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New Trimethylaluminum-Induced Mannich-Type Reaction of Hydrazones

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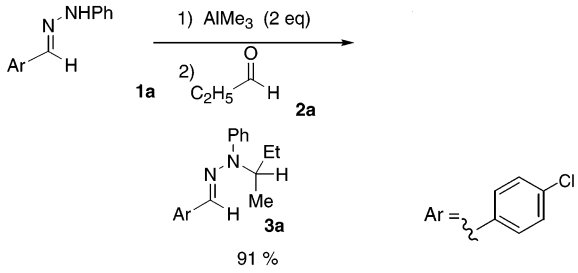
Abstract: Trimethylaluminum addition to *N*-monoalkyl or *N*-monoaryl hydrazones followed by aldehyde addition leads to the formation of *N*-alkylated hydrazones in a new formal Mannich-type process. Addition compounds were also obtained in moderate yields with ketones. The mechanism as well as possible intermediates involved in the reaction are discussed.

Following our studies on the *C*-alkylation of hydrazones through Mannich coupling with aldehydes and *N*-benzylpiperazine,[1] we were interested in testing various conditions to promote the direct coupling of hydrazones with aldehydes. In this sense, trialkylaluminum species were selected for their high oxygen affinity and their ability to form *N*-aluminated compounds with relatively acidic NH compounds.[2]

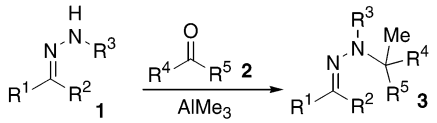
When trimethylaluminum (2 equiv) was added to a solution of hydrazone **1a** in 1,2-dichloroethane at −20 °C, fast gas evolution was observed; propionaldehyde **2a** was then added to this solution and the mixture left at room temperature for 24 h to give instead of the *C*-alkylated expected hydrazone, the new *N*-alkylated hydrazone **3a** in 91% isolated yield (Scheme 1).

SCHEME 1



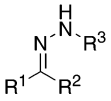
Several hydrazones and aldehydes behaved similarly as shown in Table 1. The reaction is usually much faster with aliphatic aldehydes than with aromatic ones. For the latter aldehydes, the coupling is best obtained by refluxing the mixture for a few hours. The α−β unsaturated aldehyde **2c** gave exclusively a 1,2 addition product in excellent yield. *N*-Alkyl and *N*-aryl hydrazones equally gave addition products in good yield with a higher reactivity of alkyl-substituted ones. Most examples have been performed on aromatic aldehydes derived from hydrazones as hydrazones amenable to easy enamine formation (**1c**) gave the expected coupling compounds with much lower yields. The same is true for hydrazones derived from ketones; cyclohexanone *N*-phenylhydrazone failed to react with aldehyde **2a** whereas benzophenone hydrazone **1d** gave an addition product in moderate yield. The high efficiency of this new reaction was demonstrated by the surprisingly successful coupling of hydrazone **1b** with ketones **2e** and **2f** leading to highly sterically hindered hydrazones.

TABLE 1. Trimethylaluminum-Induced Reaction of Hydrazones 1 with Carbonyl Derivatives 2[a]

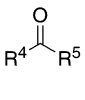


entry	1	2	product	time, h (temp, °C)	yield, %
1	**1a**	**2a**	**3a**	24 (rt)	91
2	**1a**	**2b**	**3b**	4 (83)	92
3	**1a**	**2c**	**3c**	4 (83)	94
4	**1b**	**2a**	**3d**	13 (rt)	82
5	**1b**	**2b**	**3e**	3 (83)	73
6	**1b**	**2d**	**3f**	7 (rt)	58
7	**1b**	**2e**	**3g**	6 (rt)	39
8	**1b**	**2f**	**3h**	6 (rt)	32
9	**1c**	**2b**	**3i**	48 (rt)	43
10	**1d**	**2a**	**3j**	72 (rt)	59

[a] Structures **1a**−**d** and **2a**−**f**.



