References and Notes

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(2) Ecole Superieure de Physique et de Chimie Industrielles de la Ville de Paris.
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A One-Carbon Homologation of Carbonyl Compounds to Carboxylic Acids, Esters, and Amides

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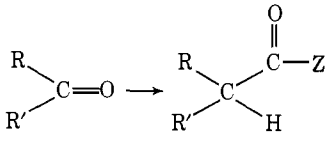
Abstract: An efficient sequence for the one-carbon homologation of aldehydes and ketones to carboxylic acids **2**, esters **3**, and amides **4** involves (1) the Horner–Emmons modification of the Wittig reaction using diethyl *tert*-butoxy(cyano)methylphosphonate $(EtO)_2POCH(CN)O$-*t*-Bu to afford α-*tert*-butoxyacrylonitriles **15**, (2) the cleavage of the *tert*-butyl ether in **15** using zinc chloride in refluxing acetic anhydride to afford α-acetoxyacrylonitriles **16**, and (3) the hydroxide, alkoxide, or amine solvolysis of **16** to afford **2**, **3**, or **4**, respectively, in 57–88% overall yield from the carbonyl compounds.

We have sought to develop useful methodology for the one-carbon homologation of carbonyl compounds **1** to carboxylic acids **2**, esters **3**, and amides **4**. To achieve this versatility, we required the generation of a transitory acyl intermediate capable of intercepting various nucleophiles to form the desired acyl derivatives. We now wish to report an efficient solution to this problem which relies on the liberation of a masked acyl cyanide.[1]



1 **2**, Z = OH; **3**, Z = OR″; **4**, Z = NR″$_2$

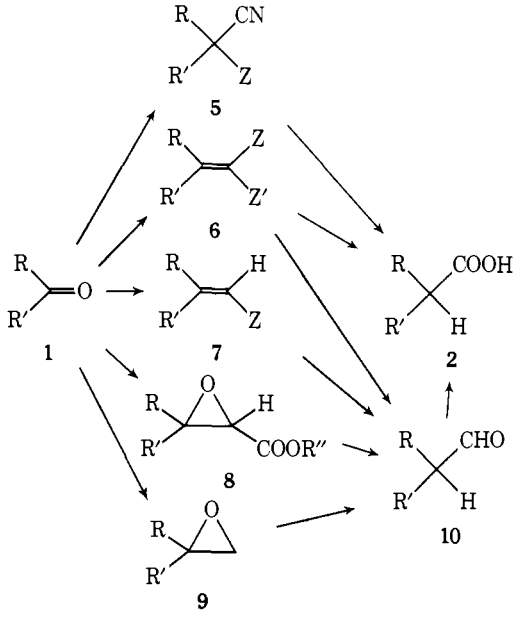
Available methodology for the transformation of carbonyl compounds **1** to carboxylic acids **2** has relied on the intermediacy of (a) cyanohydrins[2] **5** (Z = OH), (b) nitriles[3] **5** (Z = H), (c) ketene thioacetals[4] **6** (Z, Z′ = SCH_3, SC_6H_5, or $S(CH_2)_3S$), (d) α,β-unsaturated sulfones[5] **6** (Z = $SO_2C_6H_5$ or $SO_2C_6H_4$-*p*-CH_3; Z′ = NHCHO), (e) α,β-unsaturated phosphonates[6] **6** (Z = $PO(OC_2H_5)_2$; Z′ = $N(CH_3)_2$), (f) enol

Table I. One-Carbon Homologation of Carbonyl Compounds **1** to Carboxylic Acids **2**

