Modification of the Passerini Reaction: Facile Synthesis of Analogues of Isoproterenol and (Aryloxy)propanolamine β-Adrenergic Blocking Agents

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The reaction of aldehydes and ketones with *tert*-butyl isocyanide and trifluoroacetic acid (Passerini reaction) was found to be markedly catalyzed by pyridine. *N-tert*-Butyl-2-hydroxy-2-aryl- and 2-[(aryloxy)methyl]acetamides were isolated after aqueous workup and reduced with borane to substituted analogues of known ligands for the β-adrenergic receptor.

The reaction of a carboxylic acid with an isocyanide, **1**, and carbonyl compound **2** (Scheme I, eq 1) to produce an α-(acyloxy)carboxamide, **3**, is known as the Passerini reaction.[1] Hagedorn and Eholzer[2] have studied the reaction in water with excess carbonyl component. These workers formulated a unifying mechanism for this reaction and the troublesome side reaction, isocyanide solvolysis (**1** → **6b**, eq 2, Scheme I).[3] The suggestions of these workers were later criticized by Ugi,[4] who reviewed mechanistic data on the Passerini reaction and favored some variation of the mechanism of Scheme I (eq 1).

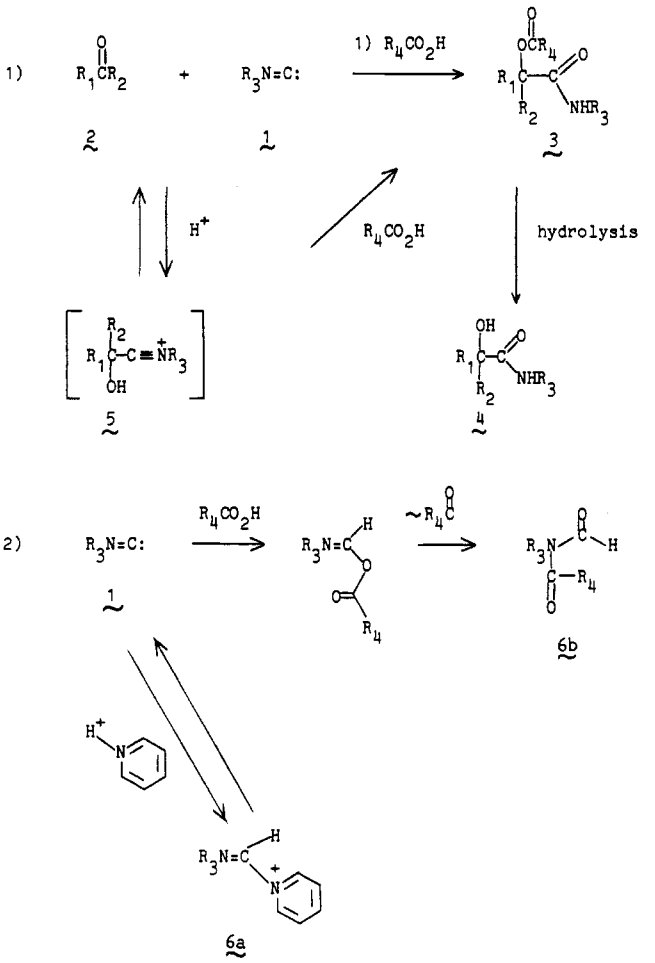
The use of pyridine–trifluoroacetic acid to promote the Passerini reaction was suggested from the various mechanistic possibilities. Pyridinium ion could be expected to promote formation of key intermediate **5** (as an acid catalyst). Pyridine might also be expected to protect the isonitrile **1** from solvolysis by reversible formation of an intermediate such as **6a** (Scheme I).

