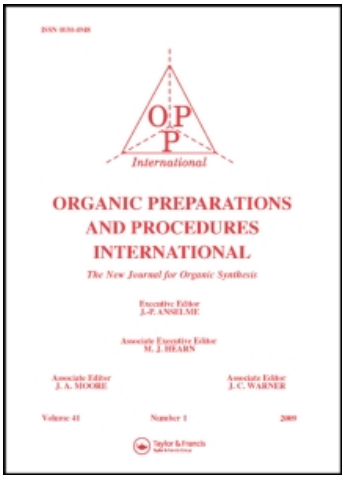

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

MILD METHOD FOR ENAMINE FORMATION

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To cite this Article Zoretic, P. A. , Barcelos, F. and Branchaud, B.(1976) 'MILD METHOD FOR ENAMINE FORMATION', Organic Preparations and Procedures International, 8: 5, 211 — 214
To link to this Article: DOI: 10.1080/00304947609355626
URL: http://dx.doi.org/10.1080/00304947609355626

ORGANIC PREPARATIONS AND PROCEDURES INT. 8(5), 211-214 (1976)

MILD METHOD FOR ENAMINE FORMATION

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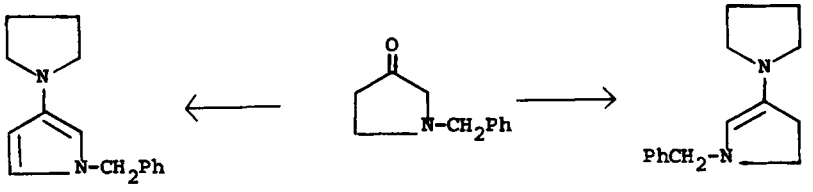
The well known Stork enamine reaction[1] is extensively utilized to effect carbon-carbon bond condensation. The method most generally used involves the removal of water produced in the condensation of a ketone with a secondary amine, by azeotropic distillation with benzene. In some related work, we were interested in synthesizing the enamine II in order to carry out further chemical elaborations of the 3-pyrrolidinone nucleus.



III I II

It was anticipated that the enamine II could be readily synthesized by employing the general enamine formation reaction. However reaction of 1-benzyl-3-pyrrolidinone I with pyrrolidine in refluxing benzene afforded a 50% yield of the pyrrole III. Presumably under these reaction conditions enamine II is formed but is readily converted via an oxidation process to the pyrrole III. The pyrrole III was invariably produced even when the reaction was carried out with deaerated benzene under nitrogen and the reaction time was shortened to 1.5 hr.

A literature search revealed that although there are numerous pro-

cedures[2] for enamine formation none of these processes could be used to form enamines under a short reaction time and very mild conditions. We now report that enamines can be obtained at room temperature during a short reaction time by allowing the ketone to react with pyrrolidine neat or in ether in the presence of anhydrous magnesium sulfate. It was also shown by nmr that enamine formation occurred prior to distillative work-up. For example, the reaction of cyclohexanone with pyrrolidine in ether in the presence of anhydrous magnesium sulfate was filtered and the reaction was concentrated on a rotary evaporator without heat. The nmr of the residue showed a strong vinyl proton resonance peak at δ4.06.

In the enamine formation reactions a 1:2 ratio of ketone to amine was employed. The yields of the pyrrolidinoenamines of cyclopentanone and cyclohexanone utilizing different reaction times and quantities of anhydrous magnesium sulfate are listed in Table I. In each case good yields of the enamine were observed.

Table I. Enamine Formation In The Presence of Magnesium Sulfate.

ketone		hrs	g of $MgSO_4$	enamine % yield
Cyclohexanone	neat	4	4	83
Cyclohexanone	Et_2O	4	5.5	84
Cyclohexanone	Et_2O	2	7	77
Cyclopentanone	Et_2O	4	6	82

The application of this method to the reaction of 1-benzyl-3-pyrrolidinone I with pyrrolidine afforded (III) in 68% yield.