	Aldehyde or ketone		Isolated yields, %		
	R	R′	**15**	**16**	**2**
a	n-C_6H_{13}	H	99[d]	*a*	97
b	$CH(CH_3)Ph$	H	87	82	97
c	Ph	H	94[d]	94	100
d	$PhCH{=}CH$	H	96	82	97[b,c]
e	CH_2CH_2Ph	CH_2CH_2Ph	84[d]	90	99
f	CH_3	Ph	93[d]	94	96[c]
g	Ph	Ph	86[d]	95	100[c]
h	$-(CH_2)_5-$		89[d]	88	95
i	2-Methylcyclohexanone		78	90	92[e]
j	2-Cyclohexenone		70	94	86[b,c]
k	Cholest-4-en-3-one		86	80	79[b,c]
l	Methyl levulinate		74	89	84[f]
m	5α-Androstane-3,17-dione		92	*a*	55
n	2,5-Hexanedione monoethylene ketal		83	*g*	

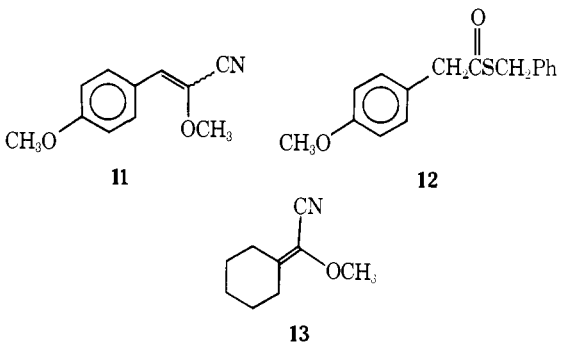
[a] Unstable to silica gel chromatography and was not isolated. [b] Isolated as a mixture of α,β- and β,γ-unsaturated isomers. [c] Hydrolysis step required reflux temperatures. [d] S. E. Dinizo, R. W. Freerksen, W. E. Pabst, and D. S. Watt, *J. Org. Chem.*, **41**, 2846 (1976). [e] Isolated as a mixture of cis and trans isomers. [f] Isolated as the diacid. [g] Reaction fails since ethylene ketal will not survive reaction conditions.

ethers[7] **7** (Z = OCH_3 or OC_6H_4-p-CH_3), (g) thioenol ethers[8] **7** (Z = SC_6H_5), (h) enamines[9] **7** (Z = $N(CH_2)_4$ or $N(CH_3)_2$), (i) glycidic esters[10] **8**, or (j) epoxides[11] **9** to introduce the requisite one-carbon unit. Most of these approaches converge on an intermediate aldehyde **10** which is subsequently oxidized to the carboxylic acid **2**. In addition, the conversion of carbonyl compounds **1** to carboxylic esters **3** and amides **4** has invariably involved the intermediacy of carboxylic acids **2**.[12]



Despite the array of methods available for the interconversion **1** → **2**, many of these methods possess limited or uncertain scope. For example, the cyanohydrin approach[2] excludes those ketones **1** (R = aryl; R′ = aryl or alkyl) which afford low yields of cyanohydrins. The α,β-unsaturated phosphonate approach[6] allows only for the one-carbon homologation of aldehydes. The ketene thioacetal approach[4] lacks an effective hydrolysis procedure[13,14] for the conversion **6** → **2**. Moreover, many of the methods cited above lack sufficient examples to evaluate accurately the scope of the method. Only the nitrile[3] and the α,β-unsaturated sulfone[5] approaches offer a general solution to the problem of converting **1** to **2**.

The α-alkoxyacrylonitrile synthon is synthetically equivalent to an acyl cyanide in which the carbonyl group is masked as an enol ether. Barton[1a] recognized this equivalence in transforming the α-methoxycinnamonitrile **11** to the thiol ester **12**



using sodium benzylthiolate to demethylate **11** as well as to trap the intermediate acyl cyanide. Accordingly, we devised a general synthesis of α-methoxyacrylonitriles from aldehydes and ketones using the Horner-Emmons modification of the Wittig reaction[15,16] of diethyl methoxy(cyano)methylphosphonate, $(EtO)_2POCH(OCH_3)CN$.[17] We were unable, however, to extend Barton's procedure to the hydrolysis of other α-methoxyacrylonitriles. For example, exposure of **13** to nucleophiles reported to effect demethylation (lithium iodide in collidine,[18] lithium n-butylthiolate in THF-HMPA[19]) failed to afford any cyclohexanecarboxylic acid **2h** or the anticipated derivatives. The acid hydrolysis of **13** likewise failed to provide **2h**.

