Silica Gel-Catalyzed Knoevenagel Condensation of Peptidyl Cyanomethyl Ketones with Aromatic Aldehydes and Ketones. A Novel Michael Acceptor Functionality for C-Modified Peptides: The Benzylidene and Alkylidene Cyanomethyl Ketone Function

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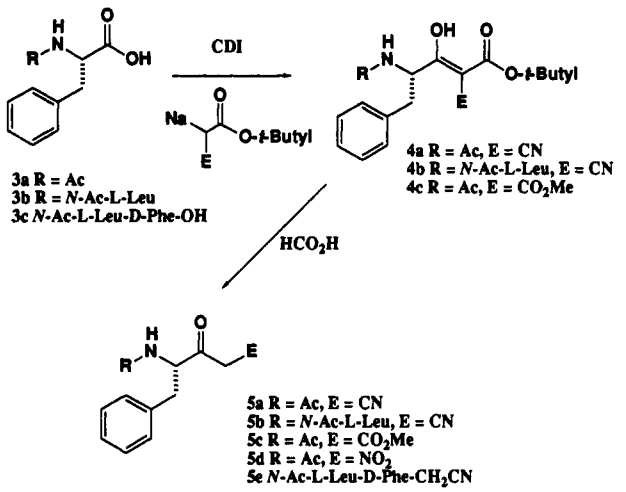
Simple preparation of cyanomethyl ketone derivatives **5a–5b** of *N*-acetylphenylalanine and *N*-acetylleucylphenylalanine is accomplished by condensation of the corresponding activated carboxylic acids **3a–3b** and the carbanion of *tert*-butyl cyanoacetate to give enols **4a–4b**, which are then hydrolyzed and decarboxylated. These cyanomethyl ketone compounds **5a–5b** are allowed to react with aromatic aldehydes and ketones in the presence of silica gel to give the Knoevenagel condensation adducts **7–18**. Malononitrile, benzoylacetonitrile, and nitroacetonitrile are also reactive. These transformations can be brought about without significant epimerization.

In connection with the synthesis of enzyme inhibitors and investigations into the mechanisms of enzymatic reactions, a large number of substrate analogues with modified carboxyl functions have been synthesized.[2,3] In particular, vinylogous amino acid esters[4] **1** (R = *N*-Ac-Phe-Gly) were found to be irreversible inhibitors (inactivators) of thiol proteases, a group of enzymes involved in several pathological processes (Figure 1). Peptidomimetics such as **1** can cause inactivation by serving as a Michael acceptors for a 1,4-addition of a nucleophile from the enzyme active site. We chose to study the introduction of a diconjugated benzylidene or alkylidene functionality[5] such as benzylidene or alkylidene cyanomethyl ketone **2a** or **2b** (R = amino acids or peptides) in place of the carboxylic function of *N*-Ac-Phe and *N*-Ac-Leu-Phe. The goal of this work is to devise potential inhibitors of α-chymotrypsin and to develop an efficient and mild procedure for the synthesis of these new benzylidene and alkylidene derivatives of peptides. We envisaged that these new derivatives could be obtained by Knoevenagel condensation using the corresponding cyanomethyl ketone as a precursor. In this article, we describe a general method which allows for the easy synthesis of these peptidic functionalized ketones.

The preparation of cyanomethyl ketone **5a** was achieved in two steps (Scheme I). First, using our procedure,[6] enol **4a** was generated by allowing carboxylic acid **3a** to react with 1,1′-carbonyldiimidazole, cooling the resulting acylimidazole intermediate solution to −78 °C, and adding the preformed sodium salt of *tert*-butyl cyanoacetate generated by using sodium hydride. In the second step, the crude enol **4a** was treated with 96% formic acid to effect the hydrolysis and decarboxylation of the *tert*-butyl ester group to give the corresponding cyanomethyl ketone **5a**

Scheme I



in 85% overall yield. The dipeptidyl cyanomethyl ketone **5b** (80%) and its diastereoisomers **5e** (*N*-Ac-L-Leu-D-Phe-CH_2CN) (75%) were also obtained in this manner from acids **3b** (*N*-Ac-L-Leu-L-Phe-OH) and **3c** (*N*-Ac-L-Leu-D-Phe-OH), respectively. These reaction conditions may also be used to generate other functionalized ketones. For example, carbomethoxymethyl ketone **5c** (51%) was obtained using the sodium salt of *tert*-butyl methyl malonate, whereas nitromethyl ketone **5d** (83%) was obtained directly from acid **3a** using excess nitromethane sodium salt.

Usually, the condensation of active methylene compounds such as cyanomethyl ketones with aromatic aldehydes or ketones can proceed via standard Knoevenagel reaction conditions from which benzylidene cyanomethyl ketone products can be obtained. Under homogeneous conditions, weak bases are known to catalyze the Knoevenagel condensation.[7] It can be performed in heterogeneous media which allows for ease of workup, but since basic aluminum oxide,[8] doped xonotlite,[9] basic anion-exchange resins[10] or functionalized silica gel with an alkylamine[11] can also potentially epimerize benzylidene deriva-

(1) Fellow of the NSERC-Canada, 1985–1995.