Results and Discussion

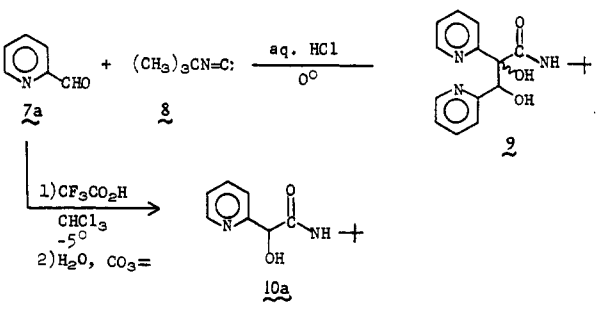
Modification of the Passerini Reaction. In this work the trifluoroacetic acid (2 equiv) promoted reactions of arenecarboxaldehydes, 2-phenoxyethanal, 1-phenoxy-2-propanone, or 2-phenoxycyclopentanone with *tert*-butyl isocyanide in the presence of 1–2 equiv of pyridine were found to give modest yields of α-hydroxy-*N-tert*-butylcarboxamides after aqueous workup. Reduction of the hydroxyamides with excess borane–dimethyl sulfide in refluxing tetrahydrofuran, followed by solvolysis of intermediate borates with glacial acetic acid or aqueous hydrochloric acid, gave moderate to excellent yields of readily isolatable amino alcohols **13a–f** (Table I). This synthetic sequence provides an alternative[7] to established methods[5,6] for synthesis of potential β-adrenergic agonists or antagonists.

Initially the reaction of 2-picolinaldehyde (**7a**) with *tert*-butyl isocyanide (**8**) was studied under various conditions. Reaction of **7a** with **8** in a 1:2 or 2:1 molar ratio with 2.4 N aqueous HCl, according to the procedure of Hagedorn and Eholzer,[2] gave complex product mixtures and, in the latter case, a low yield (6.6%) of a 2:1 condensation product **9** (stereochemistry undetermined) was isolated (Scheme II). When the 2:1 reaction was carried out in $CHCl_3$ solution with anhydrous CF_3CO_2H, the desired hydroxy amide **10** was obtained in 32% yield after

Scheme I



Scheme II



(1) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.
(2) Hagedorn, I.; Eholzer, U. *Chem. Ber.* **1964**, *98*, 936.
(3) These workers used excess carbonyl component, presumably to favor competition between the Passerini and isocyanide solvolysis reactions. Their mechanistic considerations are not reproduced here.
(4) Marquarding, D.; Gokel, G.; Hoffman, P.; Ugi, I. In "Isonitrile Chemistry"; Ugi, I., Ed.; Academic Press: New York, 1971; p 133 ff.
(5) Howe, R. *J. Med. Chem.* **1969**, *12*, 642.
(6) Gnewuch, C. T.; Friedman, H. L. *J. Med. Chem.* **1972**, *15*, 1321.
(7) During preparation of this work for publication, an account of similar synthetic strategy appeared: (a) Jen, T. Y. W.; Kaiser, C. U.S. Patent 3 952 101; *Chem. Abstr.* **1976**, *85*, 46409. (b) Jen, T.; Frazee, J. S.; Schwartz, M. S.; Kaiser, C.; Colella, D. F.; Wardell, J. R., Jr. *J. Med. Chem.* **1977**, *20*, 1258.

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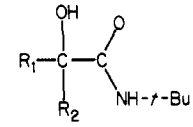
Table I. Borane Reduction Products



