Synthesis of α-Hydroxyhydrazones from Aldehydes

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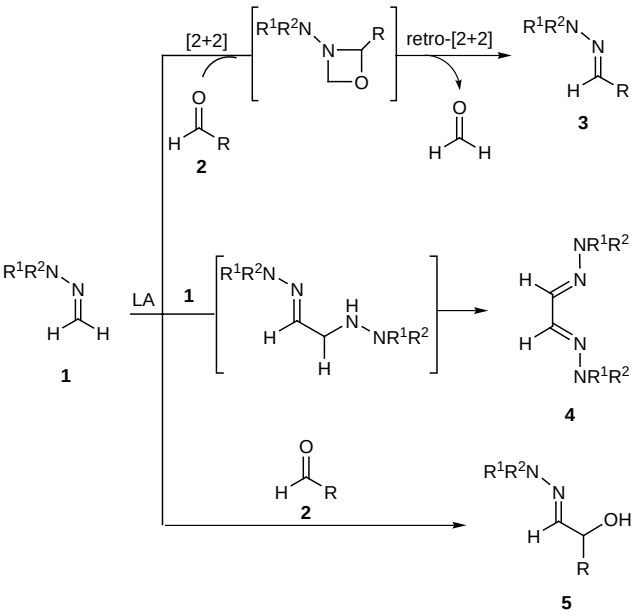
Abstract: The 1,2-addition of formaldehyde *N*,*N*-dialkylhydrazones to simple aldehydes takes place in the presence of $ZnCl_2$ or Et_2AlCl to afford the corresponding α-hydroxyhydrazones. More reactive aldehydes undergo addition of these reagents in the absence of promoters. Use of (*S*)-1-methyleneamino-2-(diphenylmethoxymethyl) pyrrolidine as the reagent afforded separable mixtures of diastereoisomers, thereby allowing for the isolation of optically pure adducts in a single step.

Key words: diastereoselectivity, hydroxyhydrazones, nucleophilic addition

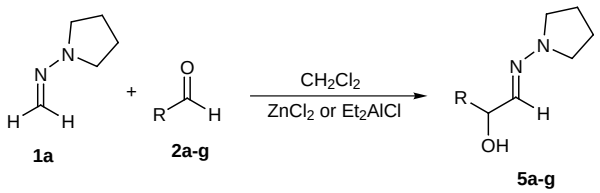
α-Hydroxy-*N*,*N*-dialkylhydrazones are useful compounds not only as protected forms of α-hydroxyaldehydes, but also as versatile intermediates for the synthesis of α-alkoxy carbonyl compounds,[1] cyanohydrins,[2] and many other compounds resulting from C–C bond-forming radical[3] or anionic[4] additions to their C=N bond. The nucleophilic properties of formaldehyde *N*,*N*-dialkylhydrazones **1**, associated to their enhanced aza-enamine character, has allowed their use as d^1 reagents toward several electrophilic substrates.[5] Thus, the Michael addition to several electrophilic alkenes such as nitroalkenes,[6] conjugated enones,[7] and unsaturated lactones,[8] has served for the synthesis of several kinds of bifunctional compounds. These precedents stimulated studies on the 1,2-addition of these reagents to carbonyl compounds for the synthesis of the title compounds. The first findings on this topic revealed that the inductive effects operating in carbohydrate-derived alkoxyaldehydes[2a] or trifluoromethyl ketones[2b] enhance the carbonyl reactivity up to the level required for the spontaneous addition of these reagents. In this paper, we wish to report on a broader scope of this reaction, given by the 1,2-addition of formaldehyde *N*,*N*-dialkylhydrazones to several types of aldehydes.