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(3) (a) Sauvé, G.; Le Berre, N.; Zacharie, B. *Tetrahedron Lett.* **1988**, *29*, 2299. (b) Sauvé, G.; Mansour, T. S.; Lachance, P.; Belleau, B. *Tetrahedron Lett.* **1988**, *29*, 2295.

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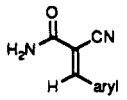
(5) The non-peptidic benzylidene compound



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(8) (a) (Al_2O_3): Texier-Boulett, F.; Foucod, A. *Tetrahedron Lett.* **1982**, *23*, 4927. (b) Varma, R. S.; Kabalka, G. W.; Evans, L. T.; Pagni, R. M. *Synth. Commun.* **1985**, *15*, 279. (c) (Al_2O_3–$AlPO_4$): Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. *J. Org. Chem.* **1984**, *41*, 5195.

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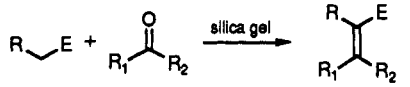
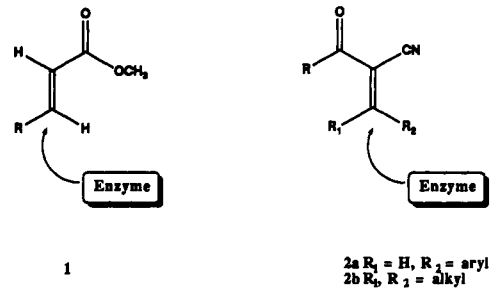
0022-3263/92/1957-1838$03.00/0

Table I. Silica Gel-Catalyzed Knoevenagel Condensation



entry	active methylene compd			aryl aldehyde and ketone reagent		reaction time (h)	product	
	compd no.	R	E	R_1	R_2		compd no.	yield[a] (%)
1		NC	CN	H	4-$MeOC_6H_4$	70	**6a**	95
2		O_2N	CN	H	4-$MeOC_6H_4$	70	**6b**	90
3		C_6H_5CO	CN	H	4-$MeOC_6H_4$	70	**6c**	76
4		MeO_2C	CN	H	4-$MeOC_6H_4$	168	**6d**	0
5		EtO_2C	NO_2	H	4-$MeOC_6H_4$	168	**6e**	0
6		MeO_2C	CO_2Me	H	4-$MeOC_6H_4$	168	**6f**	0
7		C_6H_5CO	COMe	H	4-$MeOC_6H_4$	168	**6g**	0
8		$C_6H_5SO_2$	CN	H	4-$MeOC_6H_4$	168	**6h**	0
9	**5a**	*N*-Ac-L-Phe	CN	H	4-$MeOC_6H_4$	15	**7**	100
10	**5a**	*N*-Ac-L-Phe	CN	H	C_6H_5	13	**8**	85
11	**5a**	*N*-Ac-L-Phe	CN	H	4-$Me_2NC_6H_4$	15	**9**	58
12	**5a**	*N*-Ac-L-Phe	CN	H	4-$NO_2C_6H_4$	13	**10**	37
13	**5a**	*N*-Ac-L-Phe	CN	H	2-$CO_2HC_6H_4$	15	**11**	97
14	**5a**	*N*-Ac-L-Phe	CN	H	3-MeO(4-OH)C_6H_3	15	**12**	93
15	**5a**	*N*-Ac-L-Phe	CN		$(CH_2)_5$	30	**13**	46
16	**5a**	*N*-Ac-L-Phe	CN		$(CH_2)_4$	50	**14**	35
17	**5a**	*N*-Ac-L-Phe	CN	Me	Me	36	**15**	44
18	**5a**	*N*-Ac-L-Phe	CN	Me	$HOCH_2$	24	**16**[b]	80
19	**5a**	*N*-Ac-L-Phe	CN	Me	Me(OH)CH	72	**17**[c]	61
20	**5b**	*N*-Ac-L-Leu-L-Phe	CN	H	4-$MeOC_6H_4$	15	**18**	98
21	**5e**	*N*-Ac-L-Leu-D-Phe	CN	H	4-$MeOC_6H_4$	15	**19**	94
22	**5c**	*N*-Ac-L-Phe	CO_2CH_3	H	4-$MeOC_6H_4$	168	**20**	0
23	**5d**	*N*-Ac-L-Phe	NO_2	H	4-$MeOC_6H_4$	168	**21**	0

[a] All yields are for chromatographically purified materials. [b] Compound **16** is a 56:44 mixture of geometrical isomers. [c] Compound **17** is a 56:44 mixture of geometrical isomers.



