diation and isolation procedure described for compound 4 to give 0.13 g (0.23 mmol, 91%) of methyl 3-*O*-(4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-2,6-dideoxy-4-*O*-(*p*-tolylsulfonyl)-α-D-*arabino*-hexopyranoside (8), identical in NMR spectra (^{1}H and ^{13}C) and purity with an authentic sample of 8 obtained by hydrogenolysis.[15]

Debenzylation of Methyl 2,6-Dideoxy-3-*O*-(2,6-dideoxy-4-*O*-(*p*-tolylsulfonyl)-β-D-*arabino*-hexopyranosyl)-4-*O*-(*p*-tolylsulfonyl)-α-D-*arabino*-hexopyranoside (6). Compound 6 (0.80 g, 1.16 mmol) and 0.27 g (1.51 mmol) of *N*-bromosuccinimide were reacted, and the product was purified as described for compound 4 to give 0.59 g (1.10 mmol, 95%) of methyl 2,6-dideoxy-3-*O*-(2,6-dideoxy-4-*O*-(*p*-tolylsulfonyl)-β-D-*arabino*-hexopyranosyl)-4-*O*-(*p*-tolylsulfonyl)-α-D-*arabino*-hexopyranoside (9): mp 106–108 °C; R_f 0.13; ^{13}C NMR (acetone-d_6) δ 18.27, 18.59 (C_6, $C_{6'}$), 21.67, 21.86 ($ArCH_3$), 35.90 (C_2), 40.32 ($C_{2'}$), 55.03 (OCH_3), 66.79 (C_5), 69.07, 70.11, 71.24 (C_3, $C_{3'}$, C_5), 85.37 (C_4), 87.50 ($C_{4'}$), 95.86 ($C_{1'}$), 98.86 (C_1), 129.31, 129.75, 130.75, 130.96, 136.35, 136.82, 145.91 (aromatic carbons); ^{1}H NMR (acetone-d_6) δ 0.81 ($H_{2a'}$, $J_{1',2a'}$ = 11.6 Hz, $J_{2a',3'}$ = 9.9 Hz), 1.09 (H_6, $J_{5,6}$ = 6.2 Hz), 1.36 ($H_{6'}$, $J_{5',6'}$ = 6.2 Hz), 1.51 (H_{2a}, $J_{1,2a}$ = 3.6 Hz, $J_{2a,3}$ = 10.8 Hz), 1.75 ($H_{2e'}$, $J_{1',2e'}$ = 1.9 Hz, $J_{2e',3'}$ = 5.4 Hz), 2.20 (H_{2e}, $J_{1,2e}$ = 1.0 Hz, $J_{2e,3}$ = 5.2 Hz), 2.45, 2.57 ($ArCH_3$), 3.28 (OCH_3), 4.20 (H_4, $J_{4,5}$ = $J_{3,4}$ = 9.0 Hz), 4.46 ($H_{1'}$), 4.71 (H_1), 4.9 ($H_{4'}$, $J_{3',4'}$ = $J_{4',5'}$ = 9.2 Hz), 7.39–7.49 and 7.78–7.89 (aromatic). Anal. Calcd for $C_{27}H_{36}O_{11}S_2$: C, 53.98; H, 6.04. Found: C, 53.55; H, 6.11.

Methyl 4-*O*-Acetyl-3-*O*-benzyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (10). Methyl 3-*O*-benzyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (0.82 g, 3.25 mmol), prepared according to the procedure of Monneret et al.,[18] was dissolved in 10 mL of pyridine, and 1.0 g (13 mmol) of acetyl chloride was added in a dropwise manner to the rapidly stirred solution. The reaction mixture was allowed to stand for 14 h at room temperature, and then 1 mL of water was added to the stirred solution, which was cooled in an ice bath. The entire reaction mixture then was poured slowly into 200 mL of a rapidly stirred solution of saturated sodium bicarbonate. The solution was extracted three times with chloroform (50 mL), the solvent was distilled from the combined organic extracts, and the residue was chromatographed in the standard fashion to give 0.86 g (2.93 mmol, 90%) of compound 10: R_f 0.56; ^{13}C NMR δ 17.63 (C_6), 20.99 (CH_3CO), 35.53 (C_2), 54.64 (CH_3O), 65.84 (C_5), 71.30 (CH_2), 74.28 (C_3), 76.33 (C_4), 98.31 (C_1), 127.36, 127.49, 128.33 (aromatic), 170.09 (C=O); ^{1}H NMR δ 1.16 (H_6, $J_{5,6}$ = 6.3 Hz), 1.71 (H_{2a}, $J_{1,2a}$ = 3.6 Hz, $J_{2a,2e}$ = 13.2 Hz, $J_{2a,3}$ = 11.2 Hz), 2.01 (CH_3CO), 2.27 (H_{2e}, $J_{1,2e}$ = 1.4 Hz, $J_{2e,3}$ = 5.2 Hz), 3.29 (OCH_3), 3.46–3.99 (H_3, H_5), 4.50, 4.55 (CH_2), 4.74 (H_1), 4.76 (H_4, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz); exact mass calcd for $C_{16}H_{22}O_5$ 294.1468, found 294.1547.

Methyl 3-*O*-Benzyl-2,6-dideoxy-4-*O*-((2-methoxyethoxy)methyl)-α-D-*arabino*-hexopyranoside (11). Methyl 3-*O*-benzyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside[18] (0.84 g, 3.3 mmol) and *N*,*N*-diisopropylethylamine (1.93 g, 15 mmol) were dissolved in 20 mL of dichloromethane, and 1.24 g (10 mmol) of (2-methoxyethoxy)methyl chloride was added to the stirred solution. The reaction mixture was heated under reflux for 14 h. The solvent was distilled under reduced pressure, and the residue was chromatographed in the normal fashion to give 0.91 g (2.7 mmol, 81%) of compound 11: R_f 0.39; ^{13}C NMR δ 17.89 (C_6), 34.87 (C_2), 54.52 (OCH_3, anomeric), 58.99 (OCH_3), 66.89 (C_5), 67.78, (C_3), 71.32 ($ArCH_2$), 71.78, 77.14 (OCH_2CH_2O), 81.49 (C_4), 97.06 (OCH_2O), 98.26 (C_1), 127.04, 127.84, 138.20 (aromatic); ^{1}H NMR δ 1.27 (H_6, $J_{5,6}$ = 6.1 Hz), 1.59 (H_{2a}, $J_{1,2a}$ = 3.6 Hz, $J_{2a,3}$ = 11.2 Hz, $J_{2a,2e}$ = 13.0 Hz), 2.33 (H_{2e}, $J_{1,2e}$ = 1.4 Hz, $J_{2e,3}$ = 5.0 Hz), 3.27, 3.32 (OCH_3), 4.54, 4.51 (OCH_2O), 4.70 (H_1), 7.27 (aromatic); exact mass calcd for $C_{18}H_{29}O_6$ (MH^+) 341.1964, found 341.2015.

