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A NOVEL NUCLEOPHILIC SUBSTITUTION OF THE FORMYL GROUP IN p-NITROBENZALDEHYDE WITH SOME CARBANIONS

Genji IWASAKI, Seitaro SAEKI, and Masatomo HAMANA*†
Faculty of Pharmaceutical Sciences, Kyushu University,
Maidashi 3-1-1, Higashi-ku, Fukuoka 812

p-Nitrobenzaldehyde reacts with some active methylene compounds in the presence of a strong base at low temperatures to give p-substituted nitrobenzenes by the two-step course involving the initial formation of the aldol adducts and the subsequent displacement of the carbinol moieties with excess carbanions.

The preceding paper has described that p-dinitrobenzene reacts with some active methylene compounds in the presence of t-BuOK in liq NH_3 at -70 °C to afford p-substituted nitrobenzenes by the nucleophilic displacement of a nitro group.$^{1)}$ As an extension of this work, we carried out the reaction of p-nitrobenzaldehyde with active methylene compounds under similar conditions, and found that p-substituted nitrobenzenes were dominantly formed by the apparent displacement of the formyl group, the substitution of the nitro group being not noticed against anticipation. Some detailed examinations indicated that the reaction followed the two-step course involving the initial formation of the aldol adducts and the subsequent displacement of the carbinol moieties with excess carbanions.

p-Nitrobenzaldehyde (**1**) was added in small portions at -70 °C to a mixture of an active methylene compound (3 equiv.) and t-BuOK (4 equiv.) in liq NH_3, and the reactants were stirred at that temperature for an appropriate time to give a dark blue solution. The usual workup gave the results given in Table 1. The majority of reactions gave only the products (**2**), in which the formyl group in **1** was replaced by active methylene residues, in moderate to good yields (runs 1, 2, 3, 4, 8,

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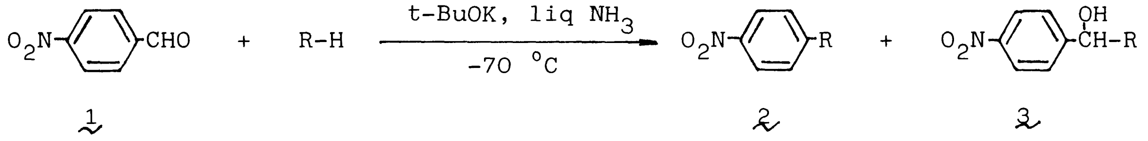
[†] Present address: Central Research Laboratories, Chugai Pharmaceutical Co., Ltd., Takada 3-41-8, Toshima-ku, Tokyo 171.

9, 10, 12, and 13 in Table 1). In some cases, however, the aldol addition products (3) were formed preferentially (runs 5, 6, and 11 in Table 1) or exclusively (runs 7 and 14 in Table 1). The bulkiness or the high acidity of active methylene compounds seems to be favorable for the formation of 3.

Table 1. Reactions of p-nitrobenzaldehyde (1) with active methylene compounds (3 equiv.) in the presence of t-BuOK (4 equiv.) in liq NH_3 at -70 °C a)



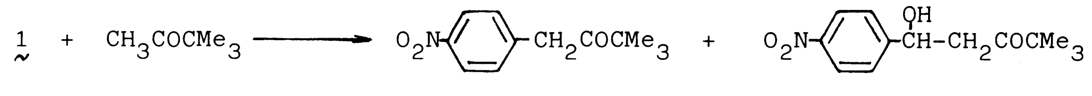
Run	R-	Yield/%		Run	R-	Yield/%	
		2	3			2	3
1	$-CH_2COPr$	85	-	8	$-CH(CO)(CH_2)_3$ b)	88	-
2	$-CH_2COCHMe_2$	68	-	9	$-CH(CO)(CH_2)_4$ c)	49	-
3	$-CH_2COCMe_3$	64	-	10	$-CH_2COOEt$	50	-
4	$-CH_2COPh$	27	-	11	$-CH_2COOCMe_3$	36	38
5	-CH(Me)COPh	5	52	12	-CH(CN)Ph	74	-
6	-CH(Me)COEt	22	41	13	$-CH(CN)C_{10}H_7$ d)	71	-
7	$-C(Me)_2COCHMe_2$	-	42	14	$-CH(CN)_2$	-	quant.

a) Reaction time: 30 min—2 h; the proceeding of reaction could be easily followed by the color-change and TLC-checking of the reactants. b) Cyclopentanone c) Cyclohexanone d) 1-Naphthylacetonitrile

In exploring the effects of the nature of base and solvent, the reaction of 1 with pinacolone was examined under various conditions (runs 1—9 in Table 2). In contrast to the reaction of p-dinitrobenzene with active methylene compounds,1) not only liq NH_3 but also t-$BuNH_2$ and THF were efficient as the reaction medium (runs 2 and 3 in Table 2), and $LiNH_2$/liq NH_3 system was not effective for the reaction to proceed, whereas the reaction occurred in KNH_2/liq NH_3 and $NaNH_2$/liq NH_3 systems as in the case of p-dinitrobenzene (runs 6 and 7 in Table 2). Among the conditions so far examined, KNH_2/liq NH_3 system gave the best result. On the other hand, only the aldol adduct 3a was obtained from the reaction in the presence of n-BuLi in THF, 2a being not detected (run 9 in Table 2); attempted reactions with t-butyl acetate and acetophenone under the same conditions also gave only aldol adducts in 76.5 and 30.0% yields, respectively.