Anticipating that a *tert*-butyl ether would be more susceptible to acid-catalyzed cleavage than a methyl ether, we again employed the phosphonate Wittig reaction of aldehydes and ketones with the sodium salt of diethyl *tert*-butoxy(cyano)-methylphosphonate[17] (**14**) to provide α-*tert*-butoxyacrylonitriles **15** in high yield (Table I). The reaction was limited, however, by the steric bulk of **14** to those ketones which possessed three or more α hydrogens.[20] Even this limitation could be turned to some advantage as the regiospecific reaction of **14** with 5α-androstane-3,17-dione illustrates.

We were again frustrated in efforts to reveal the masked acyl cyanide in **15** under a variety of acidic conditions. For example, exposure of **15f** to trifluoroacetic acid (5 equiv of 1 M TFA in dichloromethane, 25 °C, 12 h) afforded acetophenone (38% yield) but no 2-phenylpropionic acid. To circumvent this problem, we opted to replace the intractable *tert*-butyl group

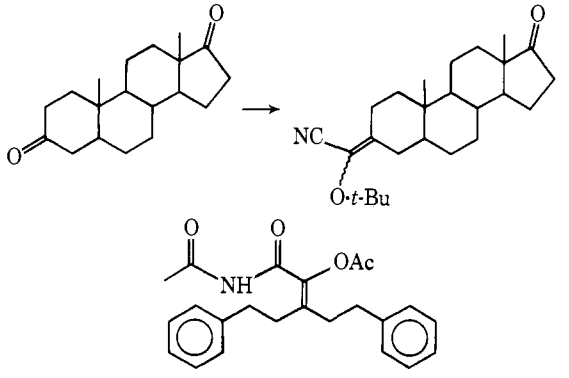
Table II. One-Carbon Homologation of Carbonyl Compounds **1** to Carboxylic Esters **3** and Amides **4**

	Aldehyde or ketone		Isolated yield,[a] %		
	R	R′	3	4	Z
e	CH_2CH_2Ph	CH_2CH_2Ph	95		OCH_3
e	CH_2CH_2Ph	CH_2CH_2Ph		100	NH_2
h	$-(CH_2)_5-$		85		OCH_3
h	$-(CH_2)_5-$			81	NH_2
h	$-(CH_2)_5-$			94	$NHCH_3$
h	$-(CH_2)_5-$			89	$N(CH_3)_2$
k	Cholest-4-en-3-one		83[b,c]		OCH_3
m	5α-Androstane-3,17-dione		60		OCH_3

[a] Isolated yields based on α-acetoxyacrylonitriles **16**. [b] Isolated as a mixture of α,β- and β,γ-unsaturated isomers. [c] Methanolysis step required reflux temperatures.

with a base-labile acetyl group.

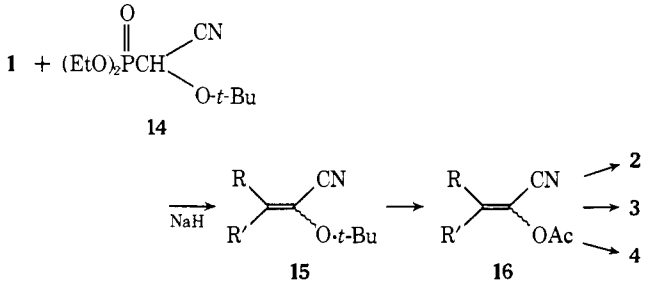
White[1b] has recently devised a synthesis of α-acetoxyacrylonitriles **16** from glycidonitriles. We found that exposure of the *tert*-butoxyacrylonitriles **15** to anhydrous zinc chloride (1.2 equiv) in acetic anhydride (2 ml/mmol of **15**, 15 min, 140 °C) furnished the α-acetoxyacrylonitriles **16** in excellent yield (Table I). Zinc chloride proved more effective than a variety of other Lewis acids tested in this connection.[21] For example, the reaction of **15e** with ferric chloride in acetic anhydride[22] furnished **16e** contaminated with the imide **17** derived from