Preliminary experiments demonstrated that simple aliphatic and aromatic aldehydes **2a-f** do not react spontaneously with formaldehyde *N*,*N*-dialkylhydrazones **1**. Attempts to activate the substrates by several Lewis acids ($BF_3{\cdot}Et_2O$, R_3SiOTf, $SnCl_4$, $ZnBr_2$) led mainly to the formation of undesired hydrazono transfer products **3**, which, in the absence of moisture, are presumably formed via [2+2] and retro-[2+2] cycloadditions.[9] Variable amounts of compounds **4** were also isolated from the reaction mixtures; their formation can be explained as an oxidative dimerization of **1** via α-hydrazinoacetaldehyde hydrazone.[10] Therefore, only small amounts of the desired products **5** were detected under these conditions (Scheme 1).



Scheme 1

Fortunately, it was finally possible to obtain the desired adducts **5a-f** in variable yields by using $ZnCl_2$[11] or Et_2AlCl[12] as suitable promoters. 1-Methyleneaminopyrrolidine **1a**, readily available from commercial *N*-nitrosopyrrolidine,[2c] was the reagent of choice, giving better yields of adducts and faster reactions than the simplest formaldehyde *N*,*N*-dimethylhydrazone **1b** (Scheme 2, Table 1).



Scheme 2

Noteworthy, *p*-nitrobenzaldehyde **2g** also reacted with **1a** in the absence of any promoter to give the corresponding 1,2-adduct **5g**, though in a lower 33% yield than that obtained (81%) for the $ZnCl_2$-promoted reaction (entries 7 and 8). This last result and the above-mentioned precedents[2a,b] prompted us to investigate the uncatalyzed addition of reagents **1** to more reactive substrates. Thus,

Table 1 Addition of 1-methyleneaminopyrrolidine (**1a)** to aldehydes **2a-g**.

entry	educt	R	promoter[a]	time (h)[a]	product	yield. (%)[b]
1	**2a**	*n*-butyl	$ZnCl_2$	7	**5a**	52
2	**2b**	*n*-pentyl	Et_4AlCl	4[c]	**5b**	63
3	**2c**	cyclohexyl	Et_2AlCl	12	**5c**	44
4	**2d**	Bn	$ZnCl_2$	4.5	**5d**	72
5	**2e**	Ph	Et_2AlCl	14	**5e**	52
6	**2f**	*p*-Br-C_6H_4	Et_2AlCl[d]	19	**5f**	54
7	**2g**	*p*-$O_2NC_6H_4$	$ZnCl_2$	4	**5g**	81
8	**2g**	*p*-$O_2NC_6H_4$	-	150	**5g**	33[e]

[a]The amounts of promoter and reaction temperatures as indicated in footnotes 11 and 12, unless otherwise specified. [b] Isolated yield after chromatography. [c]-78 °C→r.t. (2 h) and then 2 h at r.t. [d]2.4 mmol of promoter were used. [e]**3g** (R^1R^2N = pyrrolidin-1-yl, R = *p*-$O_2NC_6H_4$) was isolated as by-product in 30% yield.

α-monoalkoxy (**2h,i**) and α,α-dialkoxy (**2j**) aldehydes, as well as chloral (**2k**) and fluoral (**2l**) also reacted with **1a** in the absence of promoters to afford the corresponding α-hydroxyhydrazones **5h-l** in good to excellent yields (Table 2).[13] As expected, the observed aldehyde reactivities were strongly dependent on the substitution pattern. Nevertheless, reasonable reaction rates were observed for all substrates at room temperature, except for α-benzyloxyacetaldehyde **2h**, which required heating at 60 °C for 18 h for completion (Table 2, entry 1).

Table 2 Uncatalyzed addition of methyleneaminopyrrolidine (**1a)** to aldehydes **2h-m.**

entry	educt	R	time (h)[a]	prod.	yield (%)[b]
1	**2h**	$BnOCH_2$	18[c]	**5h**	63
2	**2i**	$TBSOCH_2$	5	**5i**	76
3	**2j**	$(MeO)_2CH$	28	**5j**	87
4	**2k**	Cl_3C	0.5	**5k**	95
5	**2l**	F_3C	1	**5l**	94
6	**2m**	F_5C_6	4	**5m**	60

[a] At room temperature, unless otherwise specified. [b] Isolated yield after chromatography. [c] At 60 °C.