1a : R^1 = 4-ClPh ; R^2 = H; R^3 = Ph
1b : R^1 = 4-ClPh ; R^2 = H; R^3 = Me
1c: R^1 = $PhCH_2CH_2$; R^2 = H; R^3 = Me
1d : R^1 = R^2 = R^3 = Ph



2a : R^4 = H ; R^5 = Et
2b : R^4 = H ; R^5 = 4-ClPh
2c : R^4 = H ; R^5 = 
2d : R^4 = H ; R^5 = 2-furyl
2e: R^4 = R^5 = $-(CH_2)_5-$
2f: R^4 = R^5 = 4-FPh

Though the *N*-alkylation of hydrazones with electrophiles (allyl chloride under basic conditions) is well-known, this coupling of hydrazones with aldehydes was rather surprising. The hydrazones **3** obtained can be viewed as formal addition compounds of trimethylaluminum onto iminium derived from hydrazones; to our knowledge, Mannich-type additions of trimethylaluminum to aldehydes in the presence of amines is not described in the literature and indeed the addition of benzaldehyde to a solution of trimethylaluminum and morpholine or *N*-benzylpiperazine failed to give any aminoalkylated compound. Trimethylaluminum-induced nucleophilic methyl addition onto iminium has however already been reported in the ring opening of cyclic N,O acetals, the methyl group being there probably delivered intramolecularly from the intermediate alkoxytrimethylaluminum.[3] In our reaction, the interaction of both nucleophilic nitrogen atoms with Lewis acid aluminum species probably plays a significant role in the product

(1) Atlan, V.; Bienaymé, H.; El Kaïm, L.; Majee, A. *Chem Commun.* **2000**, 1585−1586.
(2) Brillaud, P.; Maire, Y.; Maire, J. C.; Ramiaramanana, J. *New J. Chem.* **1995**, *19*, 1009−1013.

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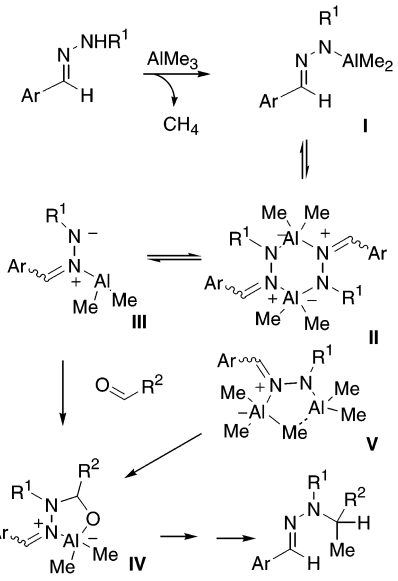
SCHEME 2. Possible Intermediates Involved in the Reaction



formation; this is consistent with the lower yields obtained when hydrazones prone to enamine formation under Lewis acid activation are involved in the reaction.

Addition products between trimethylaluminum and hydrazones already have been studied and several X-ray structures are available. These studies suggest that the addition product exists as a dimeric complex **II** in nonchelating solvent.[4] From this dimer one can easily imagine different monomeric complexes in equlibrium, the obvious *N*-aluminated **I** but also the zwitterionic complex **III** (Scheme 2). Interaction of **III** with an aldehyde would form a transient aluminacycle **IV** that could easily break into iminium species followed by methyl transfer. Alternatively, the dinuclear aluminum complex **V** could also be proposed as the active structure reacting with aldehyde; a similar dinuclear complex has been isolated from the reaction of 2-pyridinecarboxaldehyde phenylhydrazone with trimethylaluminum.[4] The faster reaction, increased yields, and the absence of alcohol formation when the reaction is conducted with 2 equiv of trimethylaluminum are in agreement with such intermediates **V** as the active species in our reaction.

An alternative mechanism involving well-documented methyl addition to aldehyde followed by ionic fragmentation and alkylation was easily discarded by a control experiment: the intermediate alkoxy compounds were formed by letting 2 equiv of trimethylaluminum react with aldehyde **2a** or **2b**; after completion hydrazone **1a** was added and the mixture was refluxed for several hours without further reaction being observed.

This reaction gives new insight on the wealth of trialkylaluminum chemistry and is of high interest for the formation of substituted hydrazine derivatives. Its mechanism and synthetic potential will be further studied in our research group.

(3) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280.

(4) Kim, S. J.; Yang, N.; Kim, D. H.; Kang, S. O.; Ko, J. *Organometallics* **2000**, *19*, 4036−4042.

Experimental Section

Proton and carbon nuclear magnetic resonance (^{1}H, ^{13}C NMR) were recorded on a 400-MHz magnetic resonance spectrometer with chloroform-*d* as a solvent. Chemical shifts are reported as *d* in units of parts per million downfield from tetramethylsilane (*d* 0.0), used as an internal standard for ^{1}H NMR spectra. ^{13}C NMR spectra were calibrated to the 77-ppm signal of $CDCl_3$. IR spectra were recorded as neat samples or in CCl_4 solution. Melting points were obtained by using a metal block and are uncorrected. The starting hydrazones were prepared from the corresponding ketones and arylhydrazines in ethanol as solvent. 1,2-Dichloroethane was dried by distilling over calcium hydride.

