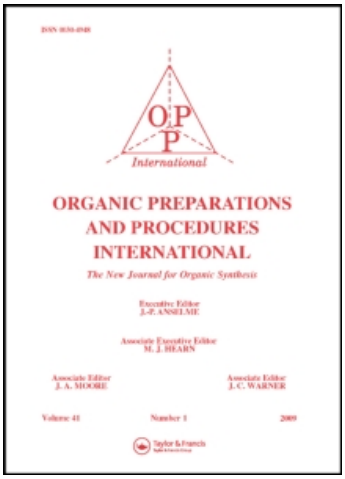

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A PRACTICAL PROCEDURE FOR THE SYNTHESIS OF 5-SUBSTITUTED γ-LACTAMS

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A PRACTICAL PROCEDURE FOR THE SYNTHESIS OF 5-SUBSTITUTED γ-LACTAMS

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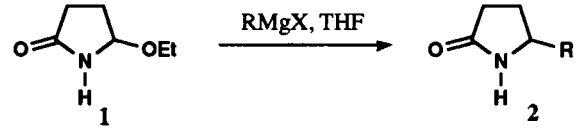
Many 5-substituted γ-lactam derivatives are useful synthons for the preparation of more complex molecules of biological importance.[1] γ-Lactams are generally synthesized using the intramolecular cyclization of the corresponding γ-amino acids,[2] and by the lactamization of γ,δ-unsaturated imidates.[3] These methods are often not practical since the γ-amino acid and γ,δ-unsaturated imidate precursors, in most cases, are not readily available. Other alternative procedures have also been reported,[4] but most of these methodologies frequently provide low yields or require multiple-step reaction sequences. α-Amidoalkylation at carbon has been shown to have great synthetic potential.[5] In this regard, the α-amidoalkylation of organometallic compounds has attracted significant attention since this C-C bond formation reaction has been used for the synthesis of 4-substituted β-lactams.[6] This communication describes an efficient utilization of this methodology for the general preparation of 5-substituted γ-lactams.

Thus, treatment of 5-ethoxy-2-pyrrolidinone (**1**)[7] with three equivalents of phenylmagnesium bromide afforded the 5-substituted γ-lactam (**2a**) in 78% yield. Since other Grignard reagents can be employed, as illustrated in the reaction scheme shown below, this versatile methodology is suitable for the synthesis of a variety of 5-substituted γ-lactams.



1 **2**

a) R = Ph (78%) b) R = CH_2=CH– (65%) c) R = *i*-Bu (74%)

In conclusion, a new and efficient reaction for the synthesis of 5-substituted γ-lactams has been developed. In comparison to other reported methods[4] for the preparation of these γ-lactams, the major advantages of our procedure are its simplicity, the low cost, and the ready availability of the reagents employed. This methodology provides a useful alternative to the procedures of Volhardt[8] and Speckamp[9] which involve the direct reaction of a succinimide with a Grignard reagent and then deoxygentation using $NaCNBH_3$ under acidic conditions to yield 5-substituted γ-lactams. Other effecient procedures for the synthesis of chiral 5-substituted γ-lactams have been reported.[10] Application of our methodology for the preparation of biological active compounds in our drug design program is currently in progress.

EXPERIMENTAL SECTION

All moisture-sensitive reactions were carried out under a positive pressure of argon gas. Tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. Grignard reagents were purchased from the Aldrich Chemical Co., and 5-ethoxy-2-pyrrolidinone (**1**) was prepared according to the literature procedure.[7] Nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR) were acquired on a Bruker AM-300 spectrometer. Infrared spectra were recorded using a Nicolet 5DX FT spectrometer, and only selected absorptions are reported. Melting points were determined using a Thomas-Hoover capillary apparatus and are uncorrected.

General Procedure for the Preparation of 5-Substituted 2-pyrrolidinones (2).- A solution of the Grignard reagent (15.0 mmol) was added dropwise with stirring to a solution of 5-ethoxy-2-pyrrolidinone (0.65 g, 5.0 mmol) in THF (20 ml) at 0°. The reaction was allowed to proceed for 1 hr at 0° prior to heating at reflux for 5 hrs. Water (2 ml) and acetic acid (4 ml) were then added to the mixture with stirring, and the reaction mixture was filtered. Removal of the solvent *in vacuo* gave a residue which was purified using MN-Kieselgel 60 (70-230 mesh) silica gel flash column chromatography.

5-Phenyl-2-pyrrolidinone (2a).- Reaction of **1** (0.65 g, 5.0 mmol) with a solution of phenylmagnesium chloride in THF (7.5 ml of a 2M solution, 15.0 mmol) as described in the general procedure, and purification of the product by silica gel flash chromatography using ethyl acetate as eluent afforded **2a** (0.63 g, 78%), mp. 107-108°, lit.[4a] mp. 107°. IR (KBr): 3220 (m), 3085 (w), 3037 (w), 2981 (w), 1687 (s), 1602 (w), 1455 (m), 1335 (w), 1258 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.91 (m, 1H), 2.38 (m, 2H), 2.50 (m, 1H), 4.71 (t, J = 7.0 Hz, 1H), 7.28 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 30.2, 31.0, 57.9, 125.4, 127.5, 128.6, 142.5, 178.8.

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.28; H, 6.82; N, 8.67

5-Vinyl-2-pyrrolidinone (2b).- The reaction of **1** (6.5 g, 50 mmol) with a solution of vinylmagnesium bromide in THF (150 ml of a 1M solution) as described in the general procedure, and purification of the product by silica gel flash chromatography using methanol:ethyl acetate (2:98, v/v) as eluent yielded **2b** as a colorless oil (3.6 g, 65%) which exhibited a ^1H NMR spectrum identical to that of an authentic sample.[11] IR (film): 3220 (m), 3086 (w), 2945 (w), 1694 (s), 1420 (w), 1251 (w), 1061 (w) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.74 (m, 1H), 2.25 (m, 3H), 4.08 (m, 1H), 5.04 (dd, J = 10.8, 0.9 Hz, 1H),

5.14 (dd, J = 17.0, 0.9 Hz, 1H), 5.72 (m, 1H), 7.43 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 27.1, 29.4, 56.0, 114.4, 138.2, 178.2.

5-Isobutyl-2-pyrrolidinone (2c).- Reaction of **1** (0.65 g, 5.0 mmol) with a solution of isobutylmagnesium chloride (7.5 ml of a 2M solution in ether, 15 mmol) as described in the general procedure, and purification of the product by silica gel flash chromatography using ethyl acetate as eluent gave **2c** (0.52g, 74%), mp. 76-77°, lit.[12] mp. 74.5-75°; IR (KBr): 3213 (m), 2959 (s), 2924 (m), 1687 (s), 1462 (w), 1391 (w), 1293 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.83 (dd, J = 6.6, 2.7 Hz, 6H), 1.18 (m, 1H), 1.37 (m, 1H), 1.55 (m, 2H), 2.15 (m, 1H), 2.22 (m, 2H), 3.63 (m, 1H), 7.67 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.2, 22.7, 24.9, 27.4, 30.2, 45.8, 52.7, 178.6.

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.33; H, 10.98; N, 9.95

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