17

the addition of acetic acid across the nitrile functionality. Finally, exposure of the α-acetoxyacrylonitriles **16** to aqueous potassium hydroxide (10 equiv in 20% aqueous methanol) provided, after acidification, the carboxylic acids **2** in excellent yield (Table I). The substitution of sodium alkoxides or amines for potassium hydroxide furnished the carboxylic esters **3** and amides **4**, respectively (Table II).

The overall sequence **1** → **2**, **3**, or **4** is reasonably efficient



14 **15** **16**

for an array of structurally diverse aldehydes and ketones. The sequence will readily accommodate the presence of carbon–carbon double bonds, aromatic rings, certain ketones,[23] and other carboxylate groups. As expected, the sequence excludes acid-labile protecting groups such as ethylene ketals. Both the scope and yields of the reported sequence eclipse many literature procedures for the one-carbon homologation of carbonyl compounds to carboxylic acids, esters, and amides.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 337 infrared spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. All ketones and aldehydes used in this study were available commercially with the exception of 1,5-diphenyl-3-pentanone (**1e**), which was prepared by the method of Conia and Gosselin.[24]

The following is a typical experimental procedure for the one-carbon homologation sequence.

***α-tert*-Butoxyacrylonitrile 15e.** The procedure of Watt[17] et al. was repeated using 238 mg of 1,5-diphenyl-3-pentanone (**1e**) to afford, after chromatography on Merck silica gel F254, 276 mg (84%) of **15e.**

Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16. Found: C, 83.00; H, 8.21.

α-Acetoxyacrylonitrile 16e. To 333 mg (1.0 mmol) of **15e** in 2 ml of distilled acetic anhydride was added 163 mg (1.2 mmol, 1.2 equiv) of anhydrous zinc chloride. The mixture was refluxed for 15 min, cooled, diluted with 50 ml of water, and extracted with three 20-ml portions of ether. The combined ether solutions were washed successively with two 25-ml portions of water and 25 ml of brine and were dried over anhydrous magnesium sulfate. The product was chromatographed on a 20 × 20 cm (2 mm thick) Merck silica gel F254 preparative layer plate in 1:1 ether–hexane. A band (R_f 0.56) was eluted to afford 287 mg (90%) of **16e:** IR (TF) 4.51 (C≡N), 5.65 (C=O), 6.08 (C=C), 6.24, and 6.32 μ (aromatic); NMR ($CDCl_3$) δ 2.11 (s, 3, $COCH_3$), 2.23–3.03 (m, 8, CH_2), and 6.97–7.48 (m, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 319 (13), 159 (47), 91 (100), and 43 (81).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63. Found: C, 79.07; H, 6.71.

Carboxylic Acid 2e. To 319 mg (1.0 mmol) of **16e** in 4 ml of methanol was added 1 ml of 10 M aqueous potassium hydroxide solution. The solution was stirred for 19 h at 25 °C, diluted with 50 ml of water, and extracted with three 20-ml portions of ether. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with three 20-ml portions of ether. The ether solutions were washed successively with 25 ml of water and 25 ml of brine and were dried over anhydrous magnesium sulfate. The solvent was evaporated to yield 266 mg (99%) of **2e:** IR (TF) 5.88 (C=O), 6.24, and 6.32 μ (aromatic); NMR ($CDCl_3$) δ 1.65–2.90 (m, 9, CH and CH_2), 7.03–7.50 (m, 10, aromatic H), and 11.51 (broad s, 1, COOH); mass spectrum (70 eV) *m/e* (rel intensity) 268 (10), 105 (29), 92 (100), and 91 (49).