Debenzylation of Compound 10. Compound 10 (0.53 g, 1.8 mmol) and 0.45 g (2.52 mmol) of *N*-bromosuccinimide were irradiated, and the reaction mixture was chromatographed as described for compound 2 to give 0.31 g (1.5 mmol, 85%) of methyl 4-*O*-acetyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (12): R_f 0.10; ^{13}C NMR δ 17.63 (C_6), 21.05 (CH_3CO), 38.28 (C_2), 54.74 (OCH_3), 65.42 (C_5), 67.48 (C_3), 78.99 (C_4), 98.29 (C_1); ^{1}H NMR δ 1.18 (H_6, $J_{5,6}$ = 6.2 Hz), 1.71 (H_{2a}, $J_{1,2a}$ = 3.6 Hz, $J_{2a,3}$ = 11.3 Hz, $J_{2a,2e}$ = 13.1), 2.12 (CH_3CO), 3.32 (OCH_3), 4.52 (H_4, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz), 4.75 (H_1); exact mass calcd for $C_9H_{16}O_5$ 204.0997, found 204.0949.

Debenzylation of Compound 11. Compound 11 (0.37 g, 1.09 mmol) and 0.25 g (1.4 mmol) of *N*-bromosuccinimide were irradiated, and the reaction mixture was chromatographed as described for compound 2 to give 0.23 g (0.94 mmol, 86%) of methyl 2,6-dideoxy-4-*O*-((2-methoxyethoxy)methyl)-α-D-*arabino*-hexopyranoside (13): R_f 0.07; ^{13}C NMR δ 17.87 (C_6), 37.05 (C_2), 54.59 (OCH_3, anomeric), 58.97 OCH_3), 65.89 (C_5), 67.87 (C_3), 67.23, 71.57 (OCH_2CH_2O), 89.04 (C_4), 97.26 (OCH_2O), 98.36 (C_1); ^{1}H NMR δ 1.25 (H_6, $J_{5,6}$ = 6.2 Hz), 1.63 (H_{2a}, $J_{1,2a}$ = 3.6 Hz, $J_{2a,3}$ = 11.5 Hz, $J_{2a,2e}$ = 13.2 Hz), 2.18 (H_{2e}, $J_{1,2e}$ = 1.2 Hz, $J_{2e,3}$ = 5.5 Hz), 2.91 (H_4, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz), 3.31 (OMe), 3.38 (OMe), 4.74 (H_1), 4.74, 4.92 (OCH_2O); exact mass calcd for $C_{11}H_{23}O_6$ (MH^+) 251.1493, found 251.1440.

Debenzylation of 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (14).[19] Compound 14 (0.52 g, 1.48 mmol) and 0.53 g (3.0 mmol) of *N*-bromosuccinimide were dissolved in 100 mL of carbon tetrachloride, and the reaction mixture was stirred for 1 h while being purged with nitrogen. The nitrogen purge was continued during 1 h of irradiation. After irradiation, the reaction mixture was poured into 20 mL of rapidly stirred, saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with 30 mL of chloroform. The solvent was distilled from the combined organic extracts, and the residue was chromatographed by the standard procedure to give 0.23 mg (0.90 mmol, 60%) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, mp 106–108 °C (lit.[5] mp 106–108 °C). The ^{1}H NMR spectrum of this material also was identical with that of the authentic sample.[20]

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Registry No. 2, 121330-33-4; 3, 14624-27-2; 4, 121330-38-9; 5, 121330-37-8; 6, 123567-40-8; 6 (monotosyl deriv), 121330-39-0; 7, 123567-41-9; 8, 121330-41-4; 9, 123567-42-0; 10, 123567-43-1; 10 (deacetyl deriv), 90762-83-7; 11, 123567-44-2; 12, 123567-45-3; 13, 123567-46-4; 14, 18685-18-2; 14 (debenzylated deriv), 582-52-5; (2-methoxyethoxy)methyl chloride, 3970-21-6.

(18) Monneret, C.; Gagnet, R.; Florent, J.-C. *J. Carbohydr. Chem.* **1987**, *6*, 221.

(19) Gramera, R. E.; Bruce, R. M.; Hirase, S.; Whistler, R. L. *J. Org. Chem.* **1963**, *28*, 1401.

(20) Aldrich Chemical Co., Milwaukee, WI.

Syntheses of Trifluoromethylated Pyridinones and Pyrimidinones

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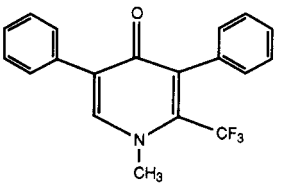
Although a large number of 6-(trifluoromethyl)uracils[1-5] and 6-(trifluoromethyl)-4(3*H*)-pyrimidinones[6,7] are known, there are few reported 2-(trifluoromethyl)-4(1*H*)-pyridinones[8-10] prior to our own investigation of the cy-

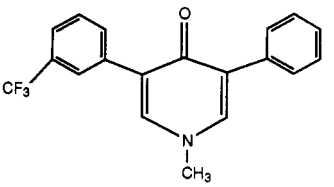
(1) Sing, Y. L.; Lee, L. F. *J. Org. Chem.* **1985**, *50*, 4642.
(2) Lutz, A. W.; Trotto, S. H. *J. Heterocycl. Chem.* **1972**, *9*, 513.
(3) (a) Gershon, H.; Grefig, A. T. *J. Heterocycl. Chem.* **1984**, *21*, 1161. (b) Gershon, H.; Grefig, A. T.; Scala, A. A. *Ibid.* **1983**, *20*, 219.
(4) Yoshimoto, M.; Hansch, C. *J. Med. Chem.* **1976**, *19*, 71.
(5) Ishihara, T.; Yamasaki, Y.; Ando, T. *Tetrahedron Lett.* **1986**, *27*, 2879.
(6) Inoue, S.; Saggiomo, A. J.; Nodiff, E. A. *J. Org. Chem.* **1961**, *26*, 4504.
(7) Bergmann, E. D.; Cohen, S.; Shahak, I. *J. Chem. Soc.* **1959**, 3278.

