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TETRAMETHYLAMMONIUM GLYCINATE: A NEW REAGENT FOR IMPROVED PYRROLE SYNTHESIS BY [3+2] CYCLIZATION

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ABSTRACT: The novel reagent tetramethylammonium glycinate has been introduced as the most effective glycine derivative for the convenient synthesis of 4,5,6,7-tetrahydroisoindoles (or pyrroles unsubstituted in the 2 and 5 positions) from 1,3-dicarbonyl compounds by [3+2] cyclization. The reaction has been shown to be catalyzed by 2,6-di(tert.butyl)pyridine reagents to triple the reported yield.

The synthesis of pyrrole-2-carboxylate esters[1-5] by a [3+2] cyclization in which a three-carbon segment of the pyrrole ring is connected with a C-N fragment, forming the N → C(2) and C(4) → C(5) bonds, is exemplified by condensation of a glycinate ester or aminomalonate ester (or its oximino precursor) with a β-dicarbonyl compound. However, the preparation of 4,5,6,7-tetrahydroisoindoles (1) unsubstituted in the 1, 2 and 3 positions requires the use of glycinate anion and only one such example has been reported:[6] The 2-acetyl derivative of compound (1) (R=H) was obtained[6] (23.5% overall yield) by the action of acetic anhydride on the condensation product of potassium glycinate and 2-formylcyclohexanone.

We have investigated this reaction in order to improve the yield of pyrrole, utilizing 4-tert.butyl-2-formylcyclohexanone as our starting material. This keto-

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aldehyde is known[7] to exist as the conjugated 4-tert.butyl-2-hydroxymethylene-cyclohexanone (2).[8] In view of favorable reports on the use of the corresponding (dimethylamino)methylene derivative in an analogous pyrrole synthesis,[9] compound (3) was prepared by the base-catalyzed condensation of dimethylformamide dimethylacetal with tert.butylcyclohexanone. The enaminone (3) was an oil highly sensitive to hydrolysis. It underwent partial conversion to (2) on standing at 0°C, and complete conversion to (2) on silica gel chromatography (pH 5.5). With dilute acid, hydrolysis to (2) occurred instantaneously at RT. It could however be purified using medium pressure liquid chromatography (MPLC) on florisil (pH 9) and was then used immediately for the next step. The enaminone was characterized as the pyrazole (9) which it formed quantitatively by reaction with hydrazine at RT.

Zavyalov *et al.*[6] prepared their potassium glycinate *in situ* from glycine and KOH, thus introducing a molar equivalent of H_2O into the system. We found that when the K^+ salt was made from an equivalent of potassium ethoxide in absolute ethanol (i.e., in the absence of water), improved yields resulted. Using a 15% excess of the glycinate salt,[6] the dry salt was then reacted with either (2) or (3), isolating the product as the N-acetylpyrrole (7). With potassium glycinate, the ketoaldehyde (2) proved to be slightly better than the enamine derivative (3) (44 *vs.* 31% yield, see Table).

The nature of the monovalent metal ion in the glycinate salt was next examined. The lithium and thallous salts, obtained from their ethoxides, gave 10% and 20%, respectively, of product (7) (Table). No record could be found in the literature of the ammonium salt of glycine, and when this compound was prepared and dried on the lyophilizer, a residue of pure glycine was left (mp and mixed mp), showing that this salt undergoes a facile dissociation. A stable univalent ammonium salt was however synthesized from tetramethylammonium hydroxide, and the use of tetramethylammonium glycinate gave an improved yield of 58% of the N-

Table

Preparation of 2-Acetyl-5-tert.butyl-4,5,6,7-tetrahydroisoindole (7)

Substrate	Glycinate $NH_2CH_2COO^-M^+$	Yield[a] (%)
keto-aldehyde (2)	Li^+	10
(2)	K^+	44
(2)	Tl^+	20
(2)	$^+N(CH_3)_4$	58
(2)	$^+N(CH_3)_4$	54[b]
(2)	$^+N(CH_3)_4$	67[c]
(2)	$^+N(CH_3)_4$	73.5[d]
enaminone (3)	K^+	31
(3)	$^+N(CH_3)_4$	52[d]
(3)	$^-C(CH_3)_3$[e]	20

[a]Average of triplicate experiments. [b]In presence of triethylamine. [c]In presence of 2,6-di(tert.butyl)pyridine. [d]In presence of 2,6-di(tert.butyl)-4-methylpyridine. [e]tert.butyl glycinate.

acetylpyrrole (7) (Table). The analogous tetra(n-butyl)ammonium glycinate was prepared, but was not further investigated because of its hygroscopic nature.

The need for a base (presumably to act as a proton sponge) was next examined. The use of triethylamine with tetramethylammonium glycinate did not improve the yield of (7) (54 *vs.* 58%, see Table). Employing the sterically hindered non-nucleophilic base 2,6-di(tert.butyl)pyridine as the base[10] increased the yield of (7) to 67% (Table), and the analogous 2,6-di(tert.butyl)-4-methylpyridine[11] raised

this further to 73.5%. It is interesting that when the enamine derivative (3) was used with the same reagents, the yield of (7) was again lower (52%, see Table).