An analytical sample was prepared by preparative layer chromatography on a 20 × 20 cm (2 mm thick) Merck silica gel F254 plate in 1:1 ether–hexane, R_f 0.48.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.30; H, 7.57.

Carboxylic Ester 3e (Z = OCH_3). To a solution of 250 mg (11

mmol) of sodium in 3.5 ml of methanol was added 319 mg (1.0 mmol) of **16e** in 1.5 ml of methanol. The solution was stirred for 17 h at 25 °C, diluted with 50 ml of 0.2 M hydrochloric acid, and extracted with three 20-ml portions of ether. The combined ether solutions were washed successively with 25 ml of water and 25 ml of brine and were dried over anhydrous magnesium sulfate. The product was chromatographed on a 20 × 20 cm (2 mm thick) Merck silica gel F254 preparative layer plate in 1:3 ether–hexane to afford 268 mg (95%) of **3e** (Z = OCH_3): R_f 0.59; IR (TF) 5.79 (C=O), 6.25 and 6.33 μ (aromatic); NMR ($CDCl_3$) δ 1.52–2.75 (m, 9, CH and CH_2), 3.61 (s, 3, OCH_3), and 6.88–7.44 (m, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 282 (1), 92 (16), 91 (11), 87 (20), and 43 (100).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.76; H, 7.85.

Imide[25] 17. The procedure described for the preparation of **16e** was repeated using ferric chloride instead of zinc chloride to afford **16e** contaminated with 5–10% of imide[25] **17** which was separated by thick layer chromatography: IR (KBr) 5.71, 5.85 sh, 5.92 (C=O), 6.17 and 6.25 μ (C=C and aromatic); UV (CH_3CN) λ_{max} 232 nm (ε 16 500); NMR ($CDCl_3$) δ 2.01–3.03 (m, 8, CH_2) and 2.21, 2.48, and 2.87 (three s, 6, $COCH_3$, the two high-field singlets presumably the result of *E/Z* isomerism involving imide functionality) and 7.01–7.55 (m, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 379 (1), 361 (1), 337 (15), 319 (23), 159 (72), 91 (100), and 43 (90).

An analytical sample was prepared by recrystallization from anhydrous ether, mp 99.5–100.5 °C.

Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.88; H, 6.66; N, 3.62.

Spectral Data for α-*tert*-Butoxyacrylonitriles. 15a. See ref 17.

15b (mixture of *E* and *Z* isomers): IR (TF) 4.61 (C≡N), 6.12 (C=C), and 6.25 μ (aromatic); NMR (CCl_4) δ 1.28 and 1.37 (two s, 9, $C(CH_3)_3$), 1.03–1.55 (m, 3, $CHCH_3$), 3.65–4.15 (m, 1, benzylic H), 5.80 and 5.93 (two d, 1, *J* = 11 Hz for each isomer, vinylic H), 7.20 and 7.23 (two s, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 229 (1), 173 (14), 131 (20), 105 (14), and 57 (100).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.48; H, 8.35.

15c. See ref 17.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.52; H, 7.52.

15d (mixture of *E* and *Z* isomers): IR (TF) 4.54 (C≡N), 6.19, 6.32, and 6.38 μ (C=C and aromatic); NMR ($CDCl_3$) δ 1.40 and 1.48 (two s, 9, $C(CH_3)_3$), 6.24–7.15 (m, 3, vinylic H), and 7.20–7.59 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 227 (0.3), 57 (6), and 43 (100).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.29; H, 7.59.

15f. See ref 17.

15g. See ref 17.

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91. Found: C, 82.19; H, 6.95.

15h. See ref 17.

