Grignard Reaction of 2-Substituted-3-Cyanoquinolines*

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Grignard Reaction, 2-Substituted Quinolines, 1,2- and 1,4-Addition

Grignard reactions of 2-morpholino and 2-methylthio-3-cyanoquinoline, 2-chloro-3-cyanoquinoline, 2-chloro-3-cyano-6-methoxyquinoline and 2-chloro-3-cyano-7-methyliquinoline with alkyl or aryl magnesium halides have been studied. It was found that 2-morpholino and 2-methylthio-3-cyanoquinolines gave 1,4-addition products followed by rapid aromatisation. 2-Chloro-3-cyanoquinoline with alkyl magnesium halides furnished 1,4-addition products but with aryl magnesium halides 1,4- and 1,2-addition products were obtained. The cyano group of 4-aryl-2-chloro-3-cyano-1,4-dihydroquinolines was found to participate in the Grignard reaction to yield 1,2-addition products. 2-Chloro-3-cyano-6-methoxyquinoline with alkyl and phenyl magnesium halides yielded exclusively 1,4-addition products. Similarly with p-methoxyphenyl magnesium bromide, 1,4-addition products were isolated which participated in the Grignard reaction to yield the expected adducts. Unlike the other chloroquinoline derivatives, 2-chloro-3-cyano-7-methylquinoline with alkyl magnesium halide formed 1,2-addition products but with aryl magnesium halides, 1,4-addition products were isolated. The 4-alkyl-2-chloro-3-cyano-1,4-dihydroquinolines were unstable as compared to their 4-aryl analogs. A couple of the Grignard reaction products were found to be unstable on activated surface.

Grignard reaction of 3-cyanoquinoline (1) with alkyl magnesium halide, reported by earlier workers [1], yielded exclusively 4-alkyl-3-cyano-1,4-dihydroquinolines. This regioselectivity was not observed in the reaction of 1 with phenyl magnesium halide since 3-cyano-2- and 4-phenyl-1,4-dihydroquinolines were obtained [2]. However, no attempt appears to have been made to study the course of the Grignard reaction with varying substituents at position-2 and on the phenyl ring of 3-cyanoquinolines. This prompted us to report here our observations relating to the reaction of 2-chloro- (2), 2-chloro-6-methoxy- (28), 2-chloro-7-methyl- (40), 2-morpholino- (50) and 2-methylthio- (53) -3-cyanoquinolines with alkyl and aryl magnesium halides.

Grignard reaction products of various cyanoquinolines are described in the Table. The structural assignments of these reaction products were made on the basis of various spectroscopic data and in cases where additional evidence was necessary, appropriate chemical reactions were carried out to support the assigned structures. For example, hydrolysis of imines 15, 22, 33, 41 and 44 to the corresponding ketones (18, 26, 35, 43 and 46 respectively), of the nitrile 13 to the carboxylic acid 16 and of 36, 37 to the amides 38 and 39 respectively helped in providing additional support to the assigned structures of imines and nitriles. Aromatisation of 2-chloro-3-cyano-4-substituted-1,4-dihydroquinolines (5, 10 and 21) with manganic acetate, acetylation of 23 and 32, and demercaptation of 7 and 24 with Raney Ni also helped to provide additional evidence for structural assignments.

The appropriate precursors required for carrying out the reactions described above were also synthesized. For example, 7 was prepared by reacting 3 with thiourea in presence of K$_2$CO$_3$ in methanol followed by the methylation of the resulting mercaptan with MeI in presence of K$_2$CO$_3$. Similarly 24 was obtained from 25. Reaction of 2-chloro-3-formyl quinoline with (p-OMe)C$_6$H$_4$MgBr [3] furnished the precursor 17. Likewise 42 and 45 were prepared by reacting 2-chloro-3-formyl-7-methyliquinoline with CH$_3$MgI and C$_6$H$_5$MgBr respectively. 3-Cyano-2-morpholinoquinoline was obtained by reacting a methanolic solution of 2 with morpholine in presence of thiourea and K$_2$CO$_3$.

The present study revealed that the course of Grignard reaction of 3-cyanoquinoline derivatives was influenced by nature of substituents at position-2 and on the phenyl ring of the quinoline nucleus. While the effect of substituents at position-2 could be attributed to their steric interference, the effect of substituents on the phenyl part of the quinoline ring appears to be electronic, which in turn possibly changes the electron density at C-4.

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Experimental

IR, PMR and mass spectral data of those compounds which are not included in the Table also were in agreement with the assigned structures and C, H, N analyses were within ±0.4% of the theory.

