Synthesis of *N*-(α-Methoxyalkyl) Amides from Imidates[1]

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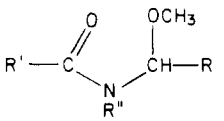
Two general routes from imidates to *N*-(α-methoxyalkyl) amides (e.g., R'CONHCH(OCH_3)R, 1) are reported. The first involves acylation of the imidate on nitrogen with an acyl chloride, followed by reduction with sodium borohydride. In the second, an aldehyde is converted, via its methyl acetal, to an α-chloro methyl ether, which is used to alkylate the imidate. Further treatment with pyridinium chloride in dry Me_2SO yields 1. Thirteen examples are reported.

N-(α-Methoxyalkyl) amides 1 occur both in nature (e.g., the insect toxin pederin and its derivatives[2]) and in a number of synthetic herbicides (e.g., Alachlor).[3] Several synthetic routes to these compounds are known, but none are very general. For example, aromatic aldehydes (and



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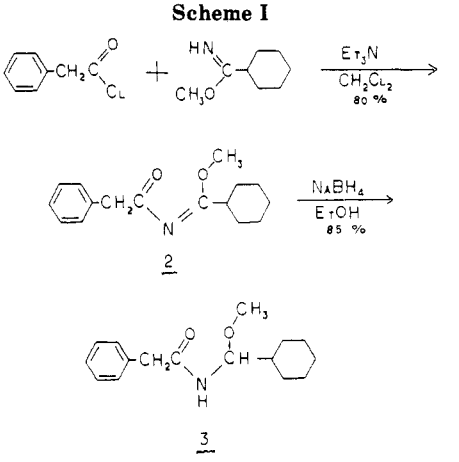
others without an α-hydrogen) react with primary amides to yield arylidene bis(amides), which can be converted to 1 (R = aryl) by pyrolysis and treatment of the resulting acyl imine with methanol.[4] Strongly electron-deficient aldehydes such as chloral or glyoxylic acid add amides to form stable carbinol amides, which can be converted to 1 (R = EWG).[5] In addition, there are a variety of routes to 1 with R = H, derivatives of formaldehyde.[6]

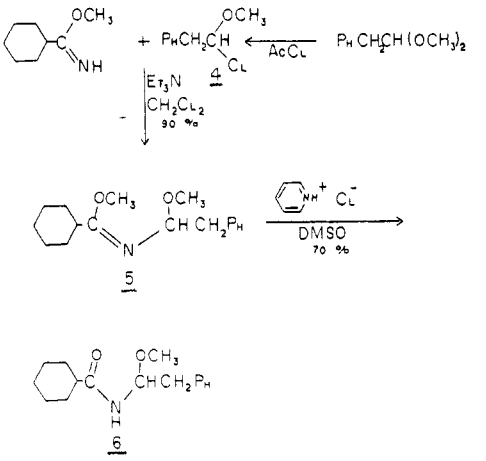
We report here two more general routes to this family of compounds and specifically to those derivatives in which R'' = H. These syntheses, which arose out of synthetic programs aimed at the total synthesis of pederin,[7] have in common the use of an imidate as one starting material. Schemes I and II illustrate the two routes.

The approach of Scheme I begins with the known[8] acylation of imidates. The resulting acyl imidates are reasonably stable substances, generally easily purified by

Scheme I



Scheme II



distillation and stable to prolonged storage. They can be efficiently reduced[1,9] with alcoholic sodium borohydride to provide 1 (R'' = H). The reduced compounds, solids in most of the cases reported here, are also easily handled materials, though they hydrolyze readily under acidic conditions.

Scheme II arose out of a desire to use an aldehyde as the starting material for the aza acetal portion of the product. Scheme I would have required that the aldehyde be oxidized and converted to an imidate, unnecessary steps if a more direct route could be developed. Although neither aldehydes nor acetals reacted cleanly and directly