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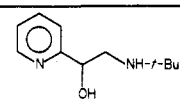
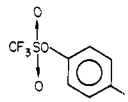
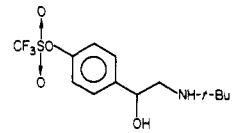
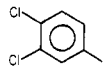
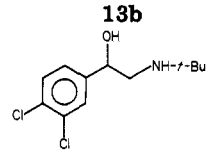
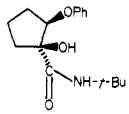
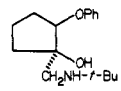
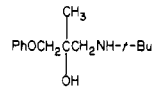
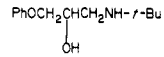
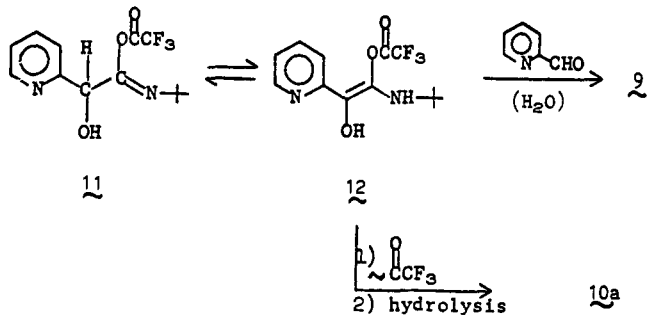
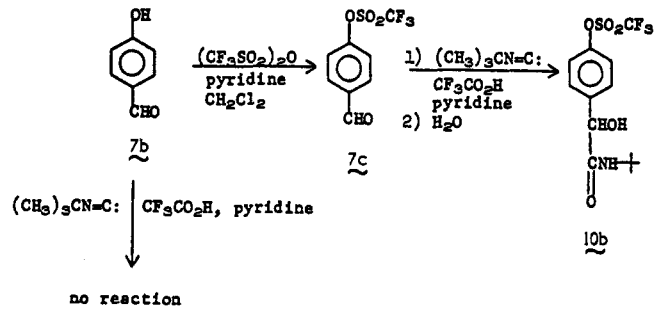
starting amide	R_1	R_2	ratio of isocyanide/carbonyl compound (% yield)	product	% yield
10a		H	2 (32)	 13a	49[a]
10b		H	1 (69)	 13b	100[a]
10c		H	0.5 (52)	 13c	100[a]
10d			2 (33)	 13d	50[b]
10e	$PhOCH_2$	CH_3	1 (33)	 13e	54[b]
10f	$PhOCH_2$	H	0.86 (69)	 13f	100[a]

[a] Yield of crude base (NMR shows no significant impurities). [b] Yield of analytical sample. [c] HCl salt, mp 96-98 °C.[10]

Scheme III



Scheme IV



aqueous workup. In this example, **7a** may function as a pyridine equivalent.

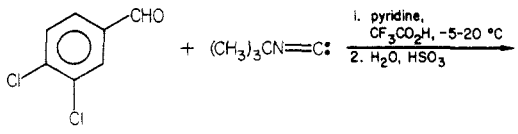
Formation of **9** can be rationalized by tautomerization of the intermediate **11** to **12** and enol condensation with **7a** (Scheme III).

Attempted reaction of *p*-hydroxybenzaldehyde (**7b**) with *tert*-butyl isocyanide in the presence of trifluoroacetic acid and pyridine gave mainly unchanged aldehyde. This result could be attributed to the unreactivity of the phenolic aldehyde since, under the same conditions (molar ratio **7c**/**8** of 1:1), the triflate (**7c**) of **7b** afforded **10b** in 69% yield (Scheme IV).

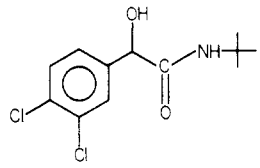
3,4-Dichlorobenzaldehyde (**7d**) reacted with *tert*-butyl isocyanide, pyridine, and trifluoroacetic acid in CH_2Cl_2 to give 42% (molar ratio of 2:1:2:2, respectively) and 52% (molar ratio of 1:2:2:2) isolated yields of **10c**. In comparison, only 28% (molar ratio of 2:1:2) of **10c** was isolated when pyridine was omitted, and, under the conditions of Hagedorn and Eholzer (molar ratio of **7d** to isocyanide of 2), only 13% of **10c** was isolated.

By use of the acetic acid procedure of Kaiser et al.[7b] (2:1 **7d**/isocyanide), a 52% overall yield of **10c** was obtained after acid hydrolysis of crude acetoxyamide (eq 3). Although, in this case, the Kaiser procedure affords a yield equivalent to that of the CF_3CO_2H procedure of the present work, it suffers from the disadvantage of requiring a separate hydrolysis step if the hydroxy amide is the desired product and requires higher reaction temperatures.