0022-3263/90/1955-0380$02.50/0

clization of alkyl 2-acetyl-3-amino-4,4,4-trifluorocrotonates to 2-(trifluoromethyl)-3-carboalkoxy-4(1*H*)-pyridinones,[11] and the 1-alkyl-4-(trifluoromethyl)-6(1*H*)-pyrimidinones are unknown. Most of the reported 6-(trifluoromethyl)-uracils are derived from ethyl 4,4,4-trifluoroacetoacetate,[3,4] ethyl 3-amino-4,4,4-trifluorocrotonate,[2] or 3,4,4,4-tetrafluorocrotonamides.[5] The 6-(trifluoromethyl)-4(3*H*)-pyrimidinones generally are prepared from reaction of amidines with ethyl 4,4,4-trifluoroacetoacetate.[6,7] The reported 2-(trifluoromethyl)-4(1*H*)-pyridinones are derived from cyclization of 1,1,1,7,7,7-hexafluoroheptane-2,4,6-trione,[8] hydrolysis of 4-halo-2-(trifluoromethyl)pyridines,[9] or reaction of 2-(trifluoromethyl)-6*H*-1,3-oxazin-6-ones, the products from the reaction of 3-aminoacrylates with trifluoroacetic anhydride, with Reformatsky reagent.[10] We are interested in the synthesis of 1-methyl-2-(trifluoromethyl)-4(1*H*)-pyridinone (**1**) due to its structural resemblance to a commercial herbicide, fluridone (**2**).[12] Recently we reported a one-step synthesis of a 6-(trifluoromethyl)uracil from reaction of *N*-(cyanoacetyl)urethane with trifluoroacetonitrile.[1] We would like to communicate here the convenient syntheses of 2-(trifluoromethyl)-4-(1*H*)-pyridinones and a 4-(trifluoromethyl)-6(1*H*)-pyrimidinone with trifluoroacetonitrile as the starting material.



1

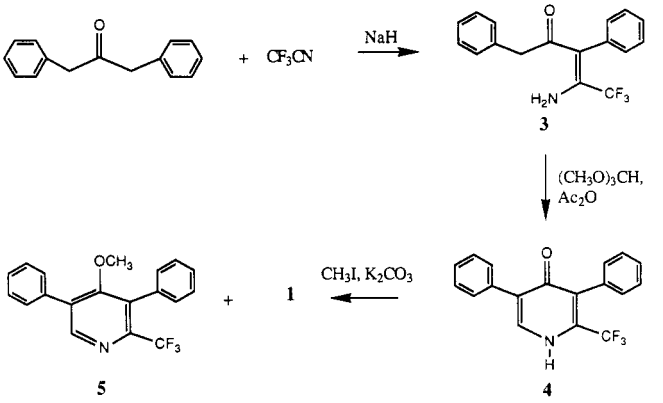


2

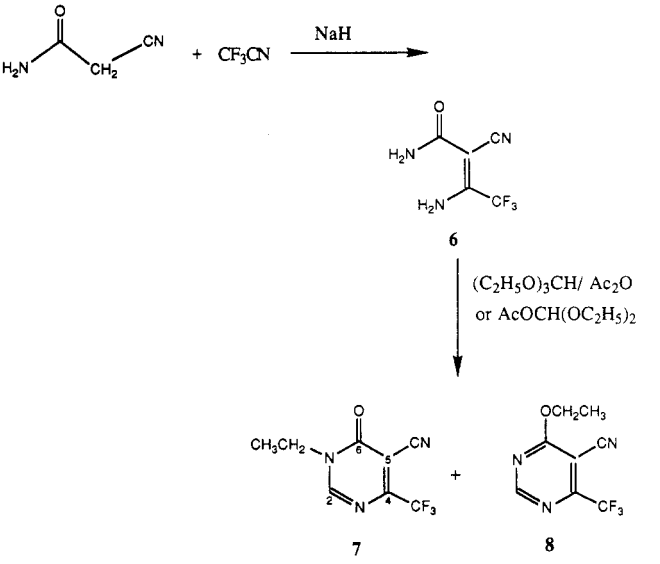
We found that **1** can be readily prepared via the route shown in Scheme I. The success of this route is based on the high reactivity of trifluoroacetonitrile toward active methylene compounds.[13,14] Reaction of the sodium enolate of 1,3-diphenylacetone, prepared from 1,3-diphenylacetone and sodium hydride, with gaseous trifluoroacetonitrile gave the enamino ketone **3** in 44% yield. Cyclization of **3** with a mixture of trimethyl orthoformate and acetic anhydride at reflux produced 3,5-diphenyl-2-(trifluoromethyl)-4-(1*H*)-pyridinone (**4**) in 45% yield. Direct cyclization of enamino ketones to 4(1*H*)-pyridinones has been achieved previously using *N*,*N*-dimethylformamide dimethyl acetal as the reagent.[15] Alkylation of **4** with methyl iodide provided **1** and the 4-methoxypyridine **5** in 27% and 68% yields, respectively. The 1-methyl-4(1*H*)-pyridinone **1** can be easily distinguished from **5** by its long-range coupling of the CF_3 fluorine to both the methyl protons and the methyl carbon in the ^1H and ^{13}C NMR spectra (see the Experimental Section).

In a similar fashion, we prepared 5-cyano-1-ethyl-4-(trifluoromethyl)-6(1*H*)-pyrimidinone (**7**) via the route shown in Scheme II. Treatment of cyanoacetamide with

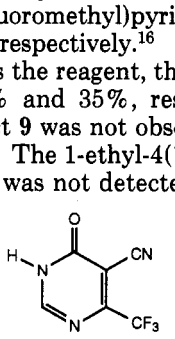
Scheme I



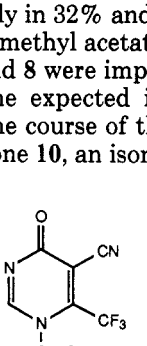
Scheme II



sodium hydride followed by passing gaseous trifluoroacetonitrile through the resulting enolate solution gave the adduct **6** in 72% yield. Unlike the reaction of **3** with a mixture of trimethyl orthoformate and acetic anhydride, reaction of **6** with a mixture of triethyl orthoformate and acetic anhydride at reflux provided **7** and the 4-ethoxy-6-(trifluoromethyl)pyrimidine **8** directly in 32% and 43% yields, respectively.[16] When diethoxymethyl acetate was used as the reagent, the yields of **7** and **8** were improved to 49% and 35%, respectively. The expected initial product **9** was not observed during the course of the reaction. The 1-ethyl-4(1*H*)-pyrimidinone **10**, an isomer of **7**, also was not detected.