Interestingly, the commercial forms of dimethoxyacetaldehyde **2j** (60% in H_2O), chloral **2k** (monohydrate), and fluoral **2l** (ethyl hemiacetal) could be used without any previous treatment. Additionally, pentafluorobenzaldehyde **2m,** chosen as representative of aromatic aldehydes, behaves also as substrate for the spontaneous addition of **1a**, affording the corresponding adduct **5m** in 60% yield.

The development of an asymmetric version of these uncatalyzed additions was also studied with limited success. Thus, the addition of chiral reagents as 1-(methyleneamino)-2-(methoxymethyl)pyrrolidine **1c**[6c] or the D-mannitol-derived C_2-symmetric hydrazone **1d**[14] (Figure) to aldehydes **2h-m** proceeded with very low asymmetric induction, affording the corresponding adducts in high yields, but as unseparable mixtures of diastereoisomers in all cases. On the other hand, the addition of (*S*)-1-methyleneamino-2-(diphenylmethoxymethyl)pyrrolidine **1e**[2c] to aldehydes **2h-m** took place with similar yields and selectivities, but in this case the resolving properties of the auxiliary allowed an easy chromatographic separation of the (*2R/S*) diastereomeric mixtures. In this reaction, compound **1e** plays two roles: it serves as a d^1 reagent and as a resolving agent at once, thereby allowing the obtention of enantiomerically pure (*R*)- and (*S*)-**6h-m** adducts in a single operation (Scheme 3). The results for the addition of **1e** to aldehydes **2h-m** are collected in Table 3.

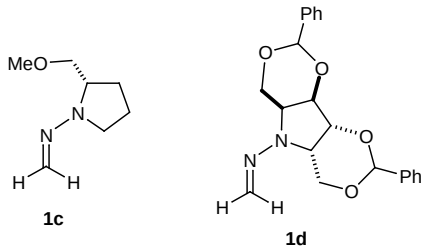
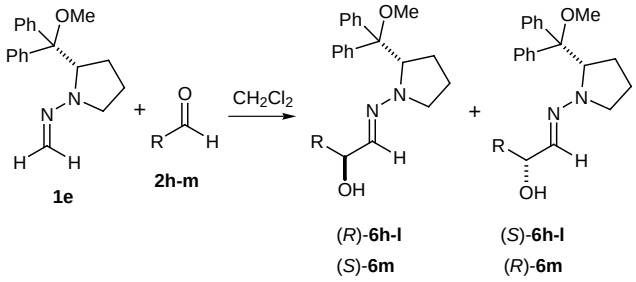


Figure Chiral hydrazones from L-proline and D-mannitol



Scheme 3

Summarizing, the nucleophilic addition of formaldehyde *N,N*-dialkylhydrazones to aldehydes represents a convenient, single step method for the synthesis of a variety of synthetically useful α-hydroxyhydrazones.

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Table 3 Uncatalyzed addition of **1e** to aldehydes **2h-m**.

entry	educt	R	time (h)[a]	product, yield (%)[b]	dr[c]
1	**2h**	$BnOCH_2$	120[d]	**6h**, 71	50:50
2	**2i**	$TBSOCH_2$	120	**6i**, 68	50:50[e]
3	**2j**	$(MeO)_2CH$	96	**6j**, 94	50:50
4	**2k**	Cl_3C	2.5	**6k**, 96	80:20
5	**2l**	F_3C	20	**6l**, 96	60:40
6	**2m**	F_5C_6	72	**6m**, 66	50:50

[a]At room temperature. [b]Isolated yield. [c]Mixture fully separable by flash chromatography. [d]At 50 °C. [e]Mixture separable after benzylation.