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Table I. Physical and Spectroscopic Data for Compounds of Type 1 (R″ = H)

compd	R′	R	method	yield, %	mp, °C [bp, °C]	infrared bands,[a] cm^{-1}	proton NMR, δ (J, Hz)
3	benzyl	cyclohexyl	1, 2	68	111–113	3420, 1673, 1500, 1453, 1075 (a)	7.37 (m, 5H), 5.53 (d, J = 10, 1 H), 4.84 (d, d, J = 6, 10, 1 H), 3.62 (s, 2H), 3.26 (s, 3 H), 1.9–0.8 (m, 11 H)
6[c]	cyclohexyl	benzyl	2	63	130.5–131.7	3290, 1650, 1550, 1117, 700 (b)	7.33 (s, 5 H), 5.45 (d, t, J = 10, 6, 1 H), 5.85 (br d, 1 H), 3.34 (s, 3 H), 2.96 (d, J = 6, 2 H), 2.4–1.1 (br m, 11 H)
7	methyl	phenyl	1	34	86.5–89	3300, 1655, 1540, 1100, 955, 697 (b)	7.39 (s, 5 H), 7.1 (br d, 1 H), 6.07 (d, J = 9, 1 H), 3.4 (s, 3 H), 1.95 (s, 3 H)
8[c]	ethyl	phenyl	1	60	102.5–103.5	3290, 1650, 1530, 1100, 695 (b)	7.45 (br s, 5 H), 6.25 (br, 2 H), 3.43 (s, 3 H), 2.25 (q, 2 H), 1.18 (t, 3 H)
9	phenyl	phenyl	1	55	102–104[b]	3300, 1644, 1515, 1095, 696 (b)	79.8 (m, 2 H), 7.35 (m, 8 H), 6.55 (br d, 1 H), 6.40 (d, 1 H), 3.52 (s, 3 H)
10[c]	methyl	benzyl	1	33	98–99.5	3300, 1650, 1530, 1125, 1080, 710 (b)	7.33 (s, 5 H), 5.5 (br m, 2 H), 3.34 (s, 3 H), 2.94 (d, 2 H), 1.96 (s, 3 H)
11	phenyl	benzyl	1	32	136–137.5	3330, 1640, 1520, 1109, 700 (b)	8.2–7.0 (m, 11 H), 6.2 (br s, 1 H), 5.65 (m, 1 H), 3.33 (s, 3 H), 3.10 (d, J = 7, 2 H) (CD_3COCD_3)
12	ethyl	propyl	1	24	[70–72 (0.25 torr)]	3300, 1650, 1530, 1080 (c)	6.25 (br, 1 H), 5.16 (d, t, J = 7, 9, 1 H), 3.34 (s, 3 H), 2.31 (q, 2 H), 1.8–1.3 (m, 4 H), 1.19 (t, 3 H), 0.92 (t, 3 H)
13	phenyl	propyl	1	34	77.5–79.5	3300, 1650, 1525, 1100, 700 (c)	7.9 (m, 2 H), 7.45 (m, 3 H), 6.85 (br, 1 H), 5.38 (m, 1 H), 3.40 (s, 3 H), 1.9–0.8 (m, 7 H)
14[c]	*p*-anisyl	benzyl	1	85	152–153	3315, 1645, 1260, 1180, 1070, 842 (b)	7.75 (d, J = 9, 2 H), 7.35 (s, 5 H), 6.95 (d, J = 9, 2 H), 6.35 (br m, 1 H), 5.65 (d, t, J = 10, 5, 1 H), 3.83 (s, 3 H), 3.38 (s, 3 H)
15[c]	benzyl	*tert*-butyl	2	20	88–89.7	3300, 1650, 1520, 1102, 705 (b)	7.40 (s, 5 H), 5.5 (br, 1 H), 3.78 (d, J = 10, 1 H), 3.66 (s, 2 H), 3.28 (s, 3 H), 0.77 (s, 9 H)
16	cyclohexyl	*tert*-butyl	2	46	139–140	3290, 1650, 1540, 1109 (b)	5.6 (br, 1 H), 4.83 (d, J = 10, 1 H), 3.33 (s, 3 H), 2.1–1.1 (m, 11 H), 0.91 (s, 9 H)
17[c]	phenyl	*tert*-butyl	2	41	101–102.5	3330, 1640, 1520, 1100, 694 (b)	7.9 (m, 2 H), 7.7 (m, 3 H), 6.5 (br, 1 H), 5.08 (d, J = 10, 1 H), 3.42 (s, 3 H), 1.00 (s, 9 H)

[a] (a) $CHCl_3$ solution, (b) KBr pellet, (c) neat liquid or melt. [b] Reference 4. [c] Satisfactory combustion analytical data were reported for this compound.