1. Reaction of 3-cyano-2-substitutedquinolines with alkyl or aryl magnesium halides: general procedure

To a well stirred suspension of alkyl or aryl magnesium halide [prepared from magnesium turnings (0.02 mol) and alkyl or aryl halide (0.02 mol)] in dry ether (50 ml) was added appropriate 3-cyanoquinoline (0.01 mol) dissolved in dry THF (25 ml). The reaction mixture was stirred at room temperature (30 °C) for 20 min, decomposed with aqueous ammonium chloride (5%, 50 ml) and extracted with ethyl acetate (2×100 ml). The organic layer was washed with water, dried over anhydrous sodium sulphate and concentrated to yield oils, which were purified by column chromatography over silica gel. However, the reaction of 40 with p-methoxy phenyl magnesium bromide proceeded only in refluxing ether: THF mixture.

2. 3-Cyano-4-ethyl quinolin-2(1H)-thione (6)

A mixture of 3 (0.01 mol) and thiourea (0.012 mol), in dry methanol (25 ml) was heated under reflux for 3 h. The separated yellow crystalline solid was collected, washed with ethanol and heated with 10% aqueous sodium hydroxide (15 ml) at 80 °C for 15 min. On cooling and acidification, the quinolinethione (6) was obtained as a yellow powder and was crystallized from a mixture of acetone:hexane (20:80); m.p. 228 °C; yield 90%.
Fig. 2. Products of the Grignard reaction of 2-chloro-3-cyanoquinoline with phenyl and p-methoxyphenyl magnesium bromides.

Fig. 3. Products of the Grignard reaction of 2-chloro-3-cyano-6-methoxyquinoline with alkyl and aryl magnesium halides.
Fig. 4. Products of the Grignard reaction of 2-chloro-3-cyano-7-methylquinoline with alkyl and aryl magnesium halides.

Fig. 5. Syntheses and Grignard reaction products of 3-cyano-2-morpholinoquinoline and 3-cyano-2-methylthioquinoline.
3. 3-Cyano-4-ethyl or phenyl-2-methylthioquinolines (7 and 24)

A mixture of 6 (0.005 mol), anhydrous potassium carbonate (0.007 mol) and methyl iodide (0.007 mol) in methanol (25 ml) was refluxed under constant stirring for 1.5 h. The solvent was removed under vacuo and the residual solid was triturated with water (10 ml) to yield the methylthioquinoline (7) as pale yellow solid. It was crystallised from a mixture of chloroform:hexane (10:90); m.p. 78 °C; yield 95%.

Similar experimental procedure was employed to obtain compound 24 from 25. 24: oil; yield 95%.

4. 3-Cyano-4-ethyl or phenylquinoline (4 and 20)

A solution of 7 (0.005 mol) in methanol (50 ml) was hydrogenated over Raney-Ni at 2.5 kg/cm² for 2.5 h. The reaction mixture was filtered through hyflo and the filtrate concentrated to yield an oil which was purified by passing through a short band of silica gel using chloroform as the eluent; compound 4 was obtained as colourless needles from chloroform-hexane mixture.

By employing similar experimental procedure 20 was obtained from 24.

5. Hydrolysis of imines 15, 22, 33, 41 and 44: formation of ketones 18, 26, 35, 43 and 46

A mixture of appropriately substituted imine (0.02 mol), aqueous HCl (10%, 7 ml) and methanol (50 ml) was first stirred at room temperature (35 °C) for 0.5 h and then heated over a steam bath for another 0.5 h. The solvent was removed in vacuo and the residual oil was extracted with chloroform (50 ml). The chloroform layer was washed with water (3 × 50 ml) and dried over anhydrous sodium sulphate. The residue obtained after the removal of the solvent crystallized from a mixture of ether:hexane (20:80) to furnish the required ketones as colourless crystalline solids. 18: m.p. 212 °C; yield 95%; 26: m.p.158 °C; yield 90%; 35: m.p.157 °C; yield 90%; 43: m.p. 58 °C; yield 90%; 46: m.p. 62 °C; yield 90%.

6. Hydrolysis of nitrile 13: formation of carboxylic acid 16

A mixture of 13 (0.002 mol), aq. HCl (25%, 20 ml) and ethanol (15 ml) was refluxed under constant stirring for 2 h. The solvent was removed under vacuo and the residual oil was extracted with ethyl acetate. Usual work up of the organic layer furnished an oil.

7. Hydrolysis of nitriles 36 and 37: formation of amides 38 and 39

A solution of appropriately substituted 3-cyanoquinoline (0.001 mol), aq. HCl (15%, 10 ml) and ethanol (20 ml) was refluxed for 0.5 h. The solvent was removed under vacuo and the residual oil was extracted with chloroform (2 × 50 ml). Usual work up of the organic layer yielded an oil which crystallized from chloroform-hexane to furnish the required amides as crystalline solids.

