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ANCHIMERIC ASSISTANCE IN THE N-ALKYLATION OF 5-ALKOXYMETHYL-2-PYRROLIDINONE DERIVATIVES

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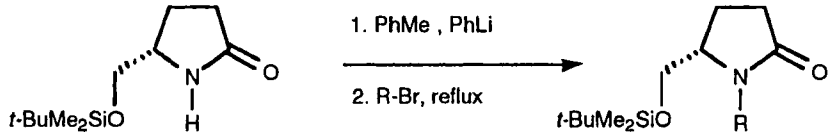
Abstract: 5-Substituted 2-pyrrolidinones are normally difficult to alkylate at nitrogen. The presence of an alkoxymethyl group at C_5, however, facilitates alkylation by a neighboring group effect.

In previous work we discovered that 5-substituted 2-pyrrolidinone derivatives reacted with allylic halides under basic conditions only with great difficulty.[1] Although Takahata[2] reported that 2-pyrrolidinone reacts with allyl halides in THF under phase transfer conditions with powdered KOH, these conditions typically gave less than 10% yields of N-alkylation when the C_5 position bore a substituent. We initially solved this problem by performing the alkylation in a sonic bath.[1] Sonication increased the yields form <10% to greater than 60% and up to 90%. We can now report that the presence of an alkoxymethyl group at C_5 greatly increases the

Table. N-Alkylation of 5-(dimethyl-*t*-butylsilyloxymethyl)-2-pyrrolidinone with Selected Halides.



2	R	% Yield
2a	$-CH_2CH=CH_2$	87
2b	n-C_5H_{11}	75
2c	CH_2CHO	55
2d	CH_2CH_2Br	<5
2e	CH_2CO_2Et	59

facility of the alkylation reaction, without sonication. In those cases where yields are relatively poor, however, ultrasound again improved the yield. Presumably, the oxygen stabilizes the N-anion shifting the equilibrium from the O-anion of the lactam. This will increase the facility of the N-alkylation reaction. Our results are shown in the Table.

5-Hydroxymethyl-2-pyrrolidinone had previously been prepared by Silverman, who reduced ethyl pyroglutamate with $LiBH_4$.[3] We have also used this alcohol in a variety of synthetic endeavors. Most of our work involves N-substituted 2-pyrrolidinone derivatives and we required facile methods for the preparation of these compounds. There appeared to be some assistance in the N-alkylation when the 5-hydroxymethyl derivative was reacted with alkyl halides under Takahata's conditions[2] but the best results were obtained when 5-hydroxymethyl-2-pyrrolidinone was converted to the O-dimethyl-*t*-butylsilyl derivative, ***1***.

Allyl bromide, as expected, gave the best result, without sonication. Amyl bromide required sonication to give 75% yield of ***2b*** but reaction of amyl bromide with other 5-substituted 2-pyrrolidinone derivatives gave <5% of the alkylated product even with sonication. 1,2-Dibromoethane gave <5% of alkylated product and is not amenable to these reaction conditions. The highly sensitive α-bromoacetaldehyde, however, gave a 55% yield of ***2c*** and ethyl α-bromoacetate gave 59% of ***2e***. The presumed anchimeric assistance provided by the 5-alkoxymethyl substituent allows the preparation of a variety of highly functionalized N-substituted 2-pyrrolidinone derivatives that are useful in organic synthesis. This is an interesting addition to the steadily increasing reports of synthetically useful 2-pyrrolidinone reactions.

EXPERIMENTAL PROCEDURES

Melting points were taken on a Thomas Hoover-capillary melting point apparatus. All melting and boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Infrared Spectrophotometer Model 283 and recorded in reciprocal centimeters. H NMR spectra were determined in d-chloroform solution on a IBM 270 MHz Spectrometer and determined in ppm using tetramethylsilane as an internal standard. High resolution mass spectra were measured on an AEI MS-902 mass spectrometer and are accurate to ±5 ppm. Apparatus for experiments requiring anhydrous conditions was flame dried, allowed to cool in a desiccator over calcium chloride and flushed with argon prior to use. Phenyllithium, 1-bromopentane, allyl bromide, α-bromoacetaldehyde and ethyl α-bromoacetate were purchased from Aldrich. Absolute ether and THF were distilled from sodium-benzophenone. During workup of the reactions, general drying of the solvent was performed over anhydrous magnesium sulfate or anhydrous sodium sulfate as indicated. Thin-layer plates were made of E. Merck AG Darmstadt silica gel pf-254. Column chromatography was

performed with silica gel 60 (70-230 mesh) from E. Merck. Ethyl pyroglutamate and 2-hydroxymethyl-2-pyrrolidinone were prepared using Silverman's procedures.[3]

5-(Dimethyl-*t*-butylsilyloxymethyl)-2-pyrrolidinone, *1*: A solution of 1.24 g (12.3 mmol) of 5-hydroxymethyl-2-pyrrolidinone[1,3] was refluxed with 1.85 g (12.3 mmol) of dimethyl-*t*-butylsilyl chloride and 0.837 g (12.3 mmol) of imidazole in THF for 15 hours. Washing with water and chromatography afforded 1.92 g (8.4 mmol, 72%) of ***1***: ^{1}H NMR ($CDCl_3$): δ 0.05 (6H, s),0.88 (9H, s), 1.80-2.45(4H, m), 3.61 (2H, br t), 3.85 (1H, br s) and 4.30(1 H, dd); ^{13}C NMR ($CDCl_3$): δ -17.5 (q) , -5.0 (s), 23.5 (q) , 26.8 (t), 32.3 (t), 43.8 (t), 58.5 (d), 65.1(t) and 174.6 ppm

General Procedure for Alkylation

The silane protected alcohol (1) was dissolved in d1 toluene (sodium) and cooled to 0°C (ice bath). Approximately 1.5 equivalents of phenyllithium in toluene was added slowly via syringe. The solution was allowed to warm to ambient temperature, and the alkyl halide was added neat via syringe. The stirred solution was either heated for reflux for 12 to 36 hours or heated at 90°C in a ultrasound bath until reaction is complete as judged by TLC. The reaction was quenched with distilled water, organic layer separated, and the aqueous layer was extracted twice with ether. The combined organic layers were dried ($MgSO_4$) and solvent evaporated. The crude oil was purified by column chromatography (SiO_2/ether).