with the amides we chose, conversion of the aldehyde to a chloro ether[10] provided a material that would alkylate imidates. We chose to prepare the chloro ethers by treatment of the corresponding methyl acetals with acetyl chloride.[10a] This conversion was rapid and complete and could be followed easily by NMR spectroscopy. Furthermore, both methyl acetate, the other reaction product, and excess acetyl chloride were easily removed in vacuo. In a few cases the chloro ether was purified by distillation; in most cases it was used in crude form because attempted purification led to an enol ether or other dehydrohalogenation products. The alkylation reactions were carried out by adding the appropriate chloro ether slowly to a cold equimolar mixture of the imidate and triethylamine or to a 2:1 mixture of triethylamine and the imidate hydrochloride. Alkylation of the imidate went smoothly and in high yield. Since hydrolysis of imidates in strong base usually leads to the corresponding amide, while acidic hydrolysis is more likely to yield esters,[11] an attempt was first made to carry out basic hydrolysis of the alkylated imidate in methanolic KOH. In one case (3) that was successful; in other cases, however, the hydrolysis produced complex mixtures, so an alternate route was sought.

Although imidate hydrochlorides are quite stable in $CDCl_3$ solution, attempts to obtain NMR spectra in Me_2SO-d_6 solution were not as successful. The salts were not stable in this solvent but reacted to produce, among other products, the corresponding amide and chloromethane. Thus we explored the protonation and demethylation of our intermediate alkylated imidates (e.g., 5) in Me_2SO. While most carboxylic acids, including chloroacetic acid, are incapable of protonating the imidate nitrogen in this solvent, as is the triethylammonium ion generated in the alkylation reaction itself, pyridinium ion is sufficiently acidic. This is consistent with the report[12] that the acidities of oxygen acids decrease relative to those of nitrogen acids in Me_2SO. Thus, addition of pyridinium hydrochloride to an NMR sample of 5 in Me_2SO-d_6 produced a rapid series of spectral changes entirely consistent with protonation of the imidate on nitrogen followed by rapid displacement of its *O*-methyl group. The initial nucleophile may be Cl^-, pyridine, or Me_2SO, but eventually most of the methyl group was accounted for in the chloromethane peak at δ 3.07.

This reaction has been used to prepare several of the compounds in Table I. We initially hoped to run both reactions of Scheme II in Me_2SO, but that fails. The chloro ethers used in the first step appear to ionize rapidly in this solvent, but trapping of the ion by the imidate is slower than methyl transfer to the solvent, which results in aldehyde formation. At best, the reaction yields a complex

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mixture containing the desired product in low yield. The method of choice is therefore to do the preparation in two steps as shown.

Table I provides data for 13 compounds prepared by one or both of these routes. The yields shown have not, in most cases, been optimized; some represent only single experiments. They are based on starting imidate and report amounts of material isolated and purified by distillation, recrystallization, or sublimation. NMR experiments show that the reactions are clean and the yields high in almost every case.

Experimental Section

General. Reactions were carried out under a nitrogen or argon atmosphere. Infrared spectra were recorded on a Perkin-Elmer Model 337 or Model 399 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-390 or Perkin-Elmer R-12B instrument in deuteriochloroform. Mass spectra were recorded on an AEI-MS-902 instrument. Commercially available solvents and chemicals were used and routine purification procedures carried out where necessary. The procedures described below illustrate general procedures and are typical of those used to prepare all the compounds in Table I. Satisfactory analytical data were obtained for each of the compounds listed in Table I.

Methyl Phenylacetimidate Hydrochloride. A 50-mL pear-shaped flask was fitted with a reflux condenser, a small-diameter gas inlet tube reaching to the bottom of the flask, and a gas outlet tube terminating in a $CaSO_4$ drying tube. The flask was charged with 2.85 mL (2.90 g, 24.7 mmol) of phenylacetonitrile, 1.00 mL (0.80 g, 24.7 mmol) of dry methanol, and 7 mL of anhydrous ether and cooled in an ice bath. HCl, dried by passing it through concentrated sulfuric acid, was passed slowly into the solution until no more was absorbed. The flask was disconnected, stoppered tightly, and stored at −10 °C overnight. The solid that formed was isolated by filtration under argon, washed with dry ether, and dried first under a stream of argon and then in vacuo for 4 h. The free-flowing white powder (4.30 g, 23.2 mmol, 94%) was stored in a desiccator over $CaSO_4$: NMR ($CDCl_3$, 90 MHz) δ 7.32 (m, 5 H), 4.23 (s, 3 H), 4.05 (s, 2 H). Other imidate salts used were prepared similarly.