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2a R_1 = H, R_2 = aryl
2b R_1, R_2 = alkyl

Figure 1.

tives 7–12 (Table I, entries 9–14), we looked for alternatives. We reasoned that since mildly acidic silica gel is a good catalyst for Michael reactions[12] and for the dehydration/cyclization of tertiary alcohol/phenol precursor,[13] we could utilize it for the Knoevenagel condensation of **5a** with various carbonyl groups.

We first tested the reaction between malononitrile, nitroacetonitrile,[14] and benzoylacetonitrile with *p*-anisaldehyde in the presence of silica gel in dichloromethane at 25 °C for 70 h. Under these conditions we obtained adducts **6a**, **6b**, and **6c** in a 95%, 90%, and 76% yield, respectively (Table I). When this procedure was applied to the peptidyl cyanomethyl ketone **5a**, we obtained the benzylidene compound **7** in quantitative yield after 15 h. No reaction was observed with other active methylene compounds (entries 4–8), carbomethoxymethyl ketone **5c** (entry 22), or nitromethyl ketone **5d** (entry 23) even after 168 h. These results show that two strongly electron-withdrawing substituents are required on the active methylene compounds for these Knoevenagel conditions to be effective, such as a nitrile group in conjunction with either a nitrile, a nitro, or ketone group (as in a benzoyl or peptidyl ketone). Since the Knoevenagel condensation is known to be affected by steric factors,[7] active methylene compounds with small nitrile groups are more reactive than those with bulky methoxycarbonyl groups.

We think that the catalytic process at the acidic silica gel surface involves the enolization of cyanomethyl ketone and the activation of the electrophilic carbonyl compounds. Although silica gel is also acting as a dehydrating agent for the aldol intermediate, we found that neither its drying prior to reaction nor the addition of dry ground molecular sieves affected either the yield or reaction time. The reaction of **5a** with benzaldehyde, 4-(dimethylamino)benzaldehyde, and 4-nitrobenzaldehyde gave products **8** (85%), **9** (58%), and **10** (37%). The cyanomethyl ketone **5a** also reacted with 2-carboxybenzaldehyde and vanillin to afford compounds **11** (97%) and **12** (93%), providing evidence that protective groups are not necessary under these experimental conditions. These conditions are compatible with many substituents, including acid or basic functions on benzaldehyde derivatives.

In order to examine the scope of these conditions, we also studied the reaction of aromatic ketones (e.g., acetophenone) with cyanomethyl ketone **5a** in the presence of silica gel. No condensation occurred, probably due to the increased steric hindrance around the carbonyl group. But with aliphatic ketones, which have a more reactive carbonyl group, the condensation proceeded successfully. For example, silica gel catalyzed the reaction of compound **5a** with cyclohexanone using an optimized 9:1 ratio of ketone/**5a** to give the alkylidene derivative **13** (46%) after 30 h. The reaction with cyclopentanone (18 equiv) is less efficient, and product **14** was obtained in a moderate 35% yield.[15] Acetone (13 equiv) gave several byproducts, but

(11) These authors report no reaction between malononitrile and benzaldehyde on a column of silica gel: (a) Angeletti, E.; Canepa, C.; Martinetti, G.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 105. (b) Angeletti, E.; Canepa, C.; Martinetti, G.; Venturello, P. *Tetrahedron Lett.* **1988**, *29*, 2261.

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(13) Strunz, G. M.; Brillon, D.; Giguère, P. *Can. J. Chem.* **1983**, *61*, 1963.

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Table II. Infrared Data, Optical Rotation, and Melting Points of Compounds 5a–e, 6a–c, 7–19

