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Diisopropoxyaluminium Trifluoroacetate/ 4-Nitrobenzaldehyde - A New Oppenauer Oxidation System for Accelerated Oxidation of Secondary Alcohols to the Corresponding Ketones

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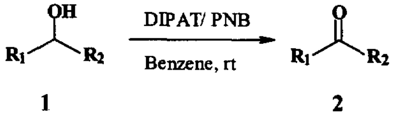
Abstract: A practical, efficient and accelerated oxidation of secondary alcohols to the corresponding ketones has been achieved at rt in high yields by a modified Oppenauer oxidation system using diisopropoxyaluminium trifluoroacetate as catalyst and 4-nitrobenzaldehyde as a hydride acceptor.

Ketones and aldehydes can be reduced by use of metal alkoxides and alcohols (Meerwein-Ponndorf-Verley reduction). The reverse reaction of which is known as Oppenauer oxidation[1]. Very often in this type of oxidation cyclohexanone is employed as a hydride acceptor. Various attempts have been made to modify the reaction by substituting cyclohexanone by other hydride acceptors like acetaldehyde[2], anisaldehyde[3], benzaldehyde[4], benzophenone[5], cinnamaldehyde[6], quinone[7] etc. More recently 1-methyl-4-piperidone has been tried as hydride acceptor[8] even though amine containing aldol condensate products were still encountered.

This type of oxidation is of interest because of its high chemoselectivity and mild reaction conditions. An important advantage is that, over-oxidation of aldehydes and ketones towards carboxylic acids is not observed. Although the procedure is effective, problems in the use of this oxidation system arises because of formation of aldol condensation products with the hydride acceptors, higher reaction temperatures and isolation of product. In an attempt to circumvent these disadvantages, attention has been focused recently on more efficient methods that would work at lower temperatures with good conversion[9]. We have reported quite recently[10] the preparation of diisopropoxyaluminium trifluoroacetate (DIPAT) and its unique property in reduction of aldehydes and ketones. We found that 4-nitrobenzaldehyde (PNB) was reduced to 4-nitrobenzyl alcohol within 15 min at rt and aldol condensation products were essentially absent.

In this letter, we wish to report a highly accelerated Oppenauer oxidation system which employs DIPAT as a catalyst and PNB as a hydride acceptor. This modified system effectively oxidises a variety of secondary alcohols to the corresponding ketones (Scheme I).



Scheme I : Accelerated Oppenauer oxidation

Using this modified system various secondary alcohols, both benzylic as well as aliphatic have been successfully oxidised to the corresponding ketones (Table 1). We found that a variety of benzylic secondary alcohols were selectively oxidised in very high yields at rt and within a reasonable period of time[11].

Table-1 : Oxidation of alcohols using DIPAT with 4-nitrobenzaldehyde as a hydride acceptor[a].

Entry	Substrate, 1	Time /min	Product, 2[b]	Yield (%)[c]
1	1-Phenyl-1-ethanol	30	Acetophenone	92
2	1-(4-Methoxyphenyl)-1-ethanol	15	4-Methoxyacetophenone	99
3	1-(4-Chlorophenyl)-1-ethanol	30	4-Chloroacetophenone	87
4	1-(4-Nitrophenyl)-1-ethanol	15	4-Nitroacetophenone	94
5	1-(2-Hydroxyphenyl)-1-ethanol	24 h	2-Hydroxyacetophenone	70[d]
6	1-Phenyl-1-propanol	20	Propiophenone	96
7	1-(4-Methoxyphenyl)-1-propanol	15	4-Methoxypropiophenone	97
8	1-(4-Chlorophenyl)-1-propanol	45	4-Chloropropiophenone	85
9	Benzhydrol	15	Benzophenone	95
10	4-Chlorobenzhydrol	30	4-Chlorobenzophenone	85
11	4-Bromobenzhydrol	30	4-Bromobenzophenone	88
12	5-Methyl-2-heptanol	90	5-Methyl-2-heptanone	71
13	Cyclohexanol	15	Cyclohexanone	96
14	Cycloheptanol	15	Cycloheptanone	92
15	Benzyl alcohol		NR[e]	
16	1-Butanol		NR[e]	

a : All the reactions were carried out on 2 mmol of alcohol; b : Characterized by mp/bp, ^{1}H-NMR; c : Yields refer to isolated products after column chromatography; the remaining is completely the starting material; d : In this case the reagent used is 2 mole equivalent of the substrate and the reaction time is 24 h; e : No reaction

It was observed that irrespective of the substrates containing either the electron withdrawing or donating groups at para position got readily oxidised within 15-30 min. (entry 2,3,4,7,10 and 11). Interestingly, 1-(2-hydroxyphenyl)-1-ethanol (entry 5) was oxidised to 2-hydroxyacetophenone in 70 % yield even in the presence of the phenolic group. With aliphatic secondary alcohols, it was noticed that the oxidations are comparatively slow and need longer reaction times for complete oxidation (entry 12). However, primary alcohols such as benzyl alcohol and 1-butanol failed to undergo oxidation under these reaction conditions (entry 15 and 16). This implies that the system may be useful for selective oxidation of secondary alcohols in the presence of primary alcohols.

To the best of our knowledge PNB has been used as a hydride acceptor for the first time in Oppenauer oxidation. The present modification is superior over the earlier modifications using different combinations of hydride acceptors and catalysts. For example the previous best system for the oxidation of 1-phenyl-1-ethanol and benzhydrol employs acetone as hydride acceptor with hydrated zirconium oxide as a catalyst to give acetophenone in 90% yield in 6 hrs and benzophenone in 100% yield in 8 hrs respectively under reflux condition[12]. Whereas the present modified system brings about the oxidation of both the substrates at rt to give the corresponding products, acetophenone in 92% yield within half an hour (entry 1).and benzophenone in 95% yield within just 15 min (entry 9). The present system also seems to be better as well, for the oxidation of various other substrates studied[13].

Important features of this modification using PNB as a hydride acceptor are: i. the reaction becomes nonequilibrating ii. having used PNB in 2 equivalents (stoichiometric requirement) with respect to DIPAT, it gets completely converted to 4-nitrobenzyl alcohol. Also, the products (ketones) formed were less polar than 4-nitrobenzyl alcohol and could be easily separated by simple chromatography. It may be possible that the DIPAT can be used in less than the stoichiometric quantity so that the system becomes a truly catalytic system. Work in this direction is currently underway.

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11. General procedure for oxidation.

    To a 100 ml round bottom flask was added DIPAT (2 mmol) and alcohol (2 mmol) in benzene (25 mL). After stirring for 1h, 4-nitrobenzaldehyde (4 mmol) was added and stirring continued at rt for the indicated time, until TLC showed PNB, the hydride acceptor, to be consumed. Aqueous HCl (0.1 N, 20 mL) was added to the reaction mixture at rt to quench the reaction and extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated *in vacuo*. Residue thus obtained on chromatography (silica gel eluted by benzene : hexane) provided pure ketone leaving behind 4-nitrobenzyl alcohol and unreacted alcohol (if any).

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