Methyl *N*-(Phenylacetyl)cyclohexanecarboximidate (2). Methyl cyclohexanecarboximidate (0.45 g, 3.18 mmol) was dissolved in 6 mL of CH_2Cl_2 containing 0.55 mL (0.38 g, 3.8 mmol) of freshly distilled triethylamine. To this mixture, cooled in an ice/salt bath, was added (dropwise over 30 min) a solution of 0.43 mL (0.50 g, 3.26 mmol) of phenylacetyl chloride in 4 mL of CH_2Cl_2. The mixture was stirred and kept at or below 0 °C for an additional 2 h and then at room temperature for 16 h. The solution was filtered to remove triethylammonium chloride and evaporated. The moist solid residue was suspended in pentane and ether and the remaining amine salt removed by filtration. The yellow oil that remained on evaporation of the filtrate represented 0.66 g (2.5 mmol, 80%) of **2**: IR (neat) 1690 (sh), 1661, 1490, 1452, 1295, 1240, 1144, 1050 cm^{-1}; NMR δ 7.30 (narrow m, 5 H), 3.71 (s, 2 H), 3.61 (s, 3 H), 2.3–0.8 (11 H).

***N*-(Methoxycyclohexylmethyl)phenylacetamide (3).** A solution of the acyl imidate **2** (0.66 g, 2.5 mmoles) in 7 mL of absolute ether was added dropwise over 30 min to a cold (ice/salt bath) mixture of 0.107 g (2.8 mmol) of $NaBH_4$ in 3 mL of absolute ethanol. The mixture was kept cold an additional 2.5 h and then warmed to room temperature over 0.5 h. The reaction mixture was partitioned between 3% $NaHCO_3$ (aqueous) and CH_2Cl_2, the aqueous layer was extracted with three portions of CH_2Cl_2, and the combined organic layers were washed with 3% $NaHCO_3$ and water before drying over K_2CO_3. Evaporation left **3** as a white solid, 0.57 g (2.17 mmol, 85%). A small sample was recrystallized twice from cyclohexane: mp 110.5–113 °C; IR ($CHCl_3$) 3420, 1673, 1500, 1453, 1078 cm^{-1}; NMR δ 7.37 (m, 5 H), 5.53 (br d, J = 10 Hz, 1 H), 4.84 (d, d, J = 6, 10 Hz, 1 H), 3.62 (s, 2 H), 3.26 (s, 3 H), 1.9–0.8 (11 H); MS [CI] (methane), m/e (relative intensity) 262 (M + 1, 2.63), 230 (100), 112(27), [EI] 246 (M − CH_3, 1), 229 (M − CH_3OH, 11), 178 (M − C_6H_{11}, 41), 95 (41), 91 (63), 60 (100).

Physical data for other products formed in the same way (**7**–**14**) are included in Table I.

1-Chloro-1-methoxy-2-phenylethane (4). Phenylacetaldehyde dimethyl acetal was quantitatively converted to the chloro ether by warming (45–50 °C) in the presence of 1 equiv of acetyl chloride for approximately 1 h (until the reaction was complete by NMR analysis of aliquots) and evaporation (aspirator pressure) of the volatile byproduct methyl acetate: NMR δ 7.33 (s, 5 H), 5.66 (t, J = 5.5 Hz, 1 H), 3.49 (s, 3 H), 3.31 (d, J = 5.5 Hz, 2 H).

Similarly prepared were α-chloro-α-methoxytoluene [NMR δ 3.67 (s, 3 H), 6.50 (s, 1 H), 7.46 (m, 5 H)], 1-chloro-1-methoxy-2,2-dimethylpropane [bp 45–47 °C (40 torr); NMR δ 1.04 (s, 9 H), 3.54 (s, 3 H), 5.26 (s, 1 H)], and methyl α-chlorocyclohexylmethyl ether [NMR δ 0.9–2.10 (11 H), 3.50 (s, 3 H), 5.32 (d, J = 4 Hz, 1 H)].