Reaction of 3-acetylpyridine with *tert*-butyl isocyanide, trifluoroacetic acid, and pyridine failed, but 2-phenoxy-



7d



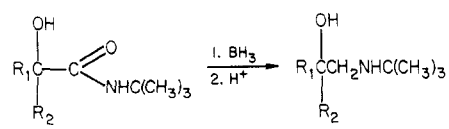
10c (3)

cyclopentanone, 3-phenoxy-2-propanone, and 2-phenoxyethanal afforded the expected hydroxy amides as summarized below (Table I). As the ratios of isocyanide to carbonyl compound indicate, the present reaction conditions are not limited by the requirement of excess carbonyl component, as in a previous procedure[2] for the Passerini reaction.

The trans stereochemistry of **10d** is supported by the presence of a doublet at δ 4.52 ($CDCl_3$, J = 5.6 Hz) in the 90-MHz ^1H NMR spectrum which is assigned to the methine proton (coupled to only one viscinal proton). Examination of Dreiding models of **10d** shows that one coupling (J_{trans}) is expected to be zero if the bulky *tert*-butylcarbamyl group is constrained to a pseudoequatorial conformation in the trans isomer. At 60 MHz in Me_2SO-d_6 the methine signal is a symmetrical, finely split triplet due to virtual coupling with one of the γ-CH_2 protons. This stereochemistry shows that, in the case of 2-phenoxycyclopentanone (**7e**), the isocyanide prefers a pseudoequatorial approach trans to the C_6H_5O substituent.

Consistent with the proposed mechanism outlined in Scheme I, the reaction of **7d** with *tert*-butyl isocyanide was extremely rapid and exothermic at 0 °C when CF_3CO_2H was added to the reaction mixture containing pyridine (procedure A) but was slow and endothermic at 25 °C when pyridinium trifluoroacetate was preformed and combined with the reactants (procedure B). This experiment suggests that protonation of the isocyanide occurs followed by rapid reaction of the protonated intermediate with excess pyridine when present, as in the preferred procedures (see Experimental Section), and is consistent with the mechanism in Scheme I (intermediate **6a**).

Reduction of Amides. The initial procedure followed for borane-tetrahydrofuran reduction was that of Brown and Heim,[8] using commercial BH_3–THF which contains some $NaBH_4$. To avoid possible ring reductions by $NaBH_4$ in the case of pyridine derivatives, etc., BH_3-dimethyl sulfide (Me_2S) in THF was selected as the preferred reducing agent (eq 4).



10 13 (4)

Reduction was carried out with 3–4.5 mol of BH_3·Me_2S in refluxing THF until starting amide was consumed (4–20 h). The complex borates were hydrolyzed with aqueous HCl according to Brown and Heim or with HOAc in case the product contained a tertiary alcohol or acid-sensitive functional group. The results of the reduction of the amides in the previous section are summarized in Table I.

(8) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.

Table II[a]

compd (formula)	mp, °C	recryst solvent
7c ($C_8H_5F_3O_4S$)	77–79[b]	
9 ($C_{17}H_{21}N_3O_3$)	125–126	n-C_4H_9Cl
10a ($C_{11}H_{16}N_2O_2$)	114–115	$CH_3CO_2C_2H_5$
10b ($C_{13}H_{16}F_3NO_5S$)	121–123	n-C_4H_9Cl
10c ($C_{12}H_{15}Cl_2NO_2$)	116–117	n-C_4H_9Cl
10d ($C_{16}H_{23}NO_3$)	109–110	n-C_4H_9Cl
10e ($C_{14}H_{21}NO_3$)	82–83	C_6H_{12}
10f ($C_{13}H_{19}NO_3$)	119–120	n-C_4H_9Cl
13a ($C_{11}H_{18}N_2O$·2HCl)	192–194	C_2H_5OH, i-C_3H_7OH
13b ($C_{13}H_{18}F_3NO_4S$·HCl)	203–204	C_2H_5OH
13c ($C_{12}H_{17}Cl_2NO$)	109–111	CH_3CN
13d ($C_{16}H_{25}NO_2$·$C_4H_4O_4$)	191	CH_3CN
13e ($C_{14}H_{23}NO_2$·$C_4H_4O_4$)	161–161.5	CH_3CN
13f ($C_{13}H_{21}NO_2$)	94–95	CH_3CN

[a] Satisfactory (±0.4%) elemental analyses were obtained for all compounds in this table. [b] Boiling point (0.6 torr).