9



10

The 6(1*H*)-pyrimidinone **7** is a solid. It has a C=O IR adsorption at 1700 cm^{-1}. The long-range couplings of the

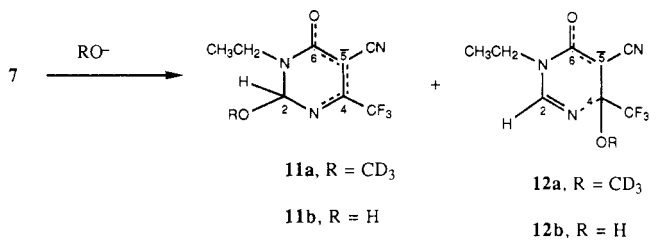
(8) Risterik, R. H. U.S. Patent 3,748,334, 1973; *Chem. Abstr.* **1973**, *79*, 78627.
(9) Torba, F. E. U.S. Patent 3,609,158, 1971; *Chem. Abstr.* **1971**, *71*, 3699.
(10) Clemence, F.; Le Martret, O.; Delevallee, F. Ger. Offen. DE 3,808,444, 1988; *Chem. Abstr.* **1989**, *110*, 38902.
(11) (a) Lee, L. F.; Miller, M. L. U.S. Patent 4,698,093, 1987; Eur. Pat. Appl. EP 182,769, 1986; *Chem. Abstr.* **1986**, *105*, 190960. (b) Miller, M. L.; Dolson, M. G.; Lee, L. F. Eur. Pat. Appl. EP 245,230; *Chem. Abstr.* **1988**, *108*, 131596. (c) Manuscripts in preparation.
(12) Waldrep, T. W.; Taylor, H. M. *J. Agric. Food Chem.* **1976**, *24*, 1250.
(13) Josey, A. D. *J. Org. Chem.* **1964**, *29*, 707.
(14) Bodnarchuk, N. D.; Gavrilenko, B. B.; Derkach, G. I. *J. Org. Chem. USSR (Engl. Transl.)* **1968**, *4*, 1645; *Zh. Org. Khim.* **1968**, *4*, 1710.
(15) (a) Abdulla, R. F.; Emmick, T. L.; Taylor, H. M. *Synth. Commun.* **1977**, *7*, 305. (b) Abdulla, R. F.; Fuhr, K. H.; Williams, J. C., Jr. *J. Org. Chem.* **1979**, *44*, 1349.
(16) In response to the suggestion of one of the referees, the reaction of **6** with a mixture of trimethyl orthoformate and acetic anhydride was caried out to give the similar results.

Table I. ^{13}C NMR Chemical Shifts (δ) and Coupling Constants (J)[a] of 7, 11a, 12a, and 12b

compd no.	C-2	C-4	C-5	C-6	CN	CF_3	CH_2	CH_3
7[b]	157.60 (td) $^1J_{CH}$ = 211.4 $^2J_{CH}$ = 5.0	154.05 (dq) $^2J_{CF}$ = 35.8 $^3J_{CH}$ = 12.5	101.86 (s)	158.45 (dt) $^2J_{CH}$ = 5.5 $^3J_{CH}$ = 3.5	110.61 (s)	119.58 (q) $^1J_{CF}$ = 276.3	44.13 (dqt) $^1J_{CH}$ = 144.3 $^2J_{CH}$ = 4.5 $^3J_{CH}$ = 2.5	12.85 (tq) $^1J_{CH}$ = 128.8 $^2J_{CH}$ = 3.6
11a[c]	97.11 (d) $^1J_{CH}$ = 178.0	159.42 (dq) $^2J_{CF}$ = 32.3 $^3J_{CH}$ = 7.6	66.33 (s)	168.95 (dt) $^2J_{CH}$ = 3.7 $^3J_{CH}$ = 3.4	123.27 (s)	123.43 (q) $^1J_{CF}$ = 250.2	41.73 (qt) $^1J_{CH}$ = 136.8 $^2J_{CH}$ = 2.5	15.96 (tq) $^1J_{CH}$ = 126.0 $^2J_{CH}$ = 2.1
12a[c]	153.76 (d) $^1J_{CH}$ = 194.4	94.68 (dt) $^2J_{CF}$ = 30.5 $^3J_{CH}$ = 12.4	66.33 (s)	167.48[d]	127.16 (s)	–[e]	42.56[d]	17.69[d]
11b[f]	94.82 (d) $^1J_{CH}$ = 175.1	155.57 $^2J_{CF}$ = 31.2 $^3J_{CH}$ = 9.0	59.65 (s)[g]	168.85 (dt)[g] $^3J_{CH}$ = 4.6 $^3J_{CH}$ = 3.6	127.40 (s)[g]	128.85 (q)[g] $^1J_{CF}$ = 292	42.71 (t)[g,h] $^1J_{CH}$ = 139.9	17.64 (q)[g,h] $^1J_{CH}$ = 126.8
12b[f]	149.85 (td) $^1J_{CH}$ = 194.5 $^3J_{CH}$ = 4.4	89.22 (dq) $^2J_{CF}$ = 28.9 $^3J_{CH}$ = 11.1	66.32 (s)[g]	166.78 (dt)[g] $^3J_{CH}$ = 4.7 $^3J_{CH}$ = 3.4	131.48 (s)[g]	123.35 (q)[g] $^1J_{CF}$ = 278	41.21 (t)[g,h] $^1J_{CH}$ = 137.6	16.60 (q)[g,h] $^1J_{CH}$ = 126.7

[a] Me_4Si was used as the reference for ^1H and ^{13}C NMR spectra; CCl_3F was used as the reference for ^{19}F NMR spectra; chemical shifts in ppm, multiplicities in parentheses; coupling constants in hertz; long range C–H coupling constants in ^{13}C NMR spectra determined by proton coupled experiments. [b] Sample dissolved in CD_3OD. [c] Formed from addition of 7 to a 10% $NaOCD_3$ solution in CD_3OD. [d] Signal in the proton coupled ^{13}C NMR spectra too weak for the determination of multiplicity and coupling constants. [e] Signal too weak to be determined. [f] Formed from addition of 7 to a 10% solution of NaOH in D_2O. [g] Signal can not be unequivocally assigned to either **11b** or **12b**. [h] Long-range C–H couplings were unresolved.