Methyl *N*-(1-Methoxy-2-phenylethyl)cyclohexanecarboximidate (5). A dry 50-mL three-neck flask was equipped with a serum cap in one neck and a reflux condenser and pressure-equalized dropping funnel in the others. Methyl cyclohexanecarboximidate hydrochloride (474.8 mg, 2.68 mmol) was dissolved in this flask in 20 mL of dry CH_2Cl_2 and the system cooled to 0 °C. Triethylamine (0.37 mL, 2.65 mmoles) was added to the solution via syringe, and the solution was stirred for 15 min. Then half of a solution of **4** (0.459 g, 2.69 mmol) in 10 mL of CH_2Cl_2 was added dropwise over 25 min. Another portion of Et_3N (0.37 mL) was added, followed by the remainder of the solution of **4**. The mixture was allowed to warm slowly to room temperature and then was refluxed for 40 min. The resulting solution was washed with water, 2% Na_2CO_3, and half-saturated brine before being dried (K_2CO_3) and evaporated to a clear, bright yellow oil (**5**) (663 mg, 2.4 mmol, 90%): NMR δ 7.27 (br s, 5 H), 4.80 (d, d, J = 4, 7 Hz, 1 H), 3.65 (s, 3 H), 3.25 (s, 3 H), 2.95 (m, 2 H), 2.4–0.9 (11 H).

***N*-(1-Methoxy-2-phenylethyl)cyclohexanecarboxamide (6).** A sample of **5** (331 mg, 1.20 mmol) was dissolved in 1 mL of Me_2SO-d_6 in an NMR tube. After a spectrum was obtained to verify the purity of the starting material, 140 mg (1.21 mmol) of dry pyridinium hydrochloride was added. The salt dissolved rapidly and completely, and the spectrum of the sample changed rapidly. After 2 h in the probe (temperature approximately 35 °C) no further change was observed, and the sample was partitioned between CH_2Cl_2 and 3% aqueous Na_2CO_3. The organic layer was washed with additional water, 3% Na_2CO_3, and half-saturated brine, dried over anhydrous K_2CO_3, and evaporated to leave 220 mg (0.84 mmol, 70%) of a powdery solid (**6**). After recrystallization from cyclohexane the fine needles melted at 130.5–131.7 °C: NMR δ 7.33 (br s, 5 H), 5.85 (br d, 1 H), 5.45 (d, t, J = 10, 6 Hz, 1 H), 3.34 (s, 3 H), 2.96 (d, J = 6 Hz, 2 H), 2.4–1.1 (11 H); IR (KBr pellet) 3290, 1650, 1550, 1117, 700 cm^{-1}.

Physical properties of other compounds (**3**, **15**–**17**) prepared this way are listed in Table I.

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Registry No. **2**, 99355-51-8; **3**, 99355-52-9; **4**, 99355-53-0; **5**, 99355-54-1; **6**, 99355-55-2; **7**, 39057-61-9; **8**, 99355-56-3; **9**, 10387-93-6; **10**, 4561-36-8; **11**, 99355-57-4; **12**, 99355-58-5; **13**, 99355-59-6; **14**, 99355-60-9; **15**, 99355-61-0; **16**, 99355-62-1; **17**, 99355-63-2; $PhCH_2C(OMe)$=NH·HCl, 39496-45-2; $PhCH_2CN$, 140-29-4; $PhCH_2C(O)Cl$, 103-80-0; $PhCH_2CH(OMe)_2$, 101-48-4; PhCHClOMe, 35364-99-9; $(CH_3)_3CCHClOMe$, 61976-71-4; $PhCH(OMe)_2$, 1125-88-8; $(CH_3)_3CCH(OMe)_2$, 62617-39-4; $CH_3C(OMe)$=NH, 14777-29-8; $CH_3CH_2C(OMe)$=NH, 20258-22-4; PhC(OMe)=NH, 7471-86-5; p-$MeOC_6H_4C(OMe)$=NH, 95064-52-1; $CH_3(CH_2)_2CH(OMe)Cl$, 5760-37-2; methyl cyclohexanecarboximidate, 66493-03-6; methyl cyclohexylchloromethyl ether, 59039-25-7; 1,1-dimethoxycyclohexane, 933-40-4.