In summary, trifluoroacetic acid promoted reaction of isocyanides with aldehydes and ketones can be catalyzed with pyridine to give α-hydroxy amides without large excesses of either the isocyanide or carbonyl component. The resulting hydroxy amides are useful for synthesis of analogues of known ligands for the β-adrenergic receptor.[5,6]

Experimental Section

NMR spectra were obtained on a Varian T-60 spectrometer in $CDCl_3$ or D_2O relative to Me_4Si or TPS as internal standard, respectively. Mass spectra were recorded on an AEI MS 902 high-resolution mass spectrometer (70 eV at 100 μA). Melting points (Table II) and boiling points are uncorrected, and the former were determined on a Thomas-Hoover Unimelt apparatus by using open capillaries. Microanalyses for the compounds in Table II were within ±0.4% of calculated values. 2-Phenoxycyclopentanone,[9] used in the synthesis of **10d**, and 2-phenoxyethanal,[10] used in the synthesis of **10f**, have been reported. The HCl salt of **24** is reported in a patent.[11]

4-[[(Trifluoromethyl)sulfonyl]oxy]benzaldehyde (7c). To a stirred solution of 4-hydroxybenzaldehyde (6.1 g, 0.050 mol) and pyridine (8 g, 0.1 mol) in 50 mL of CH_2Cl_2 was added dropwise trifluoromethanesulfonic anhydride (14.5 g, 0.052 mol) in 50 mL of CH_2Cl_2 at 20–35 °C (ice cooling) under N_2. The mixture was stirred 30 min at room temperature and then shaken with two 50-mL portions of 1.2 N aqueous hydrochloric acid and 50 mL of saturated NaCl solution. The CH_2Cl_2 layer was dried (Na_2SO_4), filtered, and concentrated under vacuum to give an oil which was distilled to give 10 g (79%) of a viscous oil [bp 77–79 °C (0.6 torr), lit.[12] bp 130–131 °C (17 torr)] which was identified as pure **7c** by its ^1H NMR spectrum: δ 7.57 (4 H A_2B_2, $\Delta\nu$ = 33 Hz), 10.1 (1 H, s). (This aldehyde trimerizes rapidly on standing.)

Anal. Calcd for $C_8H_5F_3O_4S$: C, 36.77; H, 1.95; F, 22.42; S, 12.62. Found: C, 37.08; H, 1.87; F, 22.37; S, 12.54.

***N*-*tert*-Butyl-2,3-dihydroxy-2,3-bis(2-pyridyl)propanamide (9).** To a stirred mixture of *tert*-butyl isocyanide[13] (5.6 g, 0.067 mol) and 2-pyridinecarboxaldehyde (15 g, 0.14 mol) at 0 °C under N_2 (dry ice–acetone cooling) was added dropwise 60 mL of 1.2 N aqueous hydrochloric acid at a rate to maintain the temperature at −5–0 °C. The mixture was warmed to 10 °C and basified to pH 9 with sodium hydroxide. The mixture was extracted with ether, and the ether extracts were back-extracted with 1.2 N hydrochloric acid. The aqueous acid extracts were basified and extracted with ether, and the ether extracts were washed with saturated aqueous sodium bisulfite to remove pyridinecarboxaldehyde and then with aqueous acetic acid (3 N) and dried (Na_2SO_4). Concentration of the filtered ether under vacuum gave 1.4 g of buff solid which was recrystallized to give 0.75 g (6.6%)