It was subsequently disclosed that the amounts of active methylene compounds and bases affect substantially the product proportions. Runs 10—12 in Table 2 present the observations obtained from the reactions carried out at -70 °C for 10 min in liq NH_3 by changing the molar equivalents of pinacolone and t-BuOK.

Table 2. Reactions of p-nitrobenzaldehyde (**1**) with pinacolone under various conditions



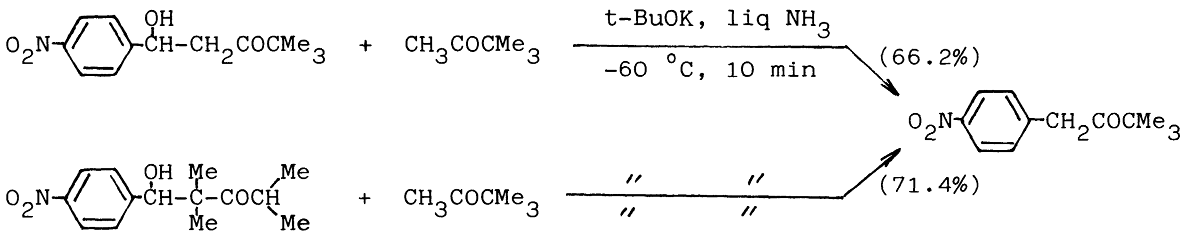
2a **3a**

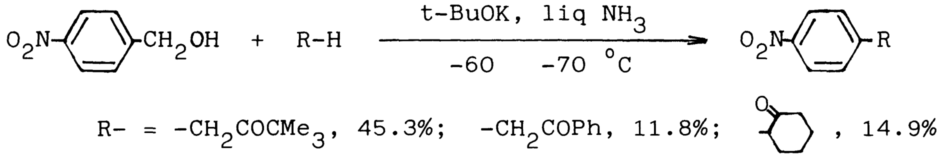
Run	CH_3COCMe_3 (equiv.)	Base (equiv.)	Solvent	Temp / °C	Time	Yield/% **2a**	Yield/% **3a**
1	(3)	t-BuOK(4)	liq NH_3	-70	10 min	64	-
2	(3)	t-BuOK(4)	t-$BuNH_2$	-70	1 h	56.7	-
3	(3)	t-BuOK(4)	THF	-60	30 min	51.6	7.5a)
4	(3)	t-BuOK(4)	ether	-70	1 h	25	22.9b)
5	(3)	t-BuOK(4)	DMF	-50	40 min	31.2	-
6	(3)	KNH_2(4)	liq NH_3	-60	50 min	72.8	-
7	(3)	$NaNH_2$(4)	liq NH_3	-60	50 min	37	-
8	(3)	$LiNH_2$(4)	liq NH_3	-60	50 min	-	-
9	(3)	n-BuLi(4)	THF	-70	1 h	-	76.5
10	(1)	t-BuOK(1)	liq NH_3	-70	10 min	17.1	29.1
11	(2)	t-BuOK(2)	liq NH_3	-70	10 min	43.6	8.3
12	(3)	t-BuOK(4)	liq NH_3	-70	10 min	64	-

a) The dehydration product of **3a**, p-O_2N-C_6H_4-CH=$CHCOCMe_3$, was also formed in 6.6% yield. b) The further oxidation product, p-O_2N-C_6H_4-C(OH)=$CHCOCMe_3$, was also formed in 17.4% yield.

These observations clearly demonstrated that products **2** did not arise from the direct displacement of the formyl group of **1** with carbanions, but its formation was the outcome of the two-step path involving the initial formation of the aldol adducts **3** and the subsequent displacement of the carbinol moieties of **3** with excess carbanions.

In order to gain further confirmation for this pathway, we carried out reactions of pinacolone with some aldol adducts, prepared from **1** and active methylene compounds, under the same conditions and successfully obtained **2a** in good yields. Further, p-nitrobenzyl alcohol was found to react with some active methylene compounds to give the corresponding p-substituted nitrobenzenes, though in lower yields. Some of these reactions are formulated below.





Although there have been a few reports on nucleophilic displacement of a nitro group in p- and o-nitrobenzaldehydes in which the formyl group acts as an activating group,[2-6] the displacement of a formyl group activated by nitro group has no precedent. While o- and m-nitrobenzaldehydes afforded also the corresponding aldol adducts upon treatment with pinacolone under similar conditions, these adducts were entirely inert to further substitution with any carbanions. The detailed mechanism of the displacement of carbinol substituents with carbanions is now under investigation.

References

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