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(11) **Typical procedure**: To a cooled (0 °C) solution of **1** (2 mmol) and **2** (1 mmol) in dry CH_2Cl_2 (7 mL) was added 1M $ZnCl_2$ in Et_2O (4 mmol). After completion, the mixture was washed with sat. $NaHCO_3$ and H_2O, concentrated and purified by column chromatography (petroleum ether-ethyl acetate). Representative characterization data for **5g** (oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87-1.94 (m, 4H), 3.14-3.20 (m, 4H), 4.05 (bs, 1H), 5.39 (d, 1H, *J* = 3.5 Hz), 6.45 (d, 1H, *J* = 3.5 Hz), 7.40-8.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 51.0, 72.6, 123.7, 126.8, 132.2, 147.2, 149.4; IR (film, cm^{-1}) 3358-3298 br, 1581; MS (EI) 249 (M^+, 24), 231 (80), 99 (66), 70 (100); HRMS m/z calcd. for $C_{12}H_{15}N_3O_3$: 249.1113; found 249. 1106.

(12) **Typical procedure**: To a cooled (-78 °C) solution of **1** (2 mmol) and **2** (1 mmol) in dry THF (4 mL) was added dropwise 1M Et_2AlCl in hexane (1.5 mmol). After completion, 5M NaOH (1 mL) was added and the mixture stirred for 30 min. at r.t. H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by column chromatography (petroleum ether-ethyl acetate). Representative characterization data for **5e**: mp 46-48 °C, ^{1}H NMR (300MHz, $CDCl_3$) δ 1.84-1.92 (m, 4H), 3.12-3.19 (m, 4H), 3.87 (bs, 1H), 5.28 (d, 1H, *J* = 3.5 Hz), 6.57 (d, 1H, *J* = 3.5 Hz), 7.31-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 51.2, 73.4, 126.3, 127.5, 128.2, 135.1, 152.6; IR (film, cm^{-1}) 3381-3230 br, 1601; MS (EI) 204 (M^+, 10), 186 (100). Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N, 13.71. Found: C, 70.25; H, 7.90; N, 13.70.

(13) **Typical procedure**: A mixture of **1a** or **1e** (1 mmol) and **2h-m** (2-5 mmol) in CH_2Cl_2 (4 mL) was allowed to react until completion, concentrated, and purified by column chromatography (petroleum ether-ethyl acetate). Representative characterization data for **5m**: mp 82-83 °C, ^{1}H NMR (300MHz, $CDCl_3$) δ 1.88-1.92 (m, 4H), 3.17-3.24 (m, 4H), 3.85 (bs, 1H), 5.65 (d, 1H, *J* = 3.4 Hz), 6.55 (d, 1H, *J* = 3.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 50.9, 65.1, 128.8, 135.8, 139.1, 143.4, 146.7; IR (film, cm^{-1}) 3300-3000 br, 1505; MS (EI) 294 (M^+, 35), 276 (15), 70 (100). Anal. Calcd. for $C_{12}H_{11}F_5N_2O$: C, 48.99; H, 3.77; N, 9.52. Found: C, 49.18; H, 3.83; N, 9.39. Data for **6l** (major isomer): $[\alpha]^{28}_D$ -156.0 (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.12-0.36 (m, 1H), 1.41-1.52 (m, 1H), 1.96-2.13 (m, 2H), 2.64-2.74 (m, 1H), 2.78-2.86 (m, 1H), 2.97 (s, 3H), 3.63 (d, 1H, *J* = 5.2 Hz), 4.40-4.44 (m, 1H), 4.77 (dd, 1H, *J* = 2.9, 8.3 Hz), 6.21 (d, 1H, *J* = 2.9 Hz), 7.31-7.61 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 25.8, 49.3, 51.6, 68.0, 69.3 (q, *J* = 31.7 Hz), 85.6, 119.6, 123.9 (q, *J* = 281 Hz), 127.2, 127.6, 129.4, 129.8, 129.9, 138.4, 140.2; IR (film, cm^{-1}) 3439, 1590; MS (EI) 392 (M^+, 1), 195 (100). Anal. Calcd for $C_{21}H_{23}F_3N_2O_2$: C, 64.27; H, 5.90; N, 7.14. Found: C, 64.62; H, 5.99; N, 7.28.

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