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An Efficient Synthesis of Dicyclohexylmethyl Diazoacetate

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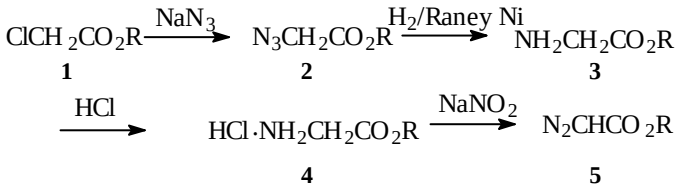
Abstract: Dicyclohexylmethyl diazoacetate was synthesized in excellent yield from the corresponding glycinate, which was derived in high yield from dicyclohexylmethyl chloroacetate *via* azide substitutuion, and reduction.

Keywords: Synthesis, alkyl diazoacetate, alkyl azidoacetate.

Diazoacetate is a versatile reagent in organic synthesis[1]. It has been widely used in cyclopropanation, etheration, *etc*. Both enantiomeric selectivity and diastereoselectivity of cyclopropanation are greatly affected by alkyl group of alkyl diazoacetate. High selectivities were obtained using steric demanding diazoacetate. Aratani has used menthyl diazoacetate (MnDA)[2], and Doyle has employed 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate[3] to achieve high selectivities. Masamune found that dicyclohexylmethyl diazoacetate (DCHMDA) was superior to the above diazoacetates in obtaining high stereoselectivity and that it has the advantage of easily removal of alcohol group by acid or basic reagents[4]. Therefore, DCHMDA is of great importance in asymmetric cyclopropanation.

Compared with the fact that MnDA was synthesized by various methods[5-7], DCHMDA was only synthesized from dicyclohexylmethanol *via* esterification with chloroacetate, aminolysis, and diazotization with isoamyl nitrate[8]. However, this method is suffered from the by-product of iminodiacetate, large amount of solvent used, and low diazotization yield (65% in patent[8]). Here we report our results of synthesis of DCHMDA.

According to our patent method of diazotization[10], DCHMDA can be synthesized *via* diazotization of the correspondng glycinate. The most convenient synthetic route of a glycinate is the direct reaction of glycine with an alcohol in the presence of an acid. *p*-Tolylsulfuric acid is more suitable to this reaction than other mineral acids when a secondary alcohol is used. However, the yield is low when dicyclohexylmethanol is used even though the reaction time of this reaction was much longer than that of other alcohols such as menthyl, cyclohexanol, whereas esters of the latter two could be obtained in yield of 84% and 94% respectively. This route was unsuccessful in the synthesis of DCHMDA. The following route is successful for the synthesis of *tert*-butyl glycinate[9].



Thus, dicyclohexylmethanol was converted to its chloroacetate ester **1** (chloroacetyl chloride, 1.2 equiv., yield 97%) according to the patent method[8]. **1** reacted with sodium azide (sodium azide, 1.5 equiv.) in water-acetone system at refluxing to give azidoacetate **2** (yield 99%), a compound has not been reported until now. **2** was reduced by Raney nickel hydrogenation to afford the corresponding glycine ester **3** (yield 87%), which was purified by converted to its hydrochloric acid salt **4**. The salt **4** was diazotized by sodium nitrite in a yield of 83% according to our patent method[10], instead of isoamyl nitrite described in literature[8].

The final product and all intermediates were characterized by spectral methods[11].

In summary, this method provided a satisfactory result and was operated effectively. It also gave similar results in the synthesis of other alkyl diazoacetate such as menthyl diazoacetate and cyclohexyl diazoacetate, *etc.*

References and Notes

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11. **2**: White solid, m.p. 50-51℃; IR: 2952, 2932, 2862, 2678, 2122, 1750, 1452, 1290, 1210, 1197, 974 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.732 (m, 1H), 3.869 (s, 2H), 1.752-1.597 (m, 12H), 1.289-0.966 (m, 10H); ^{13}CNMR (100.6 MHz, $CDCl_3$) δ 168.12, 83.31, 50.08, 38.05, 29.62, 27.27, 26.11, 25.96, 25.77.
3: IR: 3400, 3340, 2940, 2860, 2672, 1750, 1452, 1200, 1098, 970 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.694-4.656 (m, 1H), 3.452 (s, 2H), 2.394 (s, 2H), 1.728-1.578 (m, 12H), 1.246-0.973 (m, 10H); ^{13}CNMR (100.6 MHz, $CDCl_3$) δ 173.69, 81.52, 57.24, 43.14, 37.97, 29.52, 27.11, 26.01, 25.85.
4: m.p. 193-195 ℃; IR 3300-2500, 1760, 1454, 1228 cm^{-1}.
5: IR: 3138, 2952, 2856, 2670, 2105, 1696, 1455, 1197, 1098, 987 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.737 (s, 1H), 4.683 (t, J = 5 Hz, 1H), 1.746-1.589 (m, 12H), 1.248-0.993 (m, 10H); ^{13}CNMR (100.6 MHz, $CDCl_3$) δ 166.91, 81.86, 45.72, 38.23, 29.75, 27.31, 26.80, 26.29, 26.13.

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