compd	IR (cm^{-1})	λ^{UV}_{max} (nm)	(log ϵ)	$[\alpha]_D^{25}$	mp (°C)
5a	3400, 1740, 1680, 1500			−31.1° (c 1 MeOH)	138–141[a]
5b	3435, 2960, 1740, 1670, 1505			−84.2° (c 1 $CHCl_3$)	147–149[a]
5c	3430, 3000, 1725, 1675, 1500, 1440, 1250			+9.1° (c 1 $CHCl_3$)	96–98[a]
5d	3300, 1745, 1677, 1565, 1495			−61.3° (c 1 MeOH)	146–148[a]
5e	3600–3100, 2960, 1740, 1658, 1511			+1.9° (c 1 $CHCl_3$)	168–170[a]
6a	3020, 2225, 1583, 1511, 1273, 1180	347 241	4.54 4.06		114–115[b]
6b	3020, 2230, 1595 1513, 1312, 1275, 1180	382 247	4.48 3.99		97–98[b]
6c	3020, 2215, 1665, 1585, 1510, 1266, 1178	348 240	4.41 4.06		98–99[c]
7	3420, 3000, 2210, 1670, 1605, 1556, 1511, 1270	339 261	3.89 3.38	−33.4° (c 1 $CHCl_3$)	153–154[d]
8	3400, 3000, 2220, 1680, 1595, 1505	317 284	3.66 3.72	0° (c 1 $CHCl_3$)	142–145[a]
9	3420, 3000, 2200, 1670, 1610, 1505, 1376, 1160	480 424 400 272	3.76 3.76 3.76 3.75	−33.4° (c 1 $CHCl_3$)	195–200[a] dec
10	3420, 3000, 2220, 1685, 1595, 1535, 1355	317 301	4.00 3.98	+4.5° (c 0.5 $CHCl_3$)	147–148[e]
11 (KBr)	3650, 2700, 2170, 1750, 1500, 1380	272	3.88	+44.1° (c 1 MeOH)	136 dec[f]
12	3520, 3020, 2215, 1670, 1505, 1290	389 487 266	4.02 3.90 3.69	−19.9° (c 1 $CHCl_3$)	81–86[g]
13	3440, 2950, 2220, 1660, 1515, 1450	271	3.66	+21.9° (c 1 $CHCl_3$)	131–132[h]
14	3450, 3020, 2990, 2220, 1690, 1415, 1400	266 1270	3.46	+14.7° (c 1 $CHCl_3$)	146–148[h]
15	3430, 2960, 2220, 1685, 1510, 1380	267	3.64	+24.0° (c 1 $CHCl_3$)	121–124[a]
16	3440, 3020, 2220, 1660, 1515	261	2.45		146–147[a]
17	3440, 3020, 2220, 1660, 1515, 1375	264	2.66		151–153[a]
18	3430, 2960, 2210, 1670, 1510, 1270	353 244	4.47 3.95	−32.1° (c 1 $CHCl_3$)	206–207[a]
19	3430, 2960, 2210, 1660, 1510, 1270	253 245	4.54 4.15	−90.2° (c 1 $CHCl_3$)	198–199[a]

[a] Recrystallization from AcOEt/hexane. [b] Recrystallization from CH_2Cl_2/hexane. [c] Recrystallization from ether/hexane. [d] Recrystallization from CH_2Cl_2/petroleum ether. [e] Recrystallization from CH_2Cl_2/AcOEt/hexane. [f] Recrystallization from AcOEt/CCl_4. [g] Recrystallization from AcOEt/CCl_4/hexane. [h] Recrystallization from $CHCl_3$/hexane.

compound **15** was isolated in 44% as a stable solid. These conditions also made it possible to directly obtain the allylic alcohols **16** (80% as an inseparable 56:44 mixture of geometrical isomers) and **17** (61% as a 56:44 mixture) by reaction of **5a** with acetol and 3-hydroxy-2-butanone, respectively.

In order to ascertain if any racemization had occurred, we prepared the diastereomeric benzylidene derivatives **18** (L,L) and **19** (L,D) in excellent yield from cyanomethyl ketones **5b** and **5e**, respectively. We were pleased to find that the HPLC analysis and ^1H NMR spectra of each diastereomeric product did not show the presence of the other diastereomer, providing evidence that no detectable racemization occurs under these experimental conditions. The same conclusion can be drawn for the transformation of acids **3b** and **3c** into cyanomethyl ketones **5b** and **5e**, respectively. The derivatives **7–12** and **18–19** exist only as the *E* isomer,[3,8a,8c,16] as observed by NMR spectroscopy, since this places the larger aromatic β-substituent cis to the smaller cyano group.

As far as we know this is the first time that a suspension of silica gel in a solvent has been used successfully to catalyze the Knoevenagel condensation. These reaction conditions are simple and high yielding. To sum up, the important features of this methodology are that it does not require any base, the reaction conditions are mild, setup and workup are easy, and no epimerization occurs. These results show that silica gel is a very selective and useful acidic catalyst for the Knoevenagel condensation of cya-

(15) We observed that the use of aluminum oxide in place of silica gel also afforded **14** but only in 20% yield. The cyanomethyl ketone **5a** and compound **14** are slowly transformed to very polar products on alumina but this reaction is even slower on silica gel. See: Gazit, A.; Yaish, P.; Gilon, C.; Levitski, A. *J. Med. Chem.* **1989**, *32*, 2344.

(16) Zabicky, J. *J. Chem. Soc.* **1961**, 683.