The advantage of the tetramethylammonium ion (approximate diameter 4.8Å) over the Li^+, K^+ and Tl^+ ions (diameter 1.5-3.0Å) may reside in the more diffuse nature of the unit charge distributed over the larger surface area of the positive ion, and the consequently greater ease of dissociation of the salt, thus initiating the final decarboxylation and dehydration process of the pyrrole formation. The mechanism of the reaction involves N-acetylation of the first-formed enamine (4), [shown in the case of (1) (R=H)[6] not to have already cyclized to the 2-carboxy-3-hydroxy-pyrroline (5)], followed by a decarboxylative and dehydrative β-elimination of the 3-hydroxy acid salt, such as is sometimes the main product in a Perkin reaction,[12] with the metal ion M^+ forming the acetate salt.

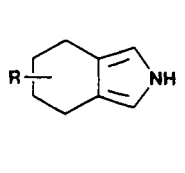
The effect of the added base on the yield of (7) can be explained in terms of its pK. It is probable that triethylamine (and stronger bases like alkoxides) cause the formation of the enolate anion of (2) and subsequently inhibit the further reaction.[8] On the other hand, the more weakly basic 2,6-di(tert.butyl)pyridines (pK_a 3.6-4.0)[13] will not form the enolate anion, while still acting as proton scavengers.

When the reaction was repeated using the enaminone (3) and glycine tert.butyl ester instead of potassium glycinate, the same product (7) was obtained but only in 20% yield (Table), suggesting that at the reaction temperature used (150-155°C) the loss of isobutylene from the tert.butyl ester was not a major process.

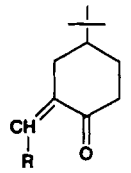
N-Deacetylation of (7) could be smoothly carried out with methanolic alkali at RT (15 min) and afforded the pyrrole (8) in excellent (85%) yield.

EXPERIMENTAL

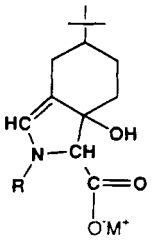
M.p.s. were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 5DXFT-

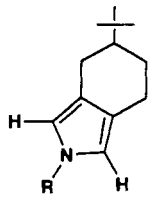


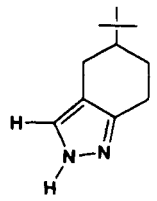
1



2 R = OH
3 R = $N(CH_3)_2$
4 R = $NHCH_2COO^-M^+$







5 R = H
6 R = $COCH_3$

7 R = $COCH_3$
8 R = H

9

IR spectrometer either as a neat liquid or a KBr pellet. ^1H NMR spectra were taken on a Varian FT 80 or GE 300 spectrometer as solutions in $CDCl_3$ with tetramethylsilane as internal standard. High resolution mass spectra were obtained on a Kratos-AEI MS902 instrument at an ionizing energy of 70 ev. Thin-layer chromatography was carried out on silica gel on polyester TLC plates of 250 μm thickness, and flash chromatography was performed using Kieselgel 60 (230-400 mesh, Merck). Microanalyses were carried out by the Microanalytical Laboratory, University of California, Berkeley. Solutions were dried over anhydrous Na_2SO_4.

N[2-(Dimethylamino)methylene]-4-tert.butylcyclohexan-1-one (3) – A mixture of 4-tert.butylcyclohexanone (Aldrich) (4 g) (25.97 mmol), dimethylformamide dimethylacetal (DMF-DMA) (Aldrich) (5.96 g, 50.0 mmol) and triethylamine (0.19 g, 1.00 mmol) was heated at 110°C for 18 h under N_2. Dry

benzene was added and excess of DMF-DMA was distilled off under reduced pressure. The residue was dissolved in ether, washed with $NaHCO_3$ solution, water, dried, and evaporated *in vacuo*. Medium pressure liquid chromatography (MPLC) using first benzene and then benzene-methylene chloride (1:1) as eluent on florisil (200-300 mesh) gave (3) (1.78 g, 47%), Rf=0.29 (5% methanol-$CHCl_3$). (Found: C, 74.33; H, 11.32; m/z 209.1797. $C_{13}H_{23}NO$ requires C, 74.59; H, 11.08%; M^+ m/z 209.1773.) υ_{max} (neat) 1735.9 (C=0), 1644.6 (C=C) cm-1; δ_H 0.92 (9H, s, $(CH_3)_3$), 1.3-3.1 (7H, m, cyclohexanone ring protons), 3.09 (6H, s, N $(CH_3)_2$), 7.47 (1H, s, =CH); EIMS m/z (relative intensity) 209 (40.5), 194 (19.7), 182 (14.3), 167 (12.4), 152 (100), 138 (13.7), 125 (23.0), 110 (26.3), 96 (16.4), 91 (18.0), 87 (45.9), 82 (28.4).

