NOVEL 1,2-DIHYDROISOQUINOLINE SYNTHESIS VIA INTRAMOLECULAR 1,3-DIPOLAR ALKYLAZIDE-OLEFIN CYCLOADDITION[1]

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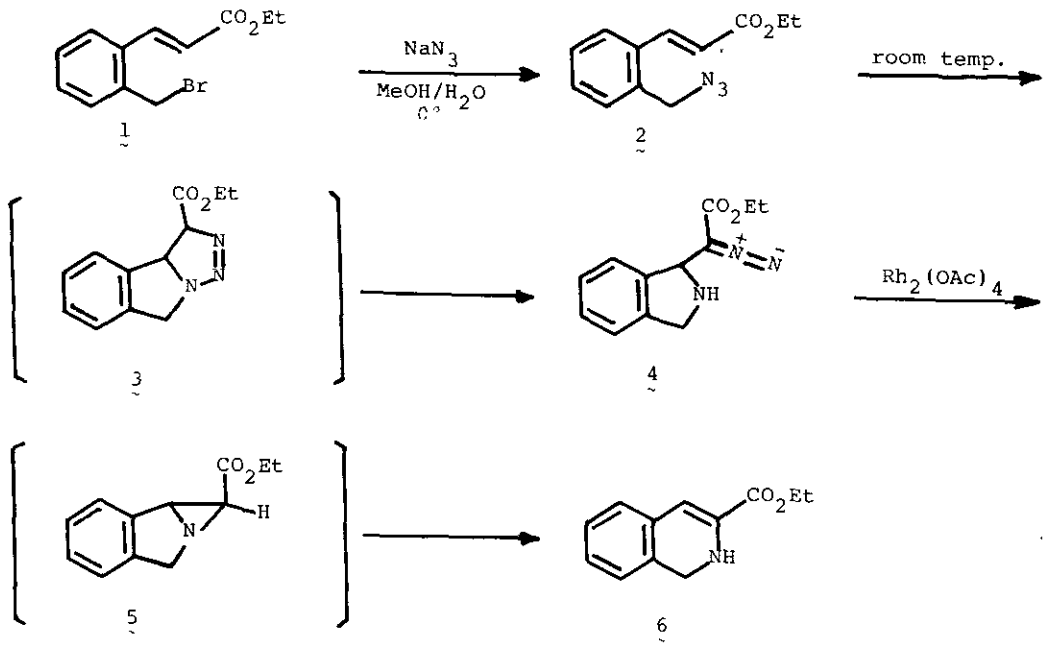
Abstract — Treatment of ethyl o-bromomethylcinnamate (1) with sodium azide in dimethylforamide at room temperature afforded ethyl o-azidomethylcinnamate (2). Compound 2 underwent intramolecular 1,3-dipolar cycloaddition to give triazoline 3. Subsequent rearrangement of 3 gave ethyl isoindoline-1-diazoacetate (4) at room temperature. Reaction of 4 with rhodium acetate in benzene gave 3-ethoxycarbonyl-1,2-dihydroisoquinoline (6) (53% overall from 1).

The importance of isoquinoline ring structure has long been recognized since its discovery by Hoogewerff and van Dorp in 1885 from coal tar. Natural occurrence of isoquinoline ring system in the alkaloids stimulated a wide range effort to search for the efficient preparation of isoquinoline structures. For instance, Bischler-Napieralski, Pictet-Spengler, and Pomeranz-Fritsch reaction are among those most usual synthetic methods for isoquinoline derivatives.[2]

In the course of our investigation on intramolecular 1,3-dipolar cycloaddition between alkylazide and olefin,[3] we discovered a new dihydroisoquinoline synthesis, as shown in scheme I.

When ethyl o-bromomethylcinnamate 1[4] was treated with sodium azide in dimethylforamide at room temperature, azide 2 was formed in excellent yield with the contamination of a small amount of triazoline 3. Subsequent, intramolecular 1,3-dipolar cycloaddition of 2 occurred at room temperature in THF solution and gave triazoline 3 and diazo-compound 4, which had been separated and characterized.[5] On standing for 15h at room temperature, all triazoline 3 rearranged into diazo-compound 4 in THF solution. Diazo-compound 4 was a stable product and was purified by flash chromatography (silica gel, hexane:ethyl acetate 4:1 as

Scheme I



1 2 3 4 5 6

eluent). Finally, treatment of diazo-compound 4 with rhodium acetate[6] in dry *benzene afforded* 1,2-dihydroisoquinoline 6 (53% yield from 1).[7] A carbene N-H insertion reaction might have occurred to give the unstable intermediate 5, which underwent rearrangement to afford dihydroisoquinoline 6. In summary this two-step sequence, (1) NaN_3/aq MeOH (2) $Rh_2(OAc)_4$, transformed the readily available ethyl o-bromomethylcinnamate into the 1,2-dihydroisoquinoline ring system under mild conditions. The limitations and scope of this reaction, as well as its application towards the synthesis of isoquinoline alkaloids, in now under active investigation.

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5. Spectral data of 3: ^{1}H NMR ($CDCl_3$): δ 1.33(t, J=7Hz, 3H), 4.27(q, J=7Hz, 2H), 4.52, 4.70, 5.00 and 5.18(AB quartet, 2H), 5.18, 5.23, 5.27 and 5.32(AB, quartet, 2H), 7.21(s, 4H). IR($CHCl_3$): 1740 cm^{-1}.
Spectral data of 4: IR(neat) 3375, 2980, 2075, 1670 cm^{-1}. ^{1}H NMR($CDCl_3$): δ 1.27(t, J=7Hz, 3H), 2.49(br s, 1H, exchangable with D_2O), 4.12-4.36(m, 4H), 5.55(br s, 1H), 7.20(s, 4H). ^{13}C NMR($CDCl_3$): δ 14.5(q), 51.2(t), 55.4(s), 59.0(d), 60.6(t), 122.5(d), 122.8(d), 127.0(d), 127.7(d), 138.9(s), 140.5(s), 166.2(s), MS(12ev, m/e): 203(M^+-28, 21%).

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7. Spectral data of 6: IR($CHCl_3$) 3450, 3040, 1660, 1600 cm^{-1}, ^{1}H NMR($CDCl_3$): δ 1.27(t, J=7Hz, 3H), 4.17(q, J=7Hz, 2H), 4.60(s, 2H), 5.15(s, 1H), 7.16-7.60 (m, 4H), 8.16(br s, 1H). ^{13}C NMR($CDCl_3$): δ 14.6(q), 51.0(t), 58.4(d), 121.2 (d), 122.3(d), 127.2(d), 129.8(d), 134.9(s), 141.0(s), 160.5(s) 170.6(s), MS(12ev, m/e): 203(M^+, 100%). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.68; H, 6.72; N, 6.81.

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