EXPERIMENTAL

Pyrrolidino-1-cyclohexene. General Procedure.- Cyclohexanone (7 g, 0.072 mole), anhydrous $MgSO_4$ (4 g) and anhydrous ethyl ether (30 ml) were placed in a 100 ml round bottom flask fitted with a magnetic stirring bar. To this mixture pyrrolidine (10.1 g, 0.143 mole) was added and the resulting mixture was stirred for 0.75 hr at room temperature. After this time period anhydrous $MgSO_4$ (3 g) was added and the reaction was stirred for an additional 1.25 hr. The reaction mixture was filtered and the $MgSO_4$ cake was washed with anhydrous ether. Evaporation of the solvent on a rotary evaporator and distillation of the residue afforded 8.3 g (77%) of pyrrolidino-1-cyclohexene, bp. 115-116°/10 mm, lit[1a] bp. 117-20°/20 mm; nmr ($CDCl_3$): δ 4.25 (t, distorted, 1H), 2.98 (t, distorted, 4H), 2.3-1.4 (m, 12H).

Pyrrolidino-1-cyclohexene. Neat reaction. - Cyclohexanone (7.0 g, 0.072 mole), pyrrolidine (10.1 g, 0.143 mole), and anhydrous $MgSO_4$ (3 g) were placed in a 50 ml round bottom flask fitted with a stirrer. After one hr of stirring at room temperature, anhydrous $MgSO_4$ (1 g) was added and the reaction was stirred for an additional 3 hr. Anhydrous ether was added and the reaction mixture was filtered and the $MgSO_4$ cake washed with additional Et_2O. Evaporation of the solvent and distillation of the resulting oil afforded 9.1 g (83%) of pyrrolidino-1-cyclohexene, bp. 115-20°/10 mm. The nmr was consistent for this structure.

Pyrrolidino-1-cyclopentene. - Cyclopentanone (6.0 g, 0.071 mole), pyrrolidine (10.1 g, 0.143 mole), anhydrous magnesium sulfate (3 g) and anhydrous ethyl ether (30 ml) were placed in a flask fitted with a stirrer. The reaction mixture was allowed to stir at room temperature for 20 min. Anhydrous $MgSO_4$ (2 g) was added and the reaction was stirred for an additional 1.5 hr. After this time period $MgSO_4$ (1.0 g) was added

and the reaction was stirred for an additional 2.15 hr. General work up and distillation afforded 8.0 g (82%) of pyrrolidino-1-cyclopentene, bp. 99-102°/10 mm, lit.[1a] bp. 97-98°/20 mm; nmr ($CDCl_3$): δ 4.0 (s, rounded, 1H), 3.05 (t, distorted, 4H), 2.6-1.5 (m, 10H).

1-Benzyl-3-pyrrolidinylpyrrole III. 3-Pyrrolidinone (5.0 g, 0.028 mole), pyrrolidine (4.0 g, 0.057 mole), anhydrous magnesium sulfate (5.0 g), anhydrous magnesium sulfate (5.0 g), and anhydrous ethyl ether (20 ml) were placed in a flask fitted with a magnetic stirrer. The reaction was allowed to stir for 4 hr at room temperature. General work up and distillation afforded 4.4 g (68%) of 1-benzyl-3-pyrrolidinylpyrrole III, bp. 139°/0.01 mm; nmr ($CDCl_3$): δ 1.70-2.15 (m, 4H), 2.86-3.22 (m, 4H), 4.84 (s, 2H), 5.78 (t, 1H, J = 2.3 Hz), 5.98 (t, 1H, J = 2.0 Hz), 6.45 (t, 1H, J = 2.5 Hz) and 6.95-7.45 (m, 5H).

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.15; H, 7.93; N, 12.25.

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† Undergraduate research participant.

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(Received July 12, 1976; in revised form Sept. 16, 1976)