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# A General Synthetic Method for 1-Substituted 1,4-Dihydro-3(2*H*)-isoquinolinones

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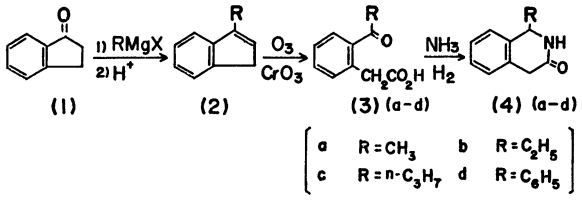
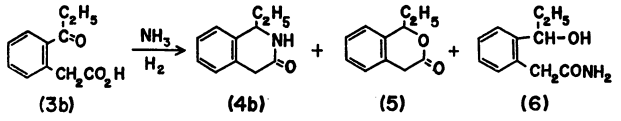
**Synopsis.** The reaction conditions for the conversion of **3** into **4** were investigated in some detail, and it was found that the reductive amination of *o*-acylphenylacetic acid was allowed to proceed smoothly by the use of deactivated Raney nickel.

In the previous paper[1] it was shown that the reductive amination of *o*-acetylphenylacetic acid (**3a**) afforded 1-methyl-1,4-dihydro-3(2*H*)-isoquinolinone (**4a**) in the presence of Raney nickel in good yield. From this result we were interested in the investigation of the general utility of the reductive amination of this type for synthesis of 1-alkyl or 1-aryl 1,4-dihydro-3(2*H*) isoquinolinones (**4**), which may be easily converted to the corresponding tetrahydroisoquinoline by the action of $LiAlH_4$ or $B_2H_6$. We report here the results of a detailed study of the reductive amination of *o*-acylphenylacetic acids and provide evidence of the generality of this method.




*o*-Acylphenylacetic acids (**3**) (**b**—**d**) were prepared easily by a Grignard reaction of indanone (**1**), followed by ozonolysis which was accompanied by oxidation with $CrO_3$.

Initially, the reaction condition was examined for the ring formation of *o*-propionylphenylacetic acid as a model. *o*-Propionylphenylacetic acid (**3b**) was treated with ammonia in the presence of Raney nickel in an autoclave to give a mixture of three compounds. After




chromatographic separation, three main compounds, **4b**, **5**, and **6**, were isolated in yields of 49, 4.4, and 34%, respectively. The structures of these compounds were confirmed by means of spectroscopic evidence and elemental analysis. This result suggested that a competing reaction took place in the reductive amination reaction. This finding showed that it was necessary to reduce the activity of Raney nickel (W-5) toward the carbonyl group in order to avoid this unfavorable competing reaction. The deactivation of Raney nickel was achieved by treatment with acetone (soaking for 1.5 h at room temperature). When the reductive amination of *o*-propionylphenylacetic acid (**3b**) was carried out under the same reaction conditions using deactivated Raney nickel, 1-ethyl-1,4-dihydro-3(2*H*)-isoquinolinone (**4b**) was obtained in high yield. 1-Propyl- and 1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**4c** and **4c**) were also obtained in high yields, as shown in the table, by the same procedure using deactivated Raney nickel.

TABLE 1. YIELDS OF **4** (**b**–**d**) FROM **3** (**b**–**d**)

| R | 3 | 4 | |
|---|---|---|---|
| | Mp (°C) | Mp (°C) | Yield (%) |
| $-CH_2CH_3$ | 137 —138 | 107 | 86 |
| $-CH_2CH_2CH_3$ | 115.5—116.5 | 97— 98 | 65 |
| $-C_6H_5$ | 128.5—130 | 141.5—144 | 74 |

## Experimental

All the melting points are uncorrected. The NMR and IR spectra were recorded on JEOL JNM-60 and JASCO IRA-1 spectrometers, respectively.

*1-Ethyl-1,4-dihydro-3(2H)-isoquinolinone (4b).* *Method A*: Raney nickel and a soln of *o*-propionylphenylacetic acid (**3b**) (300 mg) in ethanol (30 ml) previously saturated with ammonia were placed in an autoclave, and the reaction was carried out for 7 h at 110 °C in an atmosphere of hydrogen at 70 atm. After the reaction, the solvent was removed *in vacuo*, and the resulting residue was subjected to preparative TLC to give three compounds: 1-ethyl-1,4-dihydro-3(2*H*)-isoquinolinone (**4b**), lactone (**5**), and amide (**6**), in yields of 49% (134 mg), 4.4% (12 mg), and 34% (103 mg), respectively. Compound **4b**: mp 107 °C; IR (KBr): 3180, 3050, 1690 $cm^{-1}$; NMR ($CDCl_3$): $\delta$ 0.90 (t, 3H), 1.79 (pentuplet, 2H), 3.55 (s, 2H), 4.41 (t, 1H), 7.14 (s, 4H), 7.55—7.90 (b, 1H); Found: C, 75.67; H, 7.43; N, 8.21%. Calcd for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99%. Compound **5**: colorless oily liquid; IR (Neat): 1740, 1235, 1150 $cm^{-1}$; NMR ($CCl_4$): $\delta$ 1.08 (t, 3H), 1.97 (dq, 2H), 3.57 (s, 2H), 5.14 (t, 1H), 7.15 (s, 4H). Compound **6**: mp 98—99.5 °C; IR (KBr): 3280, 3100, 1650, 1010 $cm^{-1}$; NMR ($CDCl_3$): $\delta$ 0.88 (t, 3H), 1.73 (pentuplet, 2H), 3.55 (s, 2H), 3.94 (bs, 1H), 4.66 (t, 1H), 6.06 (bs, 2H), 7.10—7.50 (m, 4H); Found: C, 68.07; H, 7.96; N, 7.27%. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25%.

*Method B*: Raney nickel (W-5) was soaked in acetone before use at room temperature in order to reduce the activity. When the reductive amination of **3b** was carried out under the same reaction conditions as described above using Raney nickel which was soaked in acetone for 90 min at room temperature, **4b** was obtained in an 86% yield accompanied by small amount of **6**. On the other hand, when the soaking time of the catalyst in acetone was shortened from 90 min to 40 min, the reductive amination gives rise to **4b**, **5**, and **6** in yields of 60%, 2.2%, and 15%, respectively.

*1-Propyl-1,4-dihydro-3(2H)-isoquinolinone (4c).* **4c** was

obtained in a 65% yield by the reductive amination of **3c** according to method B. Mp 97—98 °C; IR (KBr): 3180, 3050, 1680 $cm^{-1}$; NMR ($CDCl_3$): $\delta$ 0.91 (t, 3H), 1.14—1.90 (m, 4H), 3.52 (s, 2H), 4.20—4.60 (t, 1H), 6.80—7.32 (m, 5H); Found: C, 75.78; H, 8.03; N, 7.24%. Calcd for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40%.

*1-Phenyl-1,4-dihydro-3(2H)-isoquinolinone (**4d**).* This compound was obtained in a 74% yield by the reductive amination of **3d** according to method B. mp 141.5—144 °C; IR (KBr): 3190, 3050, 1660 $cm^{-1}$; NMR ($CDCl_3$): $\delta$ 3.60 (s, 2H), 5.50 (s, 1H), 6.77—7.34 (m, 10H): Found: C, 80.36; H, 5.69; N, 6.31%. Calcd for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.27%.

## Reference

1) H. Kotake, A. Kawashiri, S. Miyashita, and H. Kinoshita, *Nippon Kagaku Zasshi*, **92**, 878 (1971).