Scheme III



11a, R = CD_3

11b, R = H

12a, R = CD_3

12b, R = H

CH_2 protons to both C-2 and C-6 in the ^{13}C NMR spectrum (see Table I) of the isolated solid clearly support the structural assignment of **7** instead of **10**. We found that **7** is surprisingly soluble in aqueous sodium hydroxide. It was separated from **8** by extraction of the crude reaction product with aqueous sodium hydroxide followed by immediate acidification of the alkaline extract with dilute hydrochloric acid.

The ^1H, ^{19}F, and ^{13}C NMR spectra reveal that **7** forms a mixture of two adducts (see Scheme III) in either aqueous sodium hydroxide or methanolic sodium methoxide-d_3 solution. The H-2 of **7** in CD_3OD appears at δ 8.76. This signal disappears upon addition of sodium methoxide-d_3 with the concurrent appearance of two new signals at δ 5.90 and 7.43 with a signal intensity ratio of 10:1. Similarly, the ^{19}F signal of **7** at δ –69.66 disappears and is replaced by the signals at δ –70.73 and –83.73 also in a 10:1 ratio. We assign the major ^1H and ^{19}F signals at δ 5.90 and –70.73 to H-2 and the CF_3 fluorine, respectively, of the predominant adduct **11a**, and the minor ^1H and ^{19}F signals at δ 7.43 and –83.73 to H-2 and the CF_3 fluorine, respectively, of the minor adduct **12a**. The formation of the predominant adduct **11a** in the presence of sodium methoxide-d_3 is also supported by the upfield shifts of the ^{13}C signals of **7** at δ 157.60 (C-2) and 101.86 (C-5) to δ 97.11 and 66.33, respectively. We believe that the predominant formation of **11a** is due to less steric hindrance at C-2 position than the C-4 position. The less sterically bulky hydroxide ion reacts with **7** to form a 1:1 mixture of adducts **11b** and **12b**. The ^1H NMR of **7** in a solution of sodium hydroxide in D_2O exhibits two signals of equal intensity at δ 6.98 and 5.81 for H-2. The ^{19}F NMR of the same solution also shows two signals at δ –68.46 and –82.33 also of equal intensity. We assign the lower field ^1H signal at 6.98 and the higher field ^{19}F signal at δ –82.33 to H-2 and the CF_3 fluorine, respectively, of **12b**. The higher field ^1H signal at δ 5.81 and the lower field ^{19}F signal at δ –68.46 are assigned as H-2 and the CF_3 fluorine, respectively, of **11b**. The appearance of ^{13}C signals at δ 94.82 for C-2 of **11b** and δ 89.22 for C-4 of **12b**, both at substantially higher field than the signals for C-2 and C-4 of **7** in $CDCl_3$, is consistent with the formation of a mixture of **11b** and **12b**. The assignments of the ^{13}C signals of C-2 and C-4 in **7**, **11a**, **11b**, **12a**, and **12b** can be unambiguously established by the long-range C–H and C–F couplings (see Table I). The methanolic solution of the mixture of **11a** and **12a** is stable for days, but the aqueous solution of the mixture of **11b** and **12b** is unstable within several hours and decomposes to unidentified products.

Although the formation of anionic σ-adducts are well known in the electron-deficient aromatic[17] and heteroaromatic[18–23] substrates, to our knowledge the formation of σ-adducts such as **11a,b** and **12a,b** is rare in 6(1*H*)-pyrimidinones which do not contain a nitro group.[24] Trifluoroacetonitrile has been utilized for the preparation of trifluoromethylated heterocycles[25–27] prior to our first communication.[1] However, these preparations are reported to produce the heterocycles in low yields. Our present results and our recent success in the syntheses of trifluoromethylated uracil,[1] pyrimidinecarboxylates,[28] pyri-

(17) For a review, see: Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667.
(18) (a) de Bie, D. A.; Geurtsen, B.; Berg, I. E.; van der Plas, H. C. *J. Org. Chem.* **1986**, *51*, 3209. (b) Holterman, H. A. J.; van Veldhuizen, A.; van der Plas, H. C. *Ibid.* **1986**, *51*, 1147.
(19) Tohda, Y.; Ariga, M.; Kawashima, T. Matsumura, E. *Chem. Lett.* **1983**, 718.
(20) Pitman, I. H.; Cho, M. J.; Rork, G. S. *J. Am. Chem. Soc.* **1974**, *96*, 1840.
(21) Biffin, M. E. C.; Miller, J.; Moritz, A. G.; Paul, D. B. *Aust. J. Chem.* **1969**, *22*, 2561.
(22) Abbolito, A.; Iavarone, C.; Illuminati, G.; Stegel, F.; Vazzoler, A. *J. Am. Chem. Soc.* **1969**, *91*, 6746.
(23) Kost, A. N.; Gromov, S. P.; Sagitullin, R. S. *Tetrahedron* **1981**, *37*, 3423.
(24) Angelino, S. A. G. F.; Buurman, D. J.; van der Plas, H. C.; Muller, F. *J. Heterocycl. Chem.* **1984**, *22*, 749.
(25) Janz, G. J.; De Crescente, M. A. *J. Org. Chem.* **1958**, *23*, 765.
(26) (a) Banks, R. E.; Thompson, J. *J. Fluorine Chem.* **1983**, *22*, 589. (b) Banks, R. E.; Thompson, J. *Ibid.* **1984**, *26*, 499.
(27) (a) Burger, K.; Hein, F.; Wassmuth, U.; Krist, H. *Synthesis* **1981**, 904. (b) Burger, K.; Wassmuth, U.; Hein, F.; Rottegger, S. *Justus Liebigs Ann. Chem.* **1984**, 991.
(28) Sing, Y. L.; Lee, L. F. *J. Heterocycl. Chem.* **1989**, *26*, 7.

dinecarboxylates,[11] and 4,6-dihydroxypyridine[29] in practical yields as well as a recent report of the synthesis of 2,4-bis(trifluoromethyl)pyrimidines[30] in modest yields, demonstrate that trifluoroacetonitrile, a commercially available gas, can be a versatile reagent for the syntheses of a variety of nitrogen-containing (trifluoromethyl)heterocycles.

