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SELECTIVE PROTECTION OF CARBONYL COMPOUNDS BY GIRARD'S REAGENT USING SILICA GEL AS A SOLID SUPPORT

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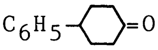
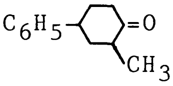
The Girard's reagent, which gives water-soluble derivatives of carbonyl compounds, was used together with silica gel as a protective reagent of them in a non-aqueous solvent system. Less hindered or more reactive carbonyl compounds were selectively protected by this method in competitive reductions.

The Girard's reagent, trimethylammonium acetohydrazide chloride (Girard-T) (**1**) or pyridinium acetohydrazide chloride (Girard-P) (**2**), condenses with carbonyl compounds to form water-soluble products. The carbonyl compounds are then recovered from the aqueous layer by extraction after heating the solution with dilute mineral acid to hydrolyze the hydrazones.1) Semicarbazide hydrochloride and hydroxylamine hydrochloride are used to protect the carbonyl groups, while the Girard's reagent, a member of substituted hydrazines, has not been used to protect the carbonyl groups because of the low solubilities of the derivatives in organic solvents.

Solid adsorbents have been used as reaction media to control reactivity or selectivity.2) Recently we used silica gel to support sodium bisulfite adducts of carbonyl compounds, and succeeded to protect selectively less hindered carbonyl groups in the reduction.3) When the Girard derivatives are adsorbed on such a solid support as in the case of sodium bisulfite adducts, they can be carried into a non-aqueous reaction system and then can be used to protect the carbonyl groups selectively. In this communication the utilization of the Girard's reagent for protection of carbonyl groups has been studied.

Typically, 0.2 mmol of *p*-phenylacetophenone (**3**) (39.2 mg), benzophenone (**4**) (36.4 mg), and **1** (33.5 mg) were added to 1.3 ml of ethanol containing 10 mg of Amberlite IRC-50 as an acidic catalyst and mixed well for 2 h at 80 °C to produce a Girard derivative.4) After removal of the catalyst by decantation, 1.57 g of silica gel was added to the solution and the solvent was evaporated under reduced pressure. To a flask containing the dried solid, 2 mmol (508.5 mg) of lithium tri-*t*-butoxyaluminum hydride5) in a tetrahydrofuran solution was added and stirred for 1 h at room temperature to reduce the carbonyl group. Then the Girard derivative was hydrolyzed by dilute hydrochloric acid or treated with aqueous formaldehyde,4) and the product was extracted with benzene. After concentration of the extract under reduced pressure, the residue was analyzed by G L C. The results

Table 1. Selective protection of unhindered carbonyl groups by the Girard-T (**1**) in competitive reduction[a)]

Entry	Substrate	Conversion to alcohol / %[b)]	Recovery / %[c)]
1	*p*-C_6H_5-C_6H_4-CO-CH_3 (**3**)	16.1	95
	C_6H_5-CO-C_6H_5 (**4**)	96.3	71
2	C_6H_5-CHO	10.1	74
	C_6H_5-CO-CH_3	61.1	82
3	CH_3-$(CH_2)_9$-CHO	9.6	83
	CH_3-$(CH_2)_8$-CO-CH_3 (**5**)	60.7	96
4	CH_3-$(CH_2)_9$-CHO	0.8	75
	CH_3-$(CH_2)_7$-CO-C_2H_5	77.9	96
5	CH_3-$(CH_2)_8$-CO-CH_3 (**5**)	38.5	80
	CH_3-$(CH_2)_7$-CO-C_2H_5	71.2	91
6		6.7	89
		73.3	95

a) Equal moles of each ketone and **1** were used. b) Based on recovered product. c) Combined amount of unreacted substrate and product.

of selective protection for pairs of carbonyl compounds are summarized in Table 1. The acetyl group of **3** in entry 1 was protected selectively, whereas the acetyl group of acetophenone in entry 2 was reduced preferentially. Similarly the acetyl group of 2-undecanone (**5**) in entry 5 was protected selectively, whereas the acetyl group of **5** in entry 3 was reduced preferentially. The carbonyl group of 2-methyl-4-phenylcyclohexanone in entry 6 was reduced preferentially. These results show that less hindered carbonyl group was selectively protected by **1**. By the method described above, **2** was also proved to be a protecting reagent for unhindered carbonyl groups. The procedure reported here can be used for the selective protection of less hindered carbonyl group in organic synthesis.

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