15i (mixture of *E* and *Z* isomers): IR (TF) 4.51 (C≡N) and 6.12 μ (C=C); NMR ($CDCl_3$) δ 0.85–2.10 (m, 9, CH and CH_2), 1.07 and 1.19 (two d, 3, *J* = 5 Hz for each isomer, $CHCH_3$), 1.36 and 1.38 (two s, 9, $C(CH_3)_3$); mass spectrum (70 eV) *m/e* (rel intensity) 207 (1), 192 (7), 124 (48), and 57 (100).

15j: IR (TF) 4.53 (C≡N), 6.18 and 6.31 μ (C=C); NMR ($CDCl_3$) δ 1.40 (s, 9, $C(CH_3)_3$), 1.45–2.70 (m, 6, CH_2), and 5.92–6.75 (m, 2, vinylic H); mass spectrum (70 eV) *m/e* (rel intensity) 191 (6), 135 (74), 108 (48), 79 (38), and 57 (100).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.24; H, 8.98.

15k (mixture of *E* and *Z* isomers): mp 114–130 °C; IR (KBr) 4.15 (C≡N), 6.18 and 6.32 μ (C=C); NMR ($CDCl_3$) δ 1.41 (s, 9, $C(CH_3)_3$) and 6.07–6.30 (m, 1, vinylic H); mass spectrum (70 eV) *m/e* (rel intensity) 465 (1), 424 (27), 135 (36), and 57 (100).

Anal. Calcd for $C_{33}H_{53}NO$: C, 82.61; H, 11.13. Found: C, 82.50; H, 11.11.

15l (mixture of *E* and *Z* isomers): IR (TF) 4.52 (C≡N), 5.75 (C=O), and 6.12 μ (C=C); NMR (CCl_4) δ 1.35 and 1.38 (two s, 9, $C(CH_3)_3$), 1.79 and 1.94 (two s, 3, vinylic CH_3), 2.32–2.64 (m, 4, CH_2), 3.65 and 3.68 (two s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 210 (3), 114 (14), and 57 (100).

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50. Found: C, 63.80; H, 8.56.

15m: IR (KBr) 4.54 (C≡N), 5.75 (C=O), and 6.14 μ (C=C); NMR ($CDCl_3$) δ 0.87 and 0.92 (two s, 6, C-18 and C-19 angular CH_3) and 1.35 (s, 9, $C(CH_3)_3$); mass spectrum (70 eV) *m/e* (rel intensity) 383 (100), 328 (12), 327 (48), 300 (24), and 57 (100).

Anal. Calcd for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72. Found: C, 78.23; H, 9.72.

15n (mixture of *E* and *Z* isomers): IR (TF) 4.54 (C≡N) and 6.12 μ (C=C); NMR ($CDCl_3$) δ 1.25–1.45 (m, 12, CH_3 and $C(CH_3)_3$), 1.58–2.01 (m, 2, CH_2CH_2C=C), 1.82 and 1.94 (two s, 3, vinylic CH_3), 2.09–2.60 (m, 2, CH_2CH_2C=C), 3.95 and 3.98 (two s, 4, OCH_2CH_2O); mass spectrum (70 eV) *m/e* (rel intensity) 238 (1), 113 (31), 87 (55), 59 (16), and 57 (100).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.11; H, 9.22.

Spectral Data for α-Acetoxyacrylonitriles. 16b (mixture of *E* and *Z* isomers): IR (TF) 4.49 (C≡N), 5.62 (C=O), 6.06 (C=C), and 6.24 μ (aromatic); NMR (CCl_4) δ 1.32 and 1.43 (two d, 3, *J* = 7 Hz for each isomer, $CHCH_3$), 2.04 and 2.08 (two s, 3, $COCH_3$), 3.61–4.18 (m, 1, benzylic H), 6.11 and 6.19 (two d, 1, *J* = 10 Hz for each isomer, vinylic H), 7.19 and 7.22 (two s, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 215 (2), 173 (14), 131 (23), 103 (10), 77 (8), and 43 (100).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.38; H, 6.16.