Table III. ^{1}H NMR and Exact Mass Data of Compounds 5a–e, 6a–c, 7–19

compd	^{1}H NMR δ (ppm)	high-resolution MS found (m/z) (calcd)
5a	2.01 (s, 3 H, CH_3), 3.06 (m, 2 H, CH_2Phe), 3.25, 3.51 (2d, J = 19.5 Hz, 2 H, CH_2CN), 4.69 (q, J = 7.2 Hz, $C_\alpha H$), 5.92 (m, 1 H, NH), 7.34 (m, 5 H arom)	230.1052 (230.1056)
5b	0.89 (d, J = 6.2 Hz, 3 H, CH_3 Leu), 0.92 (d, J = 6.5 Hz, 3 H, CH_3 Leu), 1.23, 1.44 (2 m, 2 H, $C_\beta H_2$ Leu), 1.59 (m, 1 H, CH Leu), 1.96 (s, 3 H, CH_3 NAc), 3.02, (dd, J = 7.9, 13.9 Hz, 1 H, $C_\beta H_2$ Phe), 3.12 (dd, J = 7.0, 13.9 Hz, 1 H, $C_\beta H_2$ Phe), 3.27, 3.51 (2 d, J = 9.6 Hz, 2 H, CH_2CN), 4.36 (m, 1 H, $C_\alpha H$ Leu), 4.62 (q, J = 6.6 Hz, 1 H, $C_\alpha H$ Phe), 5.71 (d, J = 8.8 Hz, 1 H, NH Leu), 6.82 (d, J = 6.1 Hz, 1 H, NH Phe), 7.18, 7.32 (2 m, 5 H arom)	343.1887 (343.1897)
5c	1.97 (s, 3 H, CH_3), 3.04 (dd, J = 6.8, 14.2 Hz, 1 H, $C_\beta H_2$), 3.15 (dd, J = 6.5, 14.1 Hz, 1 H, $C_\beta H_2$), 3.46, 3.49 (2 d, J = 15.9 Hz, 2 H, CH_2CO_2), 3.71 (s, 3 H, CH_3O), 4.90 (q, J = 7.2 Hz, 1 H, $C_\alpha H$), 5.98 (m, 1 H, NH), 7.13, 7.29 (2 m, 5 H arom)	M^+ = 263 (263)
5d	2.00 (s, 3 H, CH_3), 3.14 (m, 2 H, $C_\beta H_2$), 4.69 (q, J = 7.1 Hz, 1 H, $C_\alpha H$), 5.06, 5.31 (2 d, J = 15.1 Hz, 2 H, CH_2NO_2), 5.85 (m, 1 H, NH), 7.39 (m, 5 H arom)	250.0904 (250.0954)
5e	0.85 (d, J = 6.2 Hz, 6 H, CH_3 Leu), 1.38 (m, 2 H, $C_\beta H_2$ Leu), 1.51 (m, 1 H, CH Leu), 2.0 (s, 3 H, CH_3 NAc), 3.01, 3.15 (2 dd, 2 H, $C_\beta H_2$ Phe), 3.35, 3.61 (2 d, J = 18.7 Hz, 2 H, CH_2CN), 4.33 (m, 1 H, $C_\alpha H$ Leu), 4.69 (q, J = 8.6 Hz, 1 H, $C_\alpha H$ Phe), 5.80 (d, J = 7.0 Hz, 1 H, NH Leu), 6.99 (d, J = 6.2 Hz, 1 H, NH Phe), 7.19, 7.32 (2 m, 5 H arom)	343.1908 (343.1898)
6a	3.91 (s, 3 H, CH_3O), 7.02 (d, J = 8.9 Hz, 2 H arom), 7.65 (s, 1 H, CH), 7.90 (d, J = 8.9 Hz, 2 H arom)	184.0621 (184.0637)
6b	3.95 (s, 3 H, CH_3O), 7.08 (d, J = 8.9 Hz, 2 H arom), 8.02 (d, J = 8.9 Hz, 2 H arom), 8.60 (s, 1 H, CH)	204.0525 (204.0535)
6c	3.91 (s, 3 H, CH_3O), 7.03 (d, J = 8.8 Hz, 2 H arom), 7.52 (m, 2 H arom), 7.62 (m, 1 H arom), 7.86 (d, J = 8.1 Hz, 2 H arom), 8.05 (s, 2 H arom), 8.07 (s, 1 H, CH)	263.0928 (263.0947)
7	2.00 (s, 3 H, CH_3), 3.10 (dd, J = 6.5, 14.0 Hz, 1 H, $C_\beta H_2$), 3.32 (dd, J = 6.1, 14.0 Hz, 1 H, $C_\beta H_2$), 3.92 (s, 3 H, CH_3O), 5.50 (q, J = 6.6 Hz, 1 H $C_\alpha H$), 6.07 (d, J = 7.0 Hz, 1 H, NH), 7.02 (d, J = 8.9 Hz, 2 H arom), 7.15, 7.27 (2 m, 5 H arom Phe), 8.02 (d, J = 8.9 Hz, 2 H arom), 8.11 (s, 1 H, CH)	348.1488 (348.1475)
8	2.01 (s, 3 H, CH_3), 3.10 (dd, J = 6.7, 14.1 Hz, 1 H, $C_\beta H_2$), 3.32 (dd, J = 6.1, 14.1 Hz, 1 H, $C_\beta H_2$), 5.52 (q, J = 6.6 Hz, 1 H, $C_\alpha H$), 6.10 (d, J = 6.9 Hz, 1 H, NH), 7.28 (m, 5 H arom), 7.52 (m, 3 H arom), 7.99 (d, J = 7.4 Hz, 2 H arom), 8.18 (s, 1 H, CH)	138.1352 (318.1369)
9	1.99 (s, 3 H, CH_3), 3.15 (s, 6 H, CH_3N), 3.13 (dd, J = 6.5, 13.9 Hz, 1 H, $C_\beta H_2$), 3.34 (dd, J = 5.8, 13.9 Hz, 1 H, $C_\beta H_2$), 5.53 (q, J = 7.5 Hz, 1 H $C_\alpha H$), 6.16 (d, J = 6.9 Hz, 1 H, NH), 6.72 (d, J = 9.2 Hz, 2 H arom), 7.13, 7.24 (2 m, 5 H arom Phe), 7.97 (d, J = 9.1 Hz, 2 H arom), 8.02 (s, 1 H, CH)	361.1804 (361.1792)
10	2.10 (s, 3 H, CH_3), 3.09 (dd, J = 7.3, 14.0 Hz, 1 H, $C_\beta H_2$), 3.28 (dd, J = 6.4, 14.0 Hz, 1 H, $C_\beta H_2$), 5.41, (q, J = 6.9 Hz, 1 H, $C_\alpha H$), 6.05 (d, J = 7.0 Hz, 1 H, NH), 7.18, 7.32 (2 m, 5 H arom Phe), 8.10 (m, 2 H arom), 8.18 (s, 1 H, CH), 8.35 (2 d, 2 H arom)	363.1218 (363.1220)