General Procedure for the Coupling of Hydrazones with Aldehydes and Ketones. To a solution of hydrazone **1** (1.0 mmol) in dichloroethane (5 mL) at −30 °C was added Al(CH$_3$)$_3$ (1.0 mL of a 2 M solution in hexane, 2.0 mmol, 2.0 equiv). The cold bath was removed and the resulting solution was stirred 5 min at room temperature under inert atmosphere. The reaction mixture was cooled at −30 °C and the carbonyl compound (1.1 mmol, 1.1 equiv) was added. The resulting solution was stirred at room temperature or at reflux while TLC monitoring. The reaction mixture was quenched with a saturated aqueous solution of dipotassium L(+)-tartrate. After usual workup, the residue was purified by flash chromatography on silica gel with diethyl ether in petroleum ether as eluent.

***N-sec*-Butyl-*N*′-(4-chlorobenzylidene)-*N*-phenylhydrazine (3a).** Reagents: **1a** (230 mg, 1.0 mmol) and propionaldehyde (80 μL, 58 mg, 1.1 mmol, 1.1equiv). The reaction mixture was stirred at room temperature for 24 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 260 mg (91%) of **3a** as a yellow oil. ^{1}H NMR δ 7.48−7.44 (m, 4H), 7.29−7.22 (m, 6H), 3.71 (sext, J = 7.13 Hz, 1H), 2.00−1.94 (m, 1H), 1.62−1.59 (m, 1H), 1.34 (d, J = 6.6 Hz, 3H), 1.04 (t, J = 7.4 Hz, 2H). ^{13}C NMR δ 145.0, 136.2, 132.7, 131.5, 129.9, 128.9, 127.7, 127.0, 126.5, 63.8, 31.4, 19.3, 11.9. IR (cm^{-1}) 2930, 1654, 1610, 1560, 1507, 1495, 1490, 1453, 1154, 1092, 1011, 845, 752, 698. MS (CI, NH$_3$) *m*/*z* 287 (M$^+$), 257. Anal. Calcd for $C_{17}H_{19}ClN_2$: C, 71.19; H, 6.68. Found: C, 71.11; H, 6.55.

***N*′-(4-Chlorobenzylidene)-*N*-[1-(4-chlorophenyl)ethyl]-*N*-phenylhydrazine (3b).** Reagents: **1a** (230 mg, 1.0 mmol) and *p*-chlorobenzaldehyde (154 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at reflux for 4 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether as eluent to afford 339 mg (92%) of **3b** as a red oil. ^{1}H NMR δ 7.51−7.05 (m, 14H), 4.99 (q, J = 7.0 Hz, 1H), 1.77 (d, J = 7.0 Hz, 3H). ^{13}C NMR δ 145.1, 141.5, 135.7, 136.4, 129.9, 129.0, 128.9, 127.2, 126.6, 63.8, 20.2. IR (cm^{-1}) 2900, 1557, 1497, 1147, 1088, 1011, 822, 752, 725, 699, 576, 530. MS (CI, NH$_3$) *m*/*z* 370 (M$^+$), 317. Anal. Calcd for $C_{21}H_{18}Cl_2N_2$: C, 68.30; H, 4.91. Found: C, 68.61; H, 5.11.

***N*′-(4-Chlorobenzylidene)-*N*-(1-methyl-3-phenylallyl)-*N*-phenylhydrazine (3c).** Reagents: **1a** (230 mg, 1.0 mmol) and cinnamaldehyde (138 μL, 145 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at reflux for 4 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether as eluent to afford 339 mg (94%) of **3c** as a yellow oil. ^{1}H NMR δ 7.55−7.29 (m, 15H, CH), 6.54 (s, 2H, CH), 4.72−4.66 (m, 1H, CH), 1.77 (d, J = 6.8 Hz, 3H). ^{13}C NMR δ 145.3, 137.5, 135.9, 133.3, 131.7, 130.8, 129.9, 129.0, 127.9, 127.3, 126.9, 126.6, 126.3, 62.4, 19.4. IR (cm^{-1}) 2923, 1652, 1558, 1506, 1490, 1453, 1090, 1012, 965, 745, 692, 668, 547, 529. MS (CI, NH$_3$) *m*/*z* 360 (M$^+$), 346, 231. Anal. Calcd for $C_{23}H_{21}ClN_2$: C, 76.55; H, 5.87. Found: C, 76.38; H, 5.87.