5-Tert.butyl-4,5,6,7-tetrahydroindazole (9) – To a solution (3) (0.27 g) (1.3 mmol) in ethanol (6 ml) was added $H_2N.NH_2.H_2O$ (0.07 g, 1.41 mmol) and the mixture was stirred at room temperature for 18 h. The solvent was evaporated *in vacuo* and the residue dissolved in water and extracted with ether. The ether layer was washed with cold dil H_2SO_4, $NaHCO_3$, water, and dried. Evaporation of the solvent gave a residue which crystallized from pentane as white crystals (0.22 g, 100%) of (9), m.p. 113-114°C (Found: C, 74.44; H, 10.02; N, 15.73. $C_{11}H_{10}N_2$ requires C, 74.15; H, 10.11; N, 15.73%).

General Procedure for the Preparation of Metal Glycinate – To a solution of monovalent metal ethoxide (27.66 mmol) in absolute ethanol was added glycine (2.075 g, 27.66 mmol) and excess ethanol was evaporated *in vacuo* at 50-55°C. The process was repeated with the same quantity of absolute ethanol until the salt solution was homogeneous. Removal of solvent gave white crystals dried *in vacuo* over P_2O_5 to constant weight. The yield was quantitative.

Tetramethylammonium Glycinate – To a solution of glycine (5 g, 66.6 mmol) in the minimum quantity of water at 60°C was added tetramethylammonium

hydroxide (6.07 g, 66.6 mmol) as a 1.0 M solution in methanol (Aldrich). After removal of solvents under reduced pressure at 50-55°C, the white solid was lyophilized to constant weight (quantitative), m.p. 94-101°C. (Found: C, 47.10; H, 10.53; N, 18.14%. $C_6H_{16}N_2O_2$. 0.25 H_2O requires C, 47.15; H, 10.80; N, 18.33%).

2-Acetyl-5-tert.butyl-4,5,6,7-tetrahydroisoindole (7) – (a) To a solution of (2) or (3) (2.74 mmol) in absolute ethanol (10 ml) was added the metal glycinate (3.17 mmol) and the mixture was refluxed with stirring under argon for 2 h. Evaporation of the solvent at reduced pressure afforded the intermediate enamine as a yellow powder. (b) Cyclization – (A) Freshly distilled acetic anhydride (7.3 ml) was added to the intermediate enamine product and the resulting solution was refluxed under argon for 2 h at 150-55°C (bath temp.). After removal of acetic anhydride under reduced pressure, water was added and the mixture extracted with methylene chloride. The organic layer was washed with saturated $NaHCO_3$, water, brine, dried and evaporated to yield an oil. Flash chromatography on silica gel ($CHCl_3$-hexane; 1:1) gave the title compound (7) which solidified on cooling to white crystals, m.p. 39°C. (Found: C, 76.29; H, 9.52; N, 5.99%; m/z 219.1624. $C_{14}H_{21}NO$ requires C, 76.66; H, 9.58; N, 6.38%; M^+ m/z 219.1617); R_f 0.59 (10% EtOAc:C_6H_6); υ_{max} (neat) 1714.8 (N-CO-CH_3), 1525 (C-N); δ_H 0.93 (9H, s $(CH_3)_3$), 1.04-2.35 (7H, m. alicyclic-H), 6.91 (2H, s, arom. α,α'-H); EIMS m/z 219.2 (71.7), 204.1 (3.7), 177.2 (71.3), 162.1 (14.3), 135.1 (5.3), 120.1 (93.0), 106.1 (8.7), 93 (100).

(B) To the adduct, freshly distilled acetic anhydride (7.3 ml) and an equimolar amount of base catalyst (2.74 mmol) was added and the resulting mixture was refluxed at 150-55°C for 2 h. The solvent was removed under reduced pressure and the residue diluted with water and extracted with CH_2Cl_2. The organic

layer was washed with cold dil H_2SO_4, $NaHCO_3$, brine, dried and evaporated. Purification by flash chromatography as described in (A) gave (7).

5-Tert.butyl-4,5,6,7-tetrahydroisoindole (8) – To a stirred solution of (7) (73.5 mg, 0.335 mmol) in methanol (7 ml) under N_2 at room temperature was added a solution of 2N NaOH (1.5 ml). The solution was stirred for 15 min, after which time TLC showed the reaction was complete. After dilution with water, and extraction with ether, the ether layer was washed with water, brine, dried and evaporated *in vacuo* to afford white crystals of (8) (50 mg, yield 85%). m.p. 109-110°C (Found: C, 81.51; H, 10.34; N, 7.73%; m/z 177.1520. $C_{12}H_{19}N$ requires C, 81.28; H, 10.72; N, 7.90; M^+ m/z 177.1512); R_f (benzene) 0.70. ϑ_{max} (KBr) 3360.1 (N-H), 1553.1 (C-N) cm^{-1}; δ_H 0.05 (9H, s $(CH_3)_3$), 1.09-2.6 (7H, m, alicyclic-H), 6.36-6.39 (2H, d, aromatic), 7.1 (1H, s, N-H); EIMS m/z (relative intensity) 177.2 (78.5), 170 (2.3), 162.1 (13.7), 134.1 (4.1), 126 (3.0), 120 (92.0), 103.1 (12.7), 93.1 (100).

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