Experimental Section

Melting points were determined with a Laboratory Devices Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Varian T-60 (60 MHz), a Varian EM-360 (60 MHz), a Varian XL 300 (300 MHz), or a Varian XL 400 (400 MHz) spectrometer. ^{13}C NMR spectra were measured either at 25.05 MHz with a JEOL FX-100, at 75.4 MHz with a Varian XL 300, or at 100 MHz with a Varian XL 400 spectrometer. ^{19}F NMR spectra were obtained with a Varian EM-390 (90 MHz) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise noted and are expressed in parts per million (ppm) downfield from Me_4Si; the coupling constants are expressed as ^nJ, where n is the number of bonds between carbon and fluorine or carbon and hydrogen; coupling constants are in hertz. ^{13}C NMR spectra were proton decoupled unless otherwise noted. Unless otherwise noted, ^{19}F NMR spectra were recorded in $CDCl_3$ using benzotrifluoride (δ −63.73) in a sealed capillary as an external standard and are expressed in ppm relative to CCl_3F, with upfield shifts taken as negative. Mass spectra were determined with a Varian Mat 311A instrument operating on either electron impact (EI) or field ionization (FI) mode. IR spectra were recorded on a Perkin-Elmer 7727 B spectrometer. Gas chromatography (GC) was performed on a Perkin-Elmer gas chromatograph using a 2 ft × 0.25 in. column packed with 10% OV 17 on 80/100 Chromosorb W. Column chromatography (CC) was performed with 60–200 mm silica gel 60(EM Reagents). Preparative medium-pressure liquid chromatography (MPLC) was done on a EM LOBAR size C silica gel column. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Unless otherwise noted, the organic layers were dried over $MgSO_4$ and concentrated in vacuo with a Büchi rotary evaporator. The flash distillations were performed using a Kugelrohr distillation apparatus, and the recorded temperature for a specific fraction was the temperature of the Kugelrohr pot.

4-Amino-5,5,5-trifluoro-1,3-diphenyl-3-penten-2-one (3). To a well-stirred cold (10 °C) mixture of 20.7 g (0.500 mol) of 58% sodium hydride oil dispersion in 150 mL of dry 1,2-dimethoxyethane (DME) was added dropwise a solution of 93.9 g (0.442 mol) of 1,3-diphenylacetone in 100 mL of DME in 50 min. The reaction mixture was kept below 22 °C with an ice–salt bath during addition of 1,3-diphenylacetone. To the reaction mixture was added an additional 50 mL of DME and then 59.0 g (0.621 mol) of trifluoroacetonitrile was passed in 5 h. The reaction mixture was poured into ice water and extracted with ether. The ether layer was separated, dried, and concentrated. The residue was crystallized from hexane to give 50.0 g (37%) of a white solid: mp 96–97 °C; IR ($CHCl_3$) 3500, 3000, 1640, 1500 cm^{-1}; ^{1}H NMR δ 7.8 (br, 2 H, NH_2), 6.8–7.4 (m, 10 H, ArH), 3.4 (s, 2 H, CH_2); ^{13}C NMR δ 200.35, 146.02 (q, $^2J_{CF}$ = 30.2), 135.45, 135.10, 132.48, 129.60, 128.27, 128.17, 127.91, 126.56, 120.48 (q, $^1J_{CF}$ = 279.5), 109.25, 47.79; ^{19}F NMR δ −64.36.

Anal. Calcd for $C_{17}H_{14}F_3NO$: C, 66.88; H, 4.62; N, 4.59. Found: C, 66.85; H, 4.67; N, 4.58.

An additional 9.0 g (6.6%) of a solid, mp 88–93 °C, which appeared to be a mixture of *E* and *Z* isomers of **3** based on a ^{1}H NMR spetrum, was isolated from the mother liquor.

3,5-Diphenyl-2-(trifluoromethyl)-4(1*H*)-pyridinone (4). A mixture of 15.0 g (0.0492 mol) of **3**, 10 g of trimethyl orthoformate, and 12 g of acetic anhydride was held at reflux for 10 days, cooled, triturated with hexane, and filtered to give 7.0 g (45%) of a white solid: mp 250–252 °C; IR (Nujol) 2000–3300 (br), 1630, 1520, 1460 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.3 (s, 1 H, H-6), 7.3–7.7 (m, 10 H, ArH), NH proton was not detectable; ^{19}F NMR (Me_2SO-d_6) δ −59.43.

Anal. Calcd for $C_{18}H_{12}F_3NO$: C, 68.57; H, 3.84; N, 4.44. Found: C, 68.96; H, 4.19; N, 4.47.

1-Methyl-3,5-diphenyl-2-(trifluoromethyl)-4(1*H*)-pyridinone (1) and 4-Methoxy-3,5-diphenyl-2-(trifluoromethyl)pyridine (5). A mixture of 3.00 g (9.52 mmol) of **4**, 10 g of methyl iodide, 1.5 g of K_2CO_3, and 50 mL of acetone was held at reflux for 2 h and concentrated. The residue was stirred with a mixture of water and $CHCl_3$. The $CHCl_3$ layer was separated, dried, and concentrated. The residue was heated with ether, cooled, and filtered to give 0.74 g (24%) of **1** as a white solid: mp 199–201 °C; IR (Nujol) 1630, 1460 cm^{-1}; ^{1}H NMR δ 7.0–7.8 (m, 11 H, ArH and H-2), 3.75 (q, $^5J_{HF}$ = 2, 3 H, CH_3); ^{13}C NMR δ 175.06, 142.99, 134.27, 134.11, 133.87, 133.68(q, $^2J_{CF}$ = 31.3), 129.42 (q, $^3J_{CF}$ = 2.1), 128.96, 128.59, 128.14, 127.95, 127.90, 127.69, 120.94(q, $^1J_{CF}$ = 277.9), 43.61 (q, $^4J_{CF}$ = 5.0); ^{19}F NMR δ −54.76 (q, $^5J_{HF}$ = 2).

Anal. Calcd for $C_{19}H_{14}F_3N$: C, 69.29; H, 4.28; N, 4.25. Found: C, 69.28; H, 4.31; N, 4.26.