***N-sec*-Butyl-*N*′-(4-chlorobenzylidene)-*N*-methylhydrazine (3d).** Reagents: **1b** (169 mg, 1.0 mmol) and propionaldehyde (80 μL, 58 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 13 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 184 mg (82%) of **3d** as a yellow oil. ^{1}H NMR δ 7.49 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.11 (s, 1H), 3.44 (sext, J = 4.5 Hz, 1H), 2.84

(s, 3H), 1.77−1.74 (m, 1H), 1.54−1.50 (m, 1H), 1.17 (d, J = 6.6 Hz, 3H), 0.94 (t, J = 6.5 Hz, 3H). ^{13}C NMR δ 136.9, 132.2, 128.9, 127.9, 127.0, 64.7, 34.5, 28.1, 18.0, 11.8. IR (cm^{-1}) 1653, 1558, 1539, 1506, 1456, 667. MS (IC, NH_3) m/z 225 (M^+), 195. Anal. Calcd for $C_{12}H_{17}ClN_2$: C, 64.13; H, 7.62. Found: C, 64.35; H, 7.51

***N′*-(4-Chlorobenzylidene)-*N*-[1-(4-chlorophenyl)ethyl]-*N*-methylhydrazine (3e).** Reagents: **1b** (169 mg, 1.0 mmol) and *p*-chlorobenzaldehyde (154 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at reflux for 3 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 225 mg (73%) of an inseparable mixture of two diastereomers as a yellow oil. Major isomer: ^{1}H NMR δ 7.55 (d, J = 8.5 Hz, 2H), 7.36−7.25 (m, 6H), 7.17 (s, 1H), 4.62 (q, J = 10.9 Hz, 1H), 2.69 (s, 3H), 1.67 (d, J = 6.9 Hz, 3H). ^{13}C NMR δ 140.9, 136.4, 133.3, 132.8, 129.1, 129.0, 127.2, 127.0, 65.7, 35.7, 19.2. Minor isomer: ^{1}H NMR δ 7.55 (d, J = 8.5 Hz, 2H), 7.36−7.25 (m, 6H), 7.17 (s, 1H), 4.89 (q, J = 10.9 Hz, 1H), 2.69 (s, 3H), 1.50 (d, J = 6.9 Hz, 3H). ^{13}C NMR δ 140.9, 136.4, 133.3, 132.8, 129.1, 129.0, 127.2, 127.0, 70.1, 35.7, 25.7. IR (cm^{-1}) 2975, 1652, 1558, 1506, 1489, 1471, 1098, 1012, 828, 668, 551. MS (CI, NH_3) m/z 307 (M^+). Anal. Calcd for $C_{23}H_{21}ClN_2$: C, 62.55; H, 5.25. Found: C, 62.78; H, 5.67.

***N′*-(4-Chlorobenzylidene)-*N*-[1-furan-2-ylethyl)-*N*-methylhydrazine (3f).** Reagents: **1b** (169 mg, 1.0 mmol) and furfural (91 μL, 106 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 7 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 152 mg (58%) of an inseparable mixture of two diastereomers as a yellow oil. Major isomer: ^{1}H NMR δ 7.53 (d, J = 8.5 Hz, 2H), 7.38 (s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.22 (s, 1H), 6.35−6.34 (m, 1H), 6.22−6.21 (m, 1H), 4.85 (q, J = 7.0 Hz, 1H), 2.75 (s, 3H), 1.58 (d, J = 7.0 Hz, 3H). ^{13}C NMR 155.9, 142.2, 136.2, 132.9, 129.0, 127.1, 110.4, 107.1, 60.3, 34.0, 16.3. Minor isomer: ^{1}H NMR δ 7.53 (d, J = 8.5 Hz, 2H), 7.38 (s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.22 (s, 1H), 6.35−6.34 (m, 1H), 6.22−6.21 (m, 1H), 4.62 (q, J = 7.0 Hz, 1H), 2.69 (s, 3H), 1.67 (d, J = 7.0 Hz, 3H). ^{13}C NMR 155.9, 142.2, 136.2, 132.9, 129.0, 127.1, 110.4, 105.5, 64.0, 34.0, 19.5. IR (cm^{-1}) 2980, 1588, 1554, 1399, 1147, 1087, 1058, 1011, 918, 883, 822, 602. MS (CI, NH_3) m/z 263 (M^+). Anal. Calcd for $C_{14}H_{55}ClN_2O$: C, 64.00; H, 5.75. Found: C, 64.12; H, 5.85.