16c (mixture of *E* and *Z* isomers): IR (TF) 4.50 (C≡N), 5.62 (C=O), 6.09 (C=C), and 6.25 μ (aromatic); NMR (CCl_4) δ 2.16 and 2.25 (two s, 3, $COCH_3$), 6.67 and 6.94 (two s, 1, vinylic H), and 7.20–7.78 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 187 (8), 145 (11), 118 (47), 90 (21), 77 (4), and 43 (100).

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85. Found: C, 70.49; H, 4.93.

16d (mixture of *E* and *Z* isomers): IR (TF) 4.51 (C≡N), 5.66 (C=O), 6.16, 6.25, and 6.37 μ (C=C and aromatic); NMR ($CDCl_3$) δ 2.19 and 2.28 (two s, 3, $COCH_3$), 6.56–7.00 (m, 3, vinylic H), and 7.18–7.60 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 213 (1), 84 (67), 43 (28).

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20. Found: C, 73.09; H, 5.26.

16f (mixture of *E* and *Z* isomers): IR (TF) 4.51 (C≡N), 5.67 (C=O), 6.22, 6.27, and 6.36 μ (C=C and aromatic); NMR ($CDCl_3$) 1.98, 2.10, 2.23, and 2.35 (four s, 6, vinyl CH_3 and $COCH_3$) and 7.13–7.67 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 201 (18), 159 (81), 132 (75), 104 (100), and 43 (43).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51. Found: C, 71.51; H, 5.62.

16g: IR (TF) 4.51 (C≡N), 5.64 (C=O), 6.16 and 6.23 μ (C=C and aromatic); NMR ($CDCl_3$) δ 2.03 (s, 3, $COCH_3$) and 7.12–7.50 (m, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 263 (10), 194 (100), and 43 (48).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98. Found: C, 77.36; H, 5.01.

16h: IR (TF) 4.51 (C≡N), 5.63 (C=O), and 6.05 μ (C=C); NMR ($CDCl_3$) δ 1.30–1.94 (m, 6, CH_2), 1.94–2.68 (m, 4, allylic CH_2), and 2.21 (s, 3, $COCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 179 (7), 110 (22), and 43 (100).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 66.91; H, 7.33.

16i (mixture of *E* and *Z* isomers): IR (TF) 4.50 (C≡N), 5.62 (C=O), and 6.08 μ (C=C); NMR ($CDCl_3$) δ 0.80–3.32 (m, 9, CH_2 and $CHCH_3$), 1.10 and 1.22 (two d, 3, *J* = 8 Hz for each isomer, $CHCH_3$), and 2.22 (s, 3, $COCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 193 (5), 151 (9), 133 (16), and 124 (100).

16j (mixture of *E* and *Z* isomers): IR (TF) 4.53 (C≡N), 5.63 (C=O), 6.14 and 6.27 μ (C=C); NMR ($CDCl_3$) δ 1.42–2.78 (m, 6, CH_2), 2.10 and 2.27 (two s, 3, $COCH_3$), and 6.18–6.68 (m, 2, vinylic H); mass spectrum (70 eV) *m/e* (rel intensity) 177 (8), 135 (16), 108 (27), 79 (18), and 43 (100).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.59; H, 6.31.

16k (mixture of *E* and *Z* isomers): IR (KBr) 4.52 (C≡N), 5.64 (C=O), and 6.18 μ (C=C); NMR ($CDCl_3$) δ 2.21 and 2.23 (two s, 3, $COCH_3$) and 5.95–6.26 (m, 1, vinylic H); mass spectrum (70 eV) *m/e* (rel intensity) 465 (8), 424 (100), and 43 (16).

Anal. Calcd for $C_{31}H_{47}NO_2$: C, 79.95; H, 10.17. Found: C, 79.79; H, 10.15.