11	(acetone-d_6/5% D_2O): 1.96 (s, 3 H, CH_3), 3.05 (dd, J = 7.8, 13.4 Hz, 1 H, $C_\beta H_2$), 3.11 (dd, J = 6.8, 13.4 Hz, 1 H, $C_\beta H_2$), 5.24 (t, J = 7.3 Hz, 1 H, $C_\alpha H$), 7.2–7.35 (m, 7 H arom), 7.52 (bs, 1 H, CH), 7.57 (t, J = 7.5 Hz, 1 H arom), 7.67 (t, J = 7.41 Hz, 1 H arom), 7.88 (d, J = 7.7 Hz, 1 H, NH)	362.1230 (362.1267)
12	2.00 (s, 3 H, CH_3), 3.06 (dd, J = 6.3, 14.0 Hz, 1 H, $C_\beta H_2$), 3.31, (dd, J = 5.9, 14.0 Hz, 1 H, $C_\beta H_2$), 4.00 (s, 3 H, CH_3O), 5.52 (q, J = 6.4 Hz, 1 H, $C_\alpha H$), 6.07 (d, J = 7.0 Hz, 1 H, NH), 6.34 (s, 1 H, OH), 7.03 (d, J = 8.3 Hz, 1 H arom), 7.15 (m, 2 H, arom Phe), 7.25 (m, 3 H, arom Phe), 7.41 (d, J = 8.4 Hz, 1 H, arom), 7.86 (s, 1 H, arom), 8.08 (s, 1 H, CH=C)	364.1417 (364.1424)
13	1.66, 1.72, 1.82 (3 m, 6 H, CH_2 cycl), 1.99 (s, 3 H, CH_3), 2.67, 2.75, 2.78 (3 m, 4 H, CH_2 cycl), 3.11, 3.33 (2 dd, 2 H, $C_\beta H_2$), 5.22 (q, J = 6.1 Hz, 1 H, $C_\alpha H$), 5.98 (m, 1 H, NH), 7.14, 7.27 (2 m, 5 H arom)	310.1689 (310.1683)
14	1.83 (m, 4 H, CH_2 cycl), 1.97 (s, 3 H, CH_3), 2.84 (m, 4 H, CH_2 cycl), 3.03 (dd, J = 7.2, 14.1 Hz, 1 H, $C_\beta H_2$), 3.3 (dd, J = 5.6, 14.1 Hz, 1 H, $C_\beta H_2$), 5.30 (q, J = 5.2 Hz, 1 H, $C_\alpha H$), 5.95 (m, 1 H, NH), 7.09, 7.28 (2 m, 5 H arom)	296.1538 (196.1526)
15	1.97 (s, 3 H, CH_3), 2.30, 2.33 (2 s, 6 H, $2CH_3$), 3.05 (dd, J = 7.3, 14.2 Hz, 1 H, $C_\beta H_2$), 3.32 (dd, J = 5.2, 14.2 Hz, 1 H, $C_\beta H_2$), 5.23 (q, J = 5.3 Hz, 1 H, $C_\alpha H$), 5.98 (m, 1 H, NH), 7.12 (m, 2 H arom), 7.27 (m, 3 H arom)	270.1346 (170.1369)
16	(56:44 mixture of isomers) 1.92, 1.94 (2 s, 55:45, 3 H, CH_3), 2.09, 2.12 (2 s, 57:43, 3 H, CH_3), 2.46, 2.65, 3.06 (3 m, 2 H, $C_\beta H_2$), 4.51 (m, 1 H, $C_\alpha H$), 4.62, 4.81 (2 m, 2 H, CH_2O), 5.6 (bs, 1 H, NH), 5.73, 6.23 (2 s, 55:45, 1 H, OH), 7.16, 7.30 (2 m, 5 H arom)	286.1311 (286.1318)
17	(56:44 mixture of isomers) 1.36, 1.45 (2 m, 1:1, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3 AcN), 2.43–3.20 (3 m, 2 H, $C_\beta H_2$), 4.45 (m, 1 H, $C_\alpha H$), 4.81, 5.05 (2 m, 1 H, CH), 5.60 (bd, J = 7.4 Hz, NH), 5.39, 5.72, 6.07, 6.13 (4 s, 18:38:14:30, 1 H, OH), 7.26 (m, 5 H arom)	300.1467 (300.1475)
18	0.90 (t, J = 5.9 Hz, 6 H, CH_3 Leu), 1.43, 1.59 (2 m, 3 H, CH and CH_2 Leu), 1.96 (s, 3 H, CH_3), 3.02 (dd, J = 7.3, 14.1 Hz, $C_\beta H_2$), 3.33 (dd, J = 5.5, 14.1 Hz, $C_\beta H_2$ Phe), 3.92 (s, 3 H, CH_3O), 4.45 (q, J = 5.8 Hz, 1 H, $C_\alpha H$ Leu), 5.47 (q, J = 5.4 Hz, 1 H, $C_\alpha H$ Phe), 5.69 (d, J = 7.1 Hz, 1 H, NH Phe), 6.65 (d, J = 7.3 Hz, 1 H, NH Leu), 7.00 (d, J = 5.0 Hz, 2 H arom), 7.28 (m, 5 H arom), 8.02 (d, J = 8.9 Hz, 2 H arom), 8.13 (s, 1 H, CH)	461.2300 (461.2316)
19	0.87 (d, J = 6.5 Hz, 6 H, CH_3 Leu), 1.3–1.6 (m, 3 H, CH, CH_2 Leu), 1.96 (s, 3 H, CH_3), 2.99 (dd, J = 7.9, 13.9 Hz, 1 H, $C_\beta H_2$), 3.33 (dd, J = 5.6, 13.9 Hz, 1 H, $C_\beta H_2$ Phe), 3.91 (s, 3 H, CH_3O), 4.44 (q, J = 6.0 Hz, 1 H, $C_\alpha H$ Leu), 5.45 (q, J = 5.4 Hz, 1 H, $C_\alpha H$ Phe), 5.72 (d, J = 7.2 Hz, 1 H, NH Phe), 6.64 (d, 7.2 Hz, 1 H, NH Leu), 7.02 (d, J = 8.9 Hz, 2 H arom), 7.29 (m, 5 H arom), 8.02 (d, J = 8.9 Hz, 2 H arom), 8.14 (s, 1 H, CH)	461.2345 (461.2316)