(9) Gelin, R.; Gelin, S. *C. R. Hebd. Seances Acad. Sci.* **1963**, *256*, 3705.
(10) Dey, A. N. *J. Chem. Soc.* **1937**, *1057*.
(11) Kuny, W.; Jacobi, H.; Koch, K., German Patent 1 236 523 (1967); *Chem. Abstr.* 1967, 64046.
(12) Hansen, R. L., U.S. Patent 3 346 612; *Chem. Abstr.* **1967**, *68*, 21698.
(13) Weber, W. P.; Gokel, G. W. *Tetrahedron Lett.* **1972**, *17*, 1637.

of colorless needles: mp 125–126 °C; ^{1}H NMR δ 8.44 (2 H, d), 5.37 (1 H, br s), 1.30 (9 H, s) inter alia; IR (KBr) 1678, 1521 (amide), 3400 cm^{-1} (OH); mass spectrum, *m/e* 315, 208, 109.

Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.34; H, 7.10; N, 13.35.

***N*-*tert*-Butyl-2-hydroxy-2-(2-pyridyl)ethanamide (10a).** To a mixture of 30 g (0.28 mol) of pyridine-2-carboxaldehyde and 10.5 g (0.12 mol) of *tert*-butyl isocyanide in 100 mL of $CHCl_3$ cooled to −5 °C (dry ice–acetone) was added dropwise with stirring at −5 to +5 °C 30 g (0.26 mol) of trifluoroacetic acid. The mixture was warmed to room temperature and stirred with 300 mL of 1 N aqueous NaOH for 2 h, and the layers were separated. The $CHCl_3$ layer was extracted with 1.2 N aqueous HCl, and the aqueous layer was basified with Na_2CO_3 and extracted with ether. The combined ether extracts were washed with aqueous $NaHSO_3$ until the starting aldehyde was removed (as indicated by TLC) and then with 3 N aqueous HOAc. The ether extract was dried (Na_2SO_4), filtered, and concentrated under vacuum to give 23 g of a dark oil which deposited 8.0 g (32%) of crude amide, mp 105–109 °C. An analytical sample was obtained by recrystallization from $CH_3CO_2C_2H_5$ to give pure *N*-*tert*-butyl-2-hydroxy-2-(2-pyridyl)ethanamide (**10a**), mp 114–115 °C.

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.75; N, 13.45. Found: C, 63.69; H, 7.92; N, 13.36.

Modified Passerini Reaction: *N*-*tert*-Butyl-2-(3,4-dichlorophenyl)-2-hydroxyethanamide (10c). (A) Preferred Procedure. A mixture of purified 3,4-dichlorobenzaldehyde (8.75 g, 0.050 mol), *tert*-butyl isocyanide (2.08 g, 0.035 mol), and pyridine (3.96 g, 0.050 mol) in 25 mL of CH_2Cl_2 was cooled to −5 °C (dry ice–acetone) under N_2 and treated dropwise with stirring at −5 to +5 °C with 2.9 g of CF_3CO_2H (0.025 mol). The mixture was warmed to room temperature for 1 h, after which TLC (2% CH_3OH–$CHCl_3$, silica gel) showed little conversion to **10c**. The mixture was treated dropwise with an additional 2.9 g of CF_3CO_2H at 20–30 °C (ice cooling); after 30 min, TLC showed significant conversion to **10c**. The mixture was stirred 2 h at room temperature and then treated with a solution of 15 g of $NaHSO_3$ in 100 mL of H_2O for 2 h at room temperature. The mixture was filtered to give 9.0 g of the $NaHSO_3$ adduct of the starting aldehyde (mp 164–165 °C), and the CH_2Cl_2 layer obtained from the filtrate was dried (Na_2SO_4) and concentrated to give crude **10c**. Recrystallization from *n*-C_4H_9Cl gave pure **10c**: mp 116–117 °C; 2.90 g (60% based on recovered $NaHSO_3$ adduct of starting aldehyde); ^{1}H NMR δ 7.42 (1 H, d, *J* = 1 Hz), 7.35 (1 H, d, *J* = 7 Hz), 7.13 (1 H, dd, *J* = 1, 7 Hz), 4.82 (1 H, d, *J* = 4 Hz, exchangeable), 4.72 (1 H, d, *J* = 4 Hz), 1.28 (9 H, s).

