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# Covert Mannich Reaction via Carbon Transfer

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## Covert Mannich Reaction via Carbon Transfer

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Abstract: 1,3-Dimethylbenzimidazolidine reacts with ketones, which can provide activating  $\alpha$  hydrogens and primary or secondary amines under acidic conditions, to yield aminomethylation derivatives by a covert Mannich reaction.

Keywords: Aminomethylation derivative, 1,3-dimethylbenzimidazolidine, Mannich reaction

In recent years, many researchers have tried to discover the mechanism of various coenzymes related to tetrahydrofolate coenzymes that lead in the biochemical transfer of a one carbon fragment at different oxidation levels.<sup>[1]</sup> The role of six one-carbon derivatives of tetrahydrofolic acid (THF 1) in the enzyme-catalyzed transfer of a C<sub>1</sub>-unit at the level of formate, formaldehyde, and methanol has been determined.<sup>[2]</sup> So, how to mimic the carbon-transfer process in model reactions and develop suitable coenzyme models for potential utilization in the "biomimetic transfer" of C<sub>1</sub>-units and larger (eventually functionalized) carbon fragments is becoming an intriguing challenge. The synthesis and application of such models has been reported.<sup>[3]</sup>

We now present results describing the transfer of synthetically useful carbon fragments from the related  $N^5$ , $N^{10}$ -methylenetetrahydrofolate models 1,<sup>[3]</sup> which can be prepared from 1,3-dimethyl-benzimidazolinium iodide by reduction with sodium borohydride.

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When a mixture of the coenzyme model **1**, primary or secondary amine, and ketones with activating  $\alpha$  hydrogens was heated (CH<sub>3</sub>CN, reflux) in the presence of acetic acid, the corresponding aminomethylation derivatives **2–7** were obtained with good yields. This carbon-transfer reaction is derived from the reported equilibrium between 1,3-dimethyl-imidazolidine and N-methyl-N-(2-N-methylamino)ethyl-N-methylenium trifluoroacetate<sup>[4]</sup> and other analogues.<sup>[5]</sup> The mechanism of formation of the aminomethylation derivatives can be rationalized via this sequence:



Actually, this carbon-transfer reaction can be regarded as a covert Mannich reaction. Furthermore it should be emphasized that the particular merit of the reported synthetic approach lies in the fact that the use of the relatively unstable aldehydes, required in the Pictet–Spengler procedure for related synthesis, is avoided.

The application of the folate model synthetic methodology to isoquinoline and  $\beta$ -carboline derivatives is being vigorously investigated, and our results on these studies will be presented elsewhere.

#### **Covert Mannich Reaction via Carbon Transfer**

### **EXPERIMENTS**

Melting points were taken on a XT-4 micromelting apparatus (Beijing) and are uncorrected. Thin-layer chromatography (TLC) analysis was carried out on glass plates coated with silica gel-G, and spots were visualized using an ultraviolet (UV) lamp. Infrared (IR) spectra in centimeters<sup>-1</sup> were recorded on a Brucker Equiox-55 spectrometer (Germany). Mass spectra were obtained with a Varian 1200-L spectrometer. <sup>1</sup>Proton magnetic resonance spectra (<sup>1</sup>H NMR) spectra were recorded at 400 MHz on a Varian Inova-400 spectrometer (USA), and chemical shifts were reported relative to internal Me<sub>4</sub>Si. With the exception of aqueous reactions, all reactions were conducted under a nitrogen atmosphere.

#### General Procedure for the Synthesis of Compounds 2–7

A mixture of 1,3-dimethyl-benzimidazolidine (296 mg, 2 mmol) **1**, appropriate amine (2 mmol), ketone (2 mmol), acetic acid (1 ml), and acetonitrile (10 ml) was refluxed for 6 h, and the solvent was removed. The residue was taken up in  $CH_2Cl_2$  and washed with NaHCO<sub>3</sub> solution; the organic layer was dried and evaporated to obtain the crude product.

