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An Intermolecular Michael Addition of Benzene

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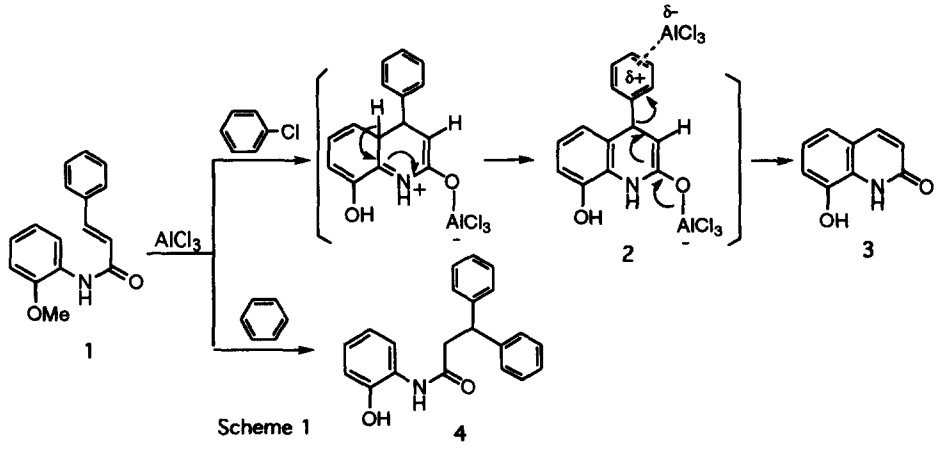
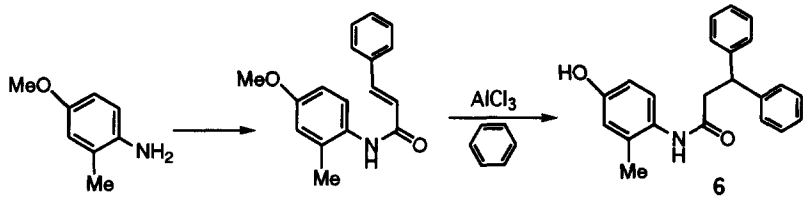
Abstract: The first intermolecular Michael addition of benzene leading to the formation of 3,3-diphenylpropionanilide is described. 2-Methoxyaniline was reacted with cinnamoyl chloride to give 2-methoxycinnamanilide (**1**) which was treated with aluminum chloride in benzene at 80°C to afford 2'-hydroxy-3,3-diphenylpropionanilide (**4**) in an 85% overall yield. Accordingly, 4'-hydroxy-2'-methyl-3,3-diphenylpropionanilide (**6**) was prepared from 4-methoxy-2-methylcinnamanilide (**5**) in 76% yield.

A number of 2(1*H*)-quinolinone derivatives have been synthesized and evaluated for their cardiovascular activities.[1-5] Recently, Fujioka *et. al.* described the preparation of 6-hydroxy-8-methyl-2(1*H*)-quinolinone, a key precursor for many novel positive inotropic agents, from 4-methoxy-2-methylaniline *via* Schotten-Baumann reaction and an intramolecular Friedel-Crafts cyclization.[2] Although the cyclization mechanism which included an unusual dearylation, was previously proposed by Manimaran *et. al.*,[6] we believe that dearylation occur *via* the enolate **2**. We have been interested in the preparation of hydroxycoumarin derivatives and examining their antiplatelet activity.[7,8] In an effort to expand these studies, *i.e.*, to synthesize their bioisosteric isomers, hydroxy-2(1*H*)-quinolinones, Fujioka's procedures were followed.[2] 2-Methoxyaniline was reacted with cinnamoyl chloride to give 2-methoxycinnamanilide (**1**) in 98% yield. Cyclization of **1** with aluminum chloride in chlorobenzene at 120°C afforded the desired 8-hydroxy-2(1*H*)-quinolinone (**3**) in 76% yield (Scheme 1).



Scheme 1

To optimize the cyclization reaction, chlorobenzene was replaced with benzene as the reaction solvent to provide a relatively mild condition (refluxed at 80°C). The ^1H NMR spectrum of the sole product isolated in this reaction showed a doublet at δ 3.22 ppm, a triplet at δ 4.56 ppm, and a multiplet at δ 6.69-7.63 ppm corresponding to CH_2, CH, and aromatic protons respectively. The ^{13}C NMR spectrum supported the ^1H NMR spectrum in confirming the presence of a methylene carbon resonance appeared at δ 41.51 ppm and a tertiary carbon resonance at δ 46.87 ppm. The intermolecular Michael addition of **1** with benzene to give 2'-hydroxy-3,3-diphenylpropionanilide (**4**) seems to be a resonable deduction. However, we were reluctant to make this critical structural assignment founded only on this evidence and therefore we sought a more definitive answer; an X-ray crystallographic analysis. A view of a single molecule of the crystal revealed that an intermolecular Michael addition occurred in which the benzene functions as a Michael donor and **1** as a Michael acceptor leading to the formation of **4** instead of the expected **3**. In order to establish and to further confirm this novel addition, 4-methoxy-2-methylaniline was converted into 4-methoxy-2-methylcinnamanilide (**5**) which was treated with aluminium chloride in refluxed benzene. 4'-Hydroxy-2'-methyl-3,3-diphenylpropionanilide (**6**) was obtained in 76% yield (Scheme 2). The structure of **6** was also established by ^1H NMR spectrum [δ 1.78 (s, 3H, CH_3), 3.03 (d, 2H, CH_2), 4.54 (t, 1H, CH), 6.44-7.36 (m, 13H, Ar-H), 9.10, 9.15 (2H, NH & OH)], ^{13}C NMR spectum [δ 17.55, 41.43, 47.06, 112.37, 116.39, 126.14, 126.94, 127.49, 127.60, 128.31, 134.06, 144.18, 154.85, 168.99] and elemental analyses.



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Scheme 2

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