8. Aromatisation of 2-chloro-3-cyano-4-substituted-1,4-dihydroquinolines (5, 10 and 21) with manganic acetate

To a well stirred solution of appropriately substituted 1,4-dihydroquinoline (0.01 mol) in toluene (50 ml) was added manganic acetate [4] (0.04 mol) in three equal portions. The whole mixture was refluxed under constant stirring for 4 h. The black manganese salt was filtered and the filtrate concentrated under vacuo to furnish an oil which on addition of hexane yielded 2-chloro-3-cyano-4-substituted-quinolines as solids. These were recrystallized from a mixture of chloroform:hexane (20:80). 25: m.p. 185 °C; yield 95%.

9. Acetylation of 23 and 32

A solution of appropriately substituted amine (0.005 mol), acetic anhydride (0.007 mol) and pyridine (0.1 ml) was stirred at room temperature (35 °C) for 4 h. It was poured onto water (50 ml) and extracted with chloroform (2 × 100 ml). Usual work up of the organic layer yielded acetyl derivatives (27 and 34). 27: m.p. 269 °C, yield 80%; 34: oil; yield 80%.

10. 3-Cyano-2-morpholinoquinoline (50)

A mixture of 2 (0.01 mol), thiourea (0.012 mol) and morpholine (0.015 mol) in methanol (50 ml) was refluxed under constant stirring for 5 h. The reaction mixture was cooled and diluted with water to furnish a solid which was purified by column chromatography over silica gel. Elution of the column with hexane gave unreacted starting material first and was followed by the required 2-morpholino derivative (50). It was recrystallized from hexane as yellow needles, m.p. 81–82 °C; yield 90%.
<table>
<thead>
<tr>
<th>Substituted cyanoquinolines</th>
<th>Grignard reagent</th>
<th>Reaction products* (m.p., % yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>3 (110 °C, 10); 4 (180 °C, 2); 5 (118–119 °C, 70); 8** (128 °C, 10)</td>
<td></td>
</tr>
<tr>
<td>2 CH&lt;sub&gt;3&lt;/sub&gt;MgI</td>
<td>9 (132 °C, 15); 10 (179 °C, 70); 11** (148–149 °C, 8)</td>
<td></td>
</tr>
<tr>
<td>(p-OMe)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;MgBr</td>
<td>12 (167–169 °C, lit. [5] 171–172 °C, 2); 13 (182 °C, 4); 14 (128–129 °C, 25); 15 (oil, 10); 16 (oil, 10)</td>
<td></td>
</tr>
<tr>
<td>2 C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>19 (69–70 °C, lit. [5] 68.5 °C, 2); 20 (195–196 °C, 2); 21 (160 °C, 60); 22 (147 °C, 8); 23 (oil, 10)</td>
<td></td>
</tr>
<tr>
<td>28 CH&lt;sub&gt;3&lt;/sub&gt;MgI</td>
<td>29 (198 °C, 80)</td>
<td></td>
</tr>
<tr>
<td>28 C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>30 (72 °C, 85)</td>
<td></td>
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<tr>
<td>28 (p-OMe)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;MgBr</td>
<td>31 (169 °C, 10); 32 (192 °C, 20); 33 (167 °C, 20)</td>
<td></td>
</tr>
<tr>
<td>28 C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>19; 36 (261–263 °C, 25); 37 (200–201 °C, 20); 38 (280–281 °C, 5); 39 (151 °C, 8)</td>
<td></td>
</tr>
<tr>
<td>40 CH&lt;sub&gt;3&lt;/sub&gt;MgI</td>
<td>41 (141 °C, 25)</td>
<td></td>
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<tr>
<td>40 C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>44 (111 °C, 30)</td>
<td></td>
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<tr>
<td>40 C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>47 (200 °C, 20); 48 (167 °C, 35)</td>
<td></td>
</tr>
<tr>
<td>40 (p-OMe)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;MgBr</td>
<td>49 (oil, 20)</td>
<td></td>
</tr>
<tr>
<td>50 C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>51 (oil, 70)</td>
<td></td>
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<tr>
<td>53 C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;MgBr</td>
<td>24 (oil, 55)</td>
<td></td>
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</tbody>
</table>

* IR, PMR and mass spectrometric data were in agreement with the assigned structures and C, H, N analyses were within ±0.4% of the theory; ** these compounds were obtained by allowing the crude Grignard reaction product to remain adsorbed on the column surface for a long time.