The filtrate was concentrated, and the residue was purified by MPLC using a 2:3 mixture of EtOAc–cyclohexane as eluent to give two fractions. The earlier fraction was 2.1 g (68%) of **5** as a white solid: mp 141–143 °C; IR (Nujol) 1460 cm^{-1}; ^{1}H NMR δ 8.67 (s, 1 H, H-6), 7.3–7.7 (m, 10 H, ArH), 3.20 (s, 3 H, OCH_3); ^{13}C NMR δ 163.65, 150.49, 146.18 (q, $^2J_{CF}$ = 32.6), 134.05, 133.01, 132.33, 131.51, 129.68 (q, $^3J_{CF}$ = 2.7), 129.05, 128.90, 128.73, 128.28, 127.95, 121.86 (q, $^1J_{CF}$ = 276.0), 60.94; ^{19}F NMR δ −60.66.

Anal. Calcd for $C_{19}H_{14}F_3NO$: C, 69.29; H, 4.28; N, 4.25. Found: C, 69.29; H, 4.33; N, 4.26.

The second fraction was an additional 0.1 g (3%) of **1**, mp 199–201 °C.

3-Amino-2-cyano-4,4,4-trifluoro-2-butenamide (6). To a mechanically stirred solution of 500 g (5.95 mol) of 2-cyanoacetamide in 2 L of DME was added slowly 57.0 g (2.38 mol) of sodium hydride under N_2. The reaction mixture was cooled in an ice–salt bath, and a slow stream of trifluoroacetonitrile was passed. After 830 g (8.74 mol) of trifluoroacetonitrile was passed, the reaction mixture was concentrated. The residue was dissolved in EtOAc and quenched slowly with 6 N HCl. The aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed with water, dried, and concentrated. The residual solid was recrystallized from water to give 764 g (72%) of light brown crystals: mp 155.5–156.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.67–9.67 (br, 2 H), 7.27 (br 2 H); ^{13}C NMR (Me_2CO-d_6) δ 169.13, 156.1 (q, $^2J_{CF}$ = 33), 120.34 (q, $^1J_{CF}$ = 279.4), 116.63, 72.34; ^{19}F NMR (Me_2SO-d_6) δ −66.90.

Anal. Calcd for $C_5H_4F_3N_3O$: C, 33.83; H, 2.25; N, 23.46. Found: C, 33.61; H, 2.29; N, 23.38.

5-Cyano-1-ethyl-4-(trifluoromethyl)-6(1*H*)-pyrimidinone (7) and 4-Ethoxy-6-(trifluoromethyl)-5-pyrimidinecarbonitrile (8). Procedure A. A mixture of 6.80 g (0.038 mol) of **6**, 30 mL of acetic anhydride, and 50 mL of triethyl orthoformate was held at reflux for 6.5 h and concentrated in vacuo. The residue was extracted with ether. The ether layer was extracted with 10% sodium hydroxide, dried, and concentrated. The residue was flash distilled at 1 Torr (65–80 °C) to give 3.5 g (43%) of **8** as a liquid: n^{25}_D 1.4450; IR (neat) 2240, 1550, 1480, 1450, 1440 cm^{-1}; ^{1}H NMR δ 9.06 (s, 1 H, H-2), 4.93 (q, J = 7, 2 H, CH_2), 1.40 (t, J = 7, 3 H, CH_3); ^{19}F NMR δ −67.23; ^{13}C NMR δ 170.33 (C-4), 160.30 (C-2), 158.63 (q, $^2J_{CF}$ = 36.6, C-6), 119.55 (q, $^1J_{CF}$ = 277.0, CF_3), 109.78 (CN), 94.25 (C-5), 66.31 (CH_2), 14.04 (CH_3).

Anal. Calcd for $C_8H_6F_3N_3O$: C, 44.24; H, 2.79; N, 19.35. Found: C, 44.25; H, 2.82; N, 19.30.

The sodium hydroxide extract was acidified with 6 N HCl. The oily precipitate was extracted into ether, and the ether extract was concentrated in vacuo to give 2.6 g (32%) of crude **7** as a solid, mp 55–64 °C. A portion (1.5 g) of this solid was recrystallized from $CHCl_3$–hexane to give pure **7** (0.85 g) as white plates: mp 70–73 °C; IR ($CHCl_3$) 2260, 1700 cm^{-1}; ^{1}H NMR δ 8.46 (s, 1 H, H-2), 4.10 (q, J = 7, 2 H, CH_2), 1.47 (t, J = 7, 3 H, CH_3); proton-coupled ^{13}C NMR δ 157.85 (dt, $^3J_{CH}$ = 4.1, 4.3, C-6), 157.31 (dq, $^2J_{CF}$ = 36.5, $^3J_{CH}$ = 12.6, C-4), 154.59 (d, $^1J_{CH}$ = 209.6, C-2), 119.15 (q, $^1J_{CF}$ = 277.7, CF_3), 110.46 (CN), 100.98 (C-5), 44.57 (qt, $^1J_{CH}$ = 145.6, $^2J_{CH}$ = 4.2, CH_2), 14.10 (tq, $^1J_{CH}$ = 128.7, $^2J_{CH}$ = 3.5, CH_3).

(29) (a) Lee, L. F. Eur. Pat. Appl. EP 181,311, 1986; U.S. Patent 4,609,399, 1986; *Chem. Abstr.* **1986**, *105*, 97334. (b) Lee, L. F.; Normansell, J. E., manuscript in preparation.

(30) Aizikovich, A. Y.; Zaripova, F. F. *J. Org. Chem. USSR (Engl. Transl.)* **1986**, *22*, 1408; *Zh. Org. Khim.* **1986**, *22*, 1564.

Anal. Calcd for $C_8H_6F_3N_3O$: C, 44.24; H, 2.79; N, 19.35. Found: C, 44.24; H, 2.80; N, 19.32.

Procedure B. A mixture of 5.37 g (0.030 mol) of **6** and 24.6 g (0.152 mol) of diethoxymethyl acetate was held at reflux for 64 h and concentrated. The residue was dissolved in ether, and the ether solution was extracted twice with 50 mL of 10% NaOH. The combined NaOH extracts were acidified with 50 mL of concentrated HCl. The oily precipitate was seeded with a crystal of **7** and began to solidify. The precipitate was filtered to give 3.2 g (49%) of **7** as white plates. The ether layer was dried and concentrated to 2.6 g of an oil, which was flash distilled at 1 Torr (90 °C) to give 2.3 g (35%) of **8**.

