed with cold water (3 × 15 ml) and brine (1 × 15 ml). The organic layer, after drying over anhydrous sodium sulfate, was concentrated on a rotavap under reduced pressure. The residue was chromatographed on a silica gel (100–200 mesh) column eluting with 10% EtOAc/hexane solution to give the products as colourless powders. The pure products were characterized by spectral data (IR, MS, ^1H NMR and ^{13}C NMR) and by comparison with authentic samples.[7]

The product **2j** obtained had the following spectral data:



2j

IR, ν_{max}/cm^{-1} (KBr): 3445, 3030, 1654, 1500, 1610, 950.

^1H NMR: ($CDCl_3$, 200 MHz): 2.40 (dd, 1H, $J = 5.5$, 13.2 Hz), 2.70 (dd, 1H, $J = 9.5$, 13.5 Hz), 3.65 (ddd, 1H, $J = 9.5$, 9.2, 5.5 Hz), 3.90 (dd, 1H, $J = 11.5$, 10.0 Hz), 4.00 (d, 1H, $J = 11.2$ Hz), 5.10 (s, 1H, OH), 6.25 (d, 1H, $J = 15.8$ Hz), 6.45 (d, 1H, $J = 15.8$ Hz), 6.85 (d, 1H, *J* = 15.9 Hz), 7.10 (d, 1H, *J* = 15.8 Hz), 7.20–7.60 (m, 20H, Ar–H).

HRMS: observed as 470.278 (M^+) (470.225 calculated for $C_{34}H_{30}O_2$).

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