Anal. Calcd for $C_{12}H_{15}Cl_2NO_2$: C, 52.19; H, 5.48; N, 5.07. Found: C, 52.18; H, 5.62; N, 5.03.

(B) Pyridinium Trifluoroacetate Procedure. To a solution of pyridine (3.96 g, 0.050 mol) and trifluoroacetic acid (3.8 mL, 5.62 g, 0.049 mol) in 25 mL of CH_2Cl_2 was added 3,4-dichlorobenzaldehyde (8.75 g, 0.050 mol) and *tert*-butyl isocyanide (2.08 g, 0.035 mol) with stirring at room temperature under N_2. The mixture was stirred 42 h at room temperature and refluxed 6 h. An NMR spectrum of the reaction mixture showed no unreacted isocyanide (characteristic *tert*-butyl triplet at δ ($CDCl_3$) 1.43). The mixture was diluted to 100 mL with CH_2Cl_2 and stirred 2 h at room temperature with a solution of 15 g of $NaHSO_3$ in 100 mL of water. The mixture was worked up as in procedure A (except that CH_2Cl_2 was evaporated after mixing with aqueous $NaHSO_3$). There was obtained 9.6 g of the $NaHSO_3$ adduct of the starting aldehyde and 1.95 g (66% of procedure A) of pure **10c**, mp 116–117.5 °C (isolated by alumina chromatography and crystallization from *n*-C_4H_9Cl).

Reduction of Hydroxy Amides: *N*-*tert*-Butyl-2-hydroxy-2-methyl-3-phenoxy-1-propanamine (13e) Hydrogen Maleate. To a cooled, stirred solution of 2.51 g (10.0 mmol) of *N*-*tert*-butyl-2-methyl-2-hydroxy-3-phenoxypropanamide (**10e**) in 40 mL of tetrahydrofuran (dried by percolating through activity I Al_2O_3) under N_2 was added 3.2 mL of borane–dimethyl sulfide from a syringe. The stirred mixture was heated to reflux for 4 h, treated with an additional 1 mL (total 44 mmol) of BH_3·$(CH_3)_2S$, and refluxed 1 h longer. The mixture was stirred overnight at room temperature, cooled to 0 °C, and treated with 8 mL of glacial CH_3CO_2H dropwise. After gas evolution ceased, water (2 mL) was added and the solvent removed by distillation. The residual suspension was diluted with water, basified with NaOH, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated under vacuum to give crude **13e** which was converted to the hydrogen maleate salt with a solution of 1.5 g maleic acid in 33 mL of CH_3CN: yield 1.9 g (54%); mp 161–161.5 °C.

Anal. Calcd for $C_{14}H_{23}NO_2$·$C_4H_4O_4$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.42; H, 7.55; N, 4.01.

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Methods for Converting *N*-Alkyl Lactams to Vinylogous Urethanes and Vinylogous Amides via (Methylthio)alkylideniminium Salts

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Treatment of enolizable (methylthio)alkylideniminium salts with active methylene compounds under basic conditions gives Knoevenagel-type adducts in excellent yields. Attempts to convert several of these adducts to vinylogous urethanes and vinylogous amides met with varied success. One-pot preparations of vinylogous urethanes and vinylogous amides from (methylthio)alkylideniminium salts and selected active methylene compounds are also described.

During the course of studies directed toward the synthesis of nitrogenous natural products we needed to convert enolizable *N*-alkyl lactams **1** to vinylogous amides and vinylogous urethanes **3**. A survey of the literature revealed that an established method for accomplishing this transformation was via the derived thiolactam **2** by use of the elegant sulfide-contraction procedure developed by the Eschenmoser group.[1-3] It also appeared that existing methods for performing Knoevenagel-type reactions on

(1) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.

(2) For the first application of the "sulfide-contraction" procedure to *N*-alkyl lactams see: Yamaguchi, H. *Chem. Abstr.* **1973**, *78*, 29617.

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