Homolytic Allyl Transfer Reactions of 1- and 3-Alkyl-Substituted Allyltributylstannanes

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Introduction

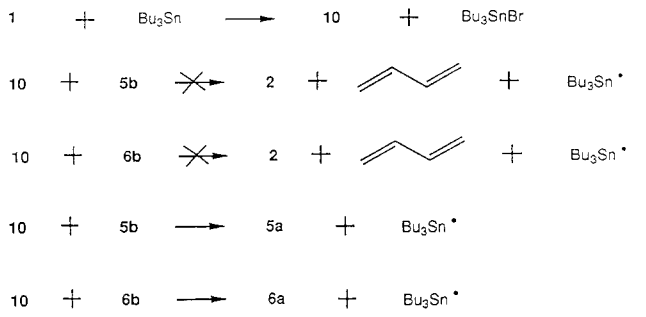
There have been several reports that homolytic allyl transfer reactions of 1- and 3-substituted allylstannanes are complicated by competing reactions.[1-4] 1,3-Rearrangement of the allylstannane, under the normal reaction conditions for homolytic allyl group transfer, can affect the integrity of the stannane and of the allylation product.[3] Alternatively, reduction of the substrate through hydrogen abstraction from the stannane can occur in preference to the allylation reaction.[1,2] This is particularly the case in reactions of 3-alkyl-substituted allylstannanes, where the steric effect of the alkyl substituent slows the rate of addition of radicals to the stannane, thus facilitating the competing reduction process. Only Pereyre and co-workers[5] have reported homolytic allyl transfer reactions of tributyl(3-methylallyl)stannane (**5b**).

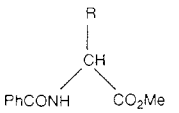
In this report we describe allyl transfer reactions of *N*-benzoyl-2-bromoglycine methyl ester (**1**) with 1-, 2-, and 3-alkyl-substituted allyltributylstannanes. These reactions illustrate that allylation with 1- and 3-alkyl-substituted allylstannanes can occur without competing reduction of the substrate. The present work is based on our preliminary study[6] of the allylation of glycine derivatives through reaction of the corresponding brominated amino acid derivatives, such as **1**, with allyltributylstannane (**3b**). Independently, Baldwin et al.[7] reported analogous allyl transfer reactions of **1** with allyltriphenylstannane and 2-functionalized allyltributylstannanes. Neither our preliminary report[6] nor the account of the work of Baldwin et al.[7] dealt with reactions of 1- or 3-substituted allylstannanes.

Results and Discussion

As described in our preliminary report,[6] the bromide **1** obtained through reaction of the glycine derivative **2** with *N*-bromosuccinimide was treated with allyltributylstannane (**3b**) (2 equiv) and azobisisobutyronitrile (ca. 0.05 equiv) in benzene at reflux under nitrogen. After chromatography of the reaction mixture on silica and recrystallization of the product from ethyl acetate–petroleum ether, the allylglycine derivative **3a** was obtained in 63% yield based on the quantity of the glycine derivative **2** used to prepare the bromide **1**. The reaction of **1** with **3b** worked equally well using carbon tetrachloride instead of benzene as the solvent, or if the reaction was carried out at room temperature instead of at reflux. Thus it was possible to prepare the bromide **1** in carbon tetrachloride and react it with the stannane **3b** in situ.

Scheme I





1 R = Br
2 R = H
3a R = $CH_2-CH=CH_2$
4a R = $CH_2-CMe=CH_2$
5a R = $CHMe-CH=CH_2$
6a R = $CH_2-CH=CHMe$
7a R = $CMe_2-CH=CH_2$
8a R = $CH_2-CH=CMe_2$
9a R = $CH-CH=CH-CH_2-CH_2$

3b R = $CH_2-CH=CH_2$
4b R = $CH_2-CMe=CH_2$
5b R = $CH_2-CH=CHMe$
6b R = $CHMe-CH=CH_2$
7b R = $CH_2-CH=CMe_2$
8b R = $CMe_2-CH=CH_2$
9b R = $CH-CH=CH-CH_2-CH_2$

Treatment of the bromide **1** with tributyl(2-methylallyl)stannane (**4b**), in benzene at reflux, gave the 4-methyl-substituted allylglycine derivative **4a** in 56% yield based on **2**. When the bromide **1** was treated with a mixture (ca. 1:1) of the (*cis*- and *trans*-3-methylallyl)-stannane **5b**, the corresponding 3-methyl-substituted allylglycine derivative **5a** was obtained in 57% yield as a 1:1 mixture of diastereomers. None of the glycine derivative **2** was detected in the reaction mixture, nor was there any evidence of formation of the 5-methyl-substituted allylglycine derivative **6a**, as determined by HPLC and ^1H NMR spectroscopic analyses of the reaction mixture. Since tributyl(1-methylallyl)stannane (**6b**) is essentially impossible to obtain in pure form due to its facile isomerization to the (3-methylallyl)stannane **5b**,[8] the reaction of **6b** with **1** was investigated by utilizing a 10-fold excess of a mixture (ca. 6:4) of the (3-methylallyl)- and (1-methylallyl)stannanes **5b** and **6b**. The reaction afforded the 3-methyl-substituted allylglycine derivative **5a** and the trans isomer of the 5-methyl-substituted analogue **6a** in yields of 5 and 19%, respectively, but none of the glycine derivative **2** was

(1) Keck, G. E.; Yates, J. B. *J. Organomet. Chem.* **1983**, *248*, C21.
(2) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.
(3) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339.
(4) For a review of the use of allylstannanes in homolytic allyl transfer reactions, see: Giese, B. In *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon: New York, 1986; Vol. 5. in the Organic Chemistry Series.
(5) Grignon, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, *61*, C33. Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1971**, *26*, C4.
(6) Easton, C. J.; Scharfbillig, I. M.; Tan, E. W. *Tetrahedron Lett.* **1988**, *29*, 1565.
(7) Baldwin, J. E.; Adlington, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G. L.; Schofield, C. J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1030.
(8) Matarasso-Tchiroukine, E.; Cardiot, P. *J. Organomet. Chem.* **1976**, *121*, 169.

0022-3263/90/1955-0384$02.50/0