nomethyl ketones with aromatic aldehydes and ketones with many applications to the synthesis of new potent peptidic inhibitors of α-chymotrypsin. The enzymatic assays of compounds 7–19 will be presented in due course.

Experimental Section

General Data. All reactions were carried out in oven-dried (120 °C) flasks. Dichloromethane was distilled over calcium hydride, and tetrahydrofuran was distilled over benzophenone and sodium prior to use. Formic acid (96%) and other chemical reagents (from Aldrich Chemical Co. Inc.) were used as received. Analytical thin-layer chromatography (TLC) was carried out on Merck Kieselgel silica gel 60 F_{254} aluminium plates. Flash chromatography[17] was performed with Merck silica gel, 230–400 mesh. Visualization of spots on TLC plates was made by use of UV light and ninhydrin in ethanol with heating. Mixtures of ethyl acetate and hexanes were used as eluents. Infrared (IR) spectra were measured in chloroform on a Beckman Acculab 8 spectrophotometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Nuclear magnetic resonance

(17) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

spectra were obtained on a Bruker WH-400 (^{1}H 400-MHz) spectrometer with chloroform-*d* as solvent and tetramethylsilane as an internal standard, except where otherwise indicated. ^{1}H NMR multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; dd, doublet doublet; t, triplet; q, quartet; m, multiplet; bs, broad; *J*, coupling constant (hertz). High-resolution mass spectra were obtained by means of a Kratos MS50TCTA spectrometer at the Université de Montréal. Melting points were measured on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were measured at 589 nm on a Rudolph Research Autopol III polarimeter. The UV spectra were recorded on a Cary 1 spectrophotometer with acetonitrile as solvent at 20 °C. HPLC's were run on an Hypersil-MOS C-8 reversed-phase column (25 cm × 4.6 mm) using TFA/CH_3CN/H_2O and TFA/MeOH/H_2O as mobile phase.