1-Phenyl-3-phenylamino-propan-1-one 2 and 4-phenylamino-butan-2-one 3 were crystallized from hexane.

**2**: A light yellow powder was obtained. Yield: 158 mg (35%). Mp: 107–108°C (lit.<sup>[6]</sup> 113°C); mass (ESI): 226 (M<sup>+</sup>); IR (KBr): 3425 (m), 1690 (s); <sup>1</sup>H NMR (DMSO-d6):  $\delta$ 7.35–7.90 (m, 5H),  $\delta$ 6.4 –7.1 (m, 5H),  $\delta$ 4.0 (d, 1H),  $\delta$ 3.40 (m, 2H),  $\delta$ 2.65 (t, 2H).

**3**: A light yellow power was obtained. Yield: 134 mg (41%). Mp:  $38-39^{\circ}$ C (lit.<sup>[7]</sup> 35-35.5°C); mass (ESI): 164 (M<sup>+</sup>); IR (KBr): 3425 (m), 1715 (s); <sup>1</sup>H NMR (DMSO-d6):  $\delta 6.4-7.1$  (m, 5H),  $\delta 4.0$  (d, 1H),  $\delta 3.40$  (m, 2H),  $\delta 2.65$  (t, 2H),  $\delta 2.1$  (s, 3H).

2-Diethylamino-1-phenyl-propan-1-one **4**, 3-diethylamino-1-methylpropan-1-one **5**, 3-diethylamino-1-phenyl-propan-1-one **6**, and N,N-dibenzyl-2-aminoethyl-methylketon **7** were purified by chromatography (SiO<sub>2</sub>, EtOAc).

**4**: A white power was obtained. Yield: 267 mg (65%). Mp:  $101-102^{\circ}C$  (lit.<sup>[8]</sup> 105-108°C); mass (ESI): 206 (M<sup>+</sup>); IR (KBr): 1690 (s); <sup>1</sup>H NMR (DMSO-d6):  $\delta$  7.35-7.90 (m, 5H),  $\delta$  2.68 (t, 2H),  $\delta$  2.50 (t, 2H),  $\delta$  2.29 (s, 6H).

**5**: A light yellow oil was obtained. Yield: 195 mg (68%). Mp (diethyl methyl (3-oxo-butyl) ammonium iodide):  $82-84^{\circ}$ C (lit.<sup>[9]</sup> 86°C); mass (ESI): 144 (M<sup>+</sup>); IR (CHCl<sub>3</sub>): 1720 (s); <sup>1</sup>H NMR (DMSO-d6):  $\delta$  2.70 (m, 6H),  $\delta$  2.52 (t, 2H),  $\delta$  2.1 (s, 3H),  $\delta$  1.1 (t, 6H).

**6**: A white power was obtained. Yield: 362 mg (55%). Mp: 37–40 (lit.<sup>[10]</sup> 35°C); mass (ESI): 330.5 (M<sup>+</sup>); IR (KBr): 1690 (s); <sup>1</sup>H NMR (DMSO-d6):  $\delta$  7.35–7.90 (m, 5H),  $\delta$  6.5–7.2 (m, 10H),  $\delta$  3.56 (s, 4H),  $\delta$  2.70 (t, 2H),  $\delta$  2.52 (t, 2H).

7: A white power was obtained. Yield: 290 mg (54%). Mp:  $63-64^{\circ}$ C (lit.<sup>[11]</sup> 59°C); mass (ESI): 268 (M<sup>+</sup>); IR (KBr): 1715 (s); <sup>1</sup>H NMR (DMSO-d6):  $\delta 6.5-7.2$  (m, 10H),  $\delta 3.56$  (s, 4H),  $\delta 2.70$  (t, 2H),  $\delta 2.52$  (t, 2H),  $\delta 2.1$  (s, 3H).

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