16l (mixture of *E* and *Z* isomers): IR (TF) 4.51 (C≡N), 5.62, 5.75 (C=O), and 6.04 μ (C=C); NMR (CCl_4) δ 1.80 and 2.07 (two s, 3, vinylic CH_3), 2.23 and 2.44 (two s, 3, $COCH_3$), 2.38–2.98 (m, 4, CH_2), and 3.64 and 3.70 (two s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 211 (1), 142 (5), 114 (11), 99 (6), and 43 (100).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20. Found: C, 56.77; H, 6.21.

Spectral Data for Carboxylic Acids. The following carboxylic acids were identified by comparison with an authentic sample (source): **2a**, **2c**, and **2g** (Matheson Coleman and Bell), **2b**, **2f**, and **2l** (Aldrich), **2d** (Pfaltz and Bauer), and **2h** (Eastman). The following carboxylic acids possessed spectral data and/or melting points in accord with literature values: **2i**,[26] **2j**,[27] **2k**,[28] and **2m**.[29]

2i (mixture of *E* and *Z* isomers): IR (TF) ca. 3.3 (OH) and 5.37 μ (C=O); NMR ($CDCl_3$) δ 0.50–2.80 (m, 10, CH and CH_2), 0.94 and 0.97 (two d, 3, J = 7 Hz for each isomer, $CHCH_3$), and 12.08 (s, 1, COOH); mass spectrum (70 eV) *m/e* (rel intensity) 142 (22), 127 (21), 124 (68), 87 (32), and 55 (100).

2j: IR (TF) 3.30 (OH), 5.92 (C=O), and 6.09 μ (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 126 (32), 108 (20), and 81 (100). This product was a 73:27 mixture of α,β-:β,γ-unsaturated isomers as determined by UV spectroscopy (lit.[27a] λ_{max} 217 nm (ϵ 10 000) for α,β-unsaturated isomer) and NMR spectroscopy (integration of δ ($CDCl_3$) 5.78–5.95 (vinylic H of β,γ-unsaturated isomer) and 6.92–7.31 (vinylic H of α,β-unsaturated isomer)).

2k (mixture of unsaturated acids of which ca. 35% is Marker's acid[28] according to TLC analysis vs. an authentic sample): IR (KBr) 2.99 (broad OH) and 5.90 μ (C=O).

2m: mp 244.5–246 °C (lit.[29] mp 253 °C); IR (KBr) 2.95 (OH), 5.76 and 5.89 μ (C=O); NMR ($CDCl_3$) δ 0.88 (broad s, 6, C-18 and C-19 angular CH_3) and 11.30 (broad s, 1, COOH); mass spectrum (70 eV) *m/e* (rel intensity) 318 (100), 303 (13), 300 (15), 274 (38), 262 (13), 108 (18), and 107 (18).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.27; H, 9.54.

Spectral Data for Carboxylic Esters. Methyl cyclohexanecarboxylate was identified by comparison with an authentic sample prepared from cyclohexanecarboxylic acid and diazomethane.

3k (Z = OCH_3) (mixture of principally two unsaturated esters): IR (TF) 5.75 and 5.82 μ (C=O); NMR ($CDCl_3$) δ 2.72 and 2.76 (two s, 3, OCH_3).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.16; H, 11.29.

3m (Z = OCH_3): IR (KBr) 5.74 and 5.80 μ (C=O); NMR ($CDCl_3$) δ 0.86 (s, 6, C-18 and C-19 angular CH_3) and 3.67 (s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 332 (100), 289 (26), 108 (29), and 107 (34).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.74; H, 9.71.

Spectral Data for Carboxamides. Cyclohexanecarboxamide and the *N*-methyl and *N,N*-dimethyl derivatives were identified by comparison with authentic samples prepared from cyclohexanecarboxylic acid chloride.

4e (Z = NH_2): IR (KBr) 2.99 and 3.17 (NH_2), 6.07 (C=O), and 6.25 μ (aromatic); NMR (Me_2SO-d_6) δ 1.52–2.85 (m, 9, CH and CH_2), 6.42–6.78 (broad s, 2, NH_2), and 7.21 (s, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 267 (1), 91 (45), and 72 (100).

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