N-(2-Propenyl)-5-(dimethyl-*t*-butylsilyloxymethyl)-2-pyrrolidinone, *2a*: Reaction of 4.45 mL of 0.48 M phenyllithium (2.14 mmol) and 0.325 g of ***1*** (1.42 mmol) and allyl bromide (O.25 mL, 2.84 mmol) was added neat via syringe. The stirred solution was heated for reflux to 12 hours and workup gave O.33 g of ***2a*** (1.24 mmol, %). ^{1}H NMR ($CDCl_3$): δ 0.05 (6H, s), 0.88 (9H, s), 1.80-2.45 (4H, m), 3.65 (4H, m), 4.30 (1 H, dd), 5.19 (2H, m), and 5.73 ppm (1H, m); ^{13}C NMR ($CDCl_3$): δ -17.5, -5.0, 23.5, 26.8, 31.1 , 44.0, 59.8, 64.5, 118.0, 133.3 and 175.5 ppm; IR (CH_2Cl_2): 3682(w), 3054(s), 2988(m), 1680(s), 1 550(m), 1422(m), 1264(m), 1158 (m), 890(m), 838(m) and 730(m).

N-(Pentyl)-5-(dimethyl-*t*-butylsilyloxymethyl)-2-pyrrolidinone, *2b*: Reaction of 3.87 mL of 0.48 M phenyl lithium (1.86 mmol), 0.284 g of ***1*** (1.24 mmol) and 2.0 mL amyl bromide (16.2 mmol added neat via syringe)

at 90°C in an ultrasonic bath for 14h gave 0.278 g of ***2b*** (0.930 mmol, 75%): R_f (O.80), ^1H NMR ($CDCl_3$): δ 0.06 (6H, s), 0.89 (9H, s), 1.22-2.45 (13H, m), 3.66 (4H, m) and 4.25 ppm (1 H, dd); ^{13}C NMR ($CDCl_3$): δ -18.0, -5.0, 12.2, 18.5, 22.3, 22.4, 23.5, 26.8, 31.9, 44.5, 60.1, 64.6, and 175.8 ppm; IR (CH_2Cl_2): 3452(w), 3054(s),2985(m), 2945(m), 1693(s), 1512(w), 1420(m), 1265(m), 1120(m), 890(m), 841 (m) and 725(m).

N-(2-Methylenecarboxaldehyde)-5-(dimethyl-*t*-butylsilyloxymethyl)-2-pyrrolidinone, *2c*: Reaction of 1.37 mL of 0.48 M phenyl lithium (0.66 mmol), 0.100 g of ***1*** (0.437 mmol) and 0.13 mL of bromoacetaldehyde (0.874 mmol added neat via syringe) for 36 hours at reflux gave 0.082 g of ***2c*** (0.24 mmol, 55%): ^1H NMR ($CDCl_3$): δ 0.05 (6H, s), 0.88 (9H, s),1.21 (7H, m), 1.78 (1H, m), 2.25(2H, m), 3.65 (8H, m) and ppm 4.66 (1H, m); ^{13}C NMR ($CDCl_3$): δ -17.0, -5.0, 14.5, 15.0, 23.5, 26.8, 31.1, 44.0, 55.0, 55.8, 59.8, 64.5, 73.6 and 175.0 ppm. IR (CH_2Cl_2): 3432(w), 3054(s), 2986(m), 2932(m), 1700(s), 1422(m),1264(m), 1114(m), 896(m), 840(m) and 756(m).

N-(2-Bromoethyl)-5-(dimethyl-*t*-butylsilyloxymethyl)-2-pyrrolidinone, *2d*: Reaction of 1.37 mL of 0.48 M phenyl lithium (0.66 mmol), 0.100 g of ***1*** (0.437 mmol) and 0.12 mL of dibromoethane (1 31 mmol added neat via syringe) was refluxed for 36 hours but gave < 5% yield of ***2d***.

N-(2-Carboethoxymethyl)-5-(dimethyl-*t*-butylsilyloxymethyl)-2-pyrrolidinone, *2e*: Reaction of 6.5 mL of 0.48 M phenyl lithium (3.12 mmol), 0.709 g of ***1*** (3.1 mmol) and 0.50 mL of ethyl bromoacetate (6.63 mmol added neat via syringe was heated at 90°C in an ultrasonic bath for 3h and gave 0.58 g of ***2e*** (1.83 mmol, 59%):.R_f (0.62), ^1H NMR ($CDCl_3$): δ 0.045 (6H, s), 0.89 (9H, s), 1.23 (3H, t), 1.80 - 2.45 (4H, m), 3.60 (4H, m) and 4.12-4.30 ppm (3H, m); ^{13}C NMR ($CDCl_3$): δ -17.5, -5.1, 18.7, 23.3, 27.1, 30.9, 44.4, 55.5, 59.8, 64.3, and 175.4 ppm; IR (CH_2Cl_2) : 3400(w), 2956 (m), 2859(m), 1745(s), 1695(s), 1465(m), 1416(m), 1254(m), 1112 (m), 840(m) and 780(m).

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