General Procedure for the Condensation, Hydrolysis, and Decarboxylation. To a solution of the carboxylic acid (14.5 mmol) in tetrahydrofuran (80 mL) was added under an argon stream 1,1'-carbonyldiimidazole (2.60g, 16.05 mmol). The solution was stirred at 20 °C for 1 h and then was purged with nitrogen and cooled at −78 °C. A solution of active methylene reagent (17.4 mmol) in tetrahydrofuran (30 mL) was reacted under argon with sodium hydride (50% in mineral oil) (0.765 g, 15.9 mmol). This solution was added over a 40-min period using a syringe pump to the first solution at −78 °C. The solution was stirred at −78 °C for 1 h and was gradually warmed to 20 °C overnight. The solvent was removed, and the residue was washed vigorously with a mixture of diethyl ether/hexanes (3 × 15 mL). Formic acid (96%, 40 mL) was then added, and the solution was stirred at 20 °C for a period of 8 h followed by coevaporation of formic acid with benzene (2 × 20 mL) on a rotary evaporator. The residue was dissolved in ethyl acetate (200 mL) and washed with water (30 mL) and 5% citric acid/brine (2:1) solution (2 × 20 mL), and the aqueous phase was back-extracted with ethyl acetate/hexane (1:1) (2 × 30 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (portions of 5–10 mL) until a neutral pH value for the aqueous layer was reached. The organic layers were washed with brine (2 × 15 mL) and dried with magnesium sulfate and then filtered on a silica gel pad (4 g) which was rinsed with ethyl acetate (30 mL). The solvent was then evaporated and the residue was recrystallized in solvents as indicated in Table II. The mother liquor was concentrated, purified by flash chromatography to afford additional portions of pure product. The products **5a–5e** were obtained as solids in 85% (**5a**), 80% (**5b**), and 75% (**5e**) yields, respectively, using *tert*-butyl cyanoacetate as the active methylene reagent. We also obtained compound **5c** in 51% yield using *tert*-butyl methyl malonate and **5d** in 83% using nitromethane (40 equiv and with sodium hydride, 12 equiv without the formic acid treatment). The physical data for products **5a–5e** are reported in Tables II and III.

General Procedure for the Silica Gel-Catalyzed Knoevenagel Condensation (Products 6a–c). The cyanomethyl ketone (1.54 mmol) and carbonyl compounds (4.6 mmol) were dissolved in dichloromethane (1.2 mL). Merck silica gel (500 mg, 230–400 mesh) was added under nitrogen. The solution was stirred at 25 °C until completion of the reaction (see reaction time in Table I) and was then filtered through a scintered glass frit prior to chromatographic purification on silica gel. Products **7–12, 18** and **19**: same procedure as above except for the ratio of reagents: silica gel (900 mg), cyanomethyl ketone (1 mmol), CH_2Cl_2 (4.5 mL), and carbonyl compound (5 mmol). Products **13–17**: same procedure as above except for the quantity of carbonyl compound used, respectively: 9, 18, 13, 9, and 18 mmol. The physical data for products **6a–6c, 7–19** are reported in Tables II and III.

HPLC Analysis of Diastereoisomers 5b and 5e. HPLC analysis with solvent A (0.1% TFA/H_2O) and solvent B (0.1% TFA/MeOH) and gradient (35% B to 60% B) in 20 min on Hypersil-MOS C-8 reversed-phase column (25 cm × 4.6 mm) at a flow rate of 1.0 mL min^{-1} indicated the presence of one isomer. For instance, injection of sample **5b** with t_{r1} 11.2 min (>99.0% optical purity) and similarly **5e** with t_{r2} 12.5 min (>99.0% optical purity).

HPLC Analysis of Diastereoisomers 18 and 19. HPLC analysis with solvent A (0.1% TFA/H_2O) and solvent B (0.1% TFA–60% CH_3CN/H_2O) and gradient (60% B to 80% B) in 15 min on Hypersil-MOS C-8 reversed-phase column (25 cm × 4.6 mm) at a flow rate of 1.0 mL min^{-1} indicated the presence of one isomer. For instance, injection of sample **18** with t_{r1} 12.8 min (>99.5% optical purity) and similarly **19** with t_{r2} 13.3 min (>99.7% optical purity).

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Supplementary Material Available: ^{1}H NMR spectra for all new compounds **5a–5e, 6a–6c**, and **7–19** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Annulation Reactions with Iron(III) Chloride: Oxidation of Imines

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Aromatic imines react with phenylacetylene or styrene in an acetonitrile solution of iron(III) chloride to give quinolines **3** or their tetrahydro derivatives **11** together with variable amounts of products **4** arising from the reduction of the imines. The initial step appears to be a one-electron oxidation to generate iron(II) and an imine radical cation. When the reactions are carried out in the presence of stoichiometric amounts of tetrachloro-*p*-benzoquinone (chloranil), only quinolines **3** are obtained.

The use of imines in constructing heterocyclic rings has been studied intensively in recent years. We have explored a series of free-radical cyclizations and annulations involving the intermediacy of imidoyl radicals generated by hydrogen abstraction from aromatic imines, by which such *N*-heterocycles as phenanthridines,[1] quinolines,[2] and

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