***N′*-(4-Chlorobenzylidene)-*N*-methyl-*N*-(1-methylcyclohexyl)hydrazine (3g).** Reagents: **1b** (169 mg, 1.0 mmol) and cyclohexanone (114 μL, 108 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 6 h. After usual workup, the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 103 mg (39%) of **3b** as a yellow oil. ^{1}H NMR δ 7.50 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.19 (s, 1H), 2.80 (s, 3H), 2.18−2.14 (m, 2H), 1.63−1.47 (m, 6H), 1.05 (s, 3H). ^{13}C NMR δ 137.4, 132.0, 129.0, 127.5, 127.0, 61.7, 36.8, 31.0, 26.4, 24.2, 22.6. IR (cm^{-1}) 2927, 2854, 1699, 1652, 1581, 1553, 1396, 1360, 1284, 1260, 1160, 993, 867, 817, 708, 668, 813, 528. MS (CI, NH_3) m/z 265 (M^+). Anal. Calcd for $C_{19}H_{25}ClN_2$: C, 68.04; H, 7.99. Found: C, 68.07; H, 7.92.

***N*-[1,1-Bis-(4-fluorophenyl)ethyl]-*N′*-(4-chlorobenzylidene)-*N*-methylhydrazine (3h).** Reagents: **1b** (169 mg, 1.0 mmol) and 4,4′-difluorobenzophenone (240 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 6 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 123 mg (32%) of **3h** as a yellow oil. ^{1}H NMR δ 7.39−7.22 (m, 10H), 7.03 (t, J = 8.7 Hz, 5H), 2.71 (s, 3H), 1.69 (s, 3H). ^{13}C NMR δ 163.1, 160.7, 141.1, 141.0, 136.5, 132.9, 129.9, 129.8, 129.0, 128.9, 115.2, 115.0, 71.9, 35.2, 23.1. IR (cm^{-1}) 2988, 1600, 1554, 1506, 1230, 1161, 1087, 832, 604. MS (CI, NH_3) m/z 386 (MH^+), 384, 306, 217, 170. Anal. Calcd for $C_{22}H_{19}ClF_2N_2$: C, 68.66; H, 4.98. Found: C, 69.25; H, 5.26.

***N*-[1-(4-Chlorophenyl)ethyl]-*N*-methyl-*N′*-(3-phenylpropylidene)hydrazine (3i).** Reagents: **1c** (162 mg, 1.0 mmol) and *p*-chlorobenzaldehyde (154 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 48 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 143 mg (43%) of **3i** as a yellow oil. ^{1}H NMR δ 7.36−7.23 (m, 9H), 6.64 (t, J = 5.0 Hz, 1H), 4.49 (q, J = 6.9 Hz, 1H), 2.90 (t, J = 7.7 Hz, 2H), 2.71−2.60 (m, 2H), 2.43 (s, 3H), 1.54 (d, J = 6.9 Hz, 3H). ^{13}C NMR δ 142.1, 140.8, 136.3, 133.1, 129.3, 128.9, 128.8, 128.6, 126.3, 64.8, 35.3, 34.3, 33.5, 17.8. IR (cm^{-1}) 2904, 1601, 1490, 1453, 1089, 1013, 831, 746, 698, 635, 620, 607 cm^{-1}. MS (CI, NH_3) m/z 302 (MH^+), 301 (M^+), 300, 295. Anal. Calcd for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04. Found: C, 71.55; H, 7.12

***N′*-Benzhydrylidene-*N*-*sec*-butyl-*N*-phenylhydrazine (3j).** Reagents: **1d** (272 mg, 1.0 mmol) and propionaldehyde (80 μL, 58 mg, 1.1 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 72 h. After usual workup the residue was purified by flash column chromatography with diethyl ether (5%) in petroleum ether to afford 194 mg (59%) of **3j** as a yellow oil. ^{1}H NMR δ 7.65−7.60 (m, 4H), 7.38−7.28 (m, 6H), 7.13−7.07 (m, 3H), 6.96 (t, J = 7.3 Hz, 1H), 6.88−6.74 (m, 1H), 3.50 (sext, J = 7.6 Hz, 1H), 2.02 (sept, J = 7.4 Hz, 1H), 1.72 (sept, J = 7.0 Hz, 1H), 1.31 (d, J = 6.5 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 158.1, 151.2, 145.0, 140.0, 130.2, 129.7, 129.6, 129.5, 129.3, 128.1, 128.7, 128.5, 128.3, 127.8, 127.0, 124.0, 122.9, 120.6, 113.4, 66.6 (CH), 28.9, 17.0, 12.3. IR (cm^{-1}) 3001, 2945, 2866, 1518, 1473, 1406, 1342, 1199. MS (CI, NH_3) m/z 328 (M^+), 298, 273, 180. Anal. Calcd for $C_{23}H_{24}N_2$: C, 84.11; H, 7.37. Found: C, 83.99; H, 7.05

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