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Anomalous Dehydration of 2-Phenylindole-3-carboxamide to 2-Phenylindole-3-carbonitrile by Lithium Aluminum Hydride

Short Communication

Tonson Abraham[a,*] and **Albert J. Sicree**[b]

[a] Research Institute, The University of Dayton, Dayton, OH 45469, U.S.A.
[b] Air Force Materials Laboratory, Wright-Patterson Air Force Base, OH 45433, U.S.A.

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Steric factors have been shown to be responsible for the anomalous dehydration of 2-phenylindole-3-carboxamide (**1**) to 2-phenylindole-3-carbonitrile (**3**) by lithium aluminum hydride. This steric effect was also reflected in the reactions of 2-phenylindole (**4**) and its derivatives.

Anomale Dehydratisierung von 2-Phenylindol-3-carbonsäureamid zu 2-Phenylindol-3-carbonitril mit Lithiumaluminiumhydrid (Kurze Mitteilung)

Es wird gezeigt, daß für die anomale Dehydratisierung von 2-Phenylindol-3-carbonsäureamid (**1**) zum entsprechenden Nitril **3** durch Lithiumaluminiumhydrid sterische Faktoren verantwortlich sind. Dieser sterische Effekt zeigt sich auch bei Reaktionen von 2-Phenylindol (**4**) und seiner Derivate.

(Keywords: Indoles; Reduction; Steric hindrance)

Carboxamides are normally reduced to amines by lithium aluminum hydride (*LAH*)[1]. The unexpected dehydration of an indole carboxamide to the indole carbonitrile in the presence of an excess of *LAH* is reported here.

When 2-phenylindole-3-carboxamide (**1**) was allowed to react with an excess of *LAH* in refluxing tetrahydrofuran (*THF*), 2-phenylindole-3-carbonitrile (**3**) was isolated in 88% yield. Normally, one would expect *LAH* to reduce 1,*N*-unsubstituted indole-3-carboxamides to 3-methyl

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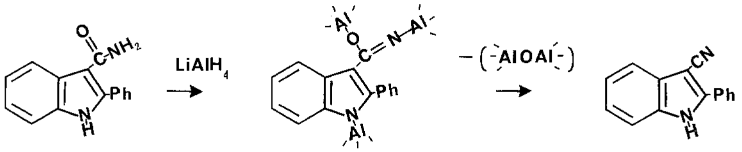

1 2 3

derivatives, by analogy with the behavior of 1-unsubstituted indole-3-carboxylic acids towards *LAH*[2]. Although we are not aware of any reported reactions of 1,*N*-unsubstituted indole-3-carboxamides with *LAH*, 1-substituted-*N*-unsubstituted indole-3-carboxamides have been reduced to amines by *LAH*[3], which is analogous to the reduction of related indole derivatives[4].

Steric hindrance due to the presence of the 2-phenyl group in **1** appeared to be responsible for the anomalous dehydration of **1** by *LAH*. This effect was reflected in the reactions of 2-phenylindole (**4**) and its derivatives.

For example, 2-phenylindolylmagnesium iodide (**5**), made from **4** and methylmagnesium iodide, failed to react with carbon dioxide when a *THF* solution of **5** was poured into dry-ice. The outcome was the same even when carbon dioxide was bubbled into a boiling solution of **5** in toluene. In both cases, **4** was recovered[5]. The expected[6] 2-phenylindole-3-carboxylic acid was not formed. The steric resistance to electrophilic substitution at the 3-position of **4** could be overcome by using more powerful electrophiles. Thus **4** underwent electrophilic substitution in the presence of acetyl cyanide[7] and reactive isocyanates[8–10].

There appears to be a delicate balance between electronic and steric effects in the case of the reactions of **4** and its derivatives. While 2-methylindole **6** condensed with the acetyl cyanide at room temperature, **4** does not, unless an acid catalyst is used. The mode of condensation with acetyl cyanide at the 3-indolyl position of **4** and its derivatives then depends upon the substituent at the 1-indolyl position[7]. In another example, 2-oxo-2-(2-phenylindol-3-yl)acetonitrile (**7**) was allowed to react with ethanolic KOH to yield ethyl 2-phenylindole-3-carboxylate (**8**)[11]. Once the positive character of the carbonyl carbon attached to the 3-indolyl position was reduced, as it was in **8** when compared to **7**, steric factors began to dominate, and **8** could not be hydrolyzed to the acid under normal ester hydrolysis conditions[11]. Also, 2-phenylindole-3-carboxaldehyde (**9**) was reduced to 3-methyl-2-phenylindole (**10**) by *LAH*[4], whereas **1** resisted reduction under similar conditions.

The intermediate **2**, expected to be formed by the action of *LAH* on **1**, apparently underwent loss of an oxide of aluminum to yield the nitrile **3**. *N*,*N*-unsubstituted or *N*-monosubstituted carboxamides were less reactive towards *LAH* then the corresponding *N*,*N*-disubstituted derivatives[12], presumably due to the reduced reduction potential[13] of the intermediates of type **2**. However, since *LAH* reduced 2-methyl-1-substituted-*N*-unsubstituted indole-3-carboxamides to aminomethyl derivatives[3], it appeared that steric rather than electronic factors prevented the reduction of **1**.

Reports of the dehydration of carboxamides to nitriles by the use of excess *LAH* are scarce. *Newman* and *Fukunaga* reported the isolation of nitriles by the reaction of *LAH* with carboxamides (four cases) only when the mole ratio of *LAH* to carboxamide was less than one[14]. 10,11-Dihydro-5*H*-dibenzo[a,d]cycloheptene-5-carboxamide and 2,2-diphenylacetamide have also been dehydrated to nitriles with *LAH*[15]. To our knowledge, these are the only reports of dehydration of carboxamides to carbonitriles with *LAH*. In other related chemistry, certain acyl hydrazines were found to be unreactive towards *LAH*[16].

2-phenylindole-3-carboxamide (**1**) was obtained by the hydrolysis of the chlorosulfonyl intermediate that resulted by the action of 2-phenylindole on chlorosulfonyl isocyanate, as reported by *Mehta*, *Dhar* and *Suri*[10]. The reactions of indole derivatives with reactive isocyanates, including chlorosulfonyl isocyanate had previously been reported by *Seefelder*[8,9]. Moreover, compounds **1**[17] and **3**[17–20] reported by *Mehta* et al.[10] were also previously known.

Experimental

2-Phenylindole-3-carboxamide (**1**)

This compound was prepared as previously described[10], mp. 184-184.5° (ethyl acetate/heptane). Lit. 189°[10] and 180-181°[17]. IR (KBr, cm^{-1}): 3510, 3400, 3340-2380 (br, ν_{max} 3100), 1635, 1590, 1570, 1465, 1450, 1330, 1225, 745, 735, 690. PMR (*DMSO-*d_6, δ): 6.3-8.9 (m). MS (chemical ionization with methane): $M + 1$ (237).

2-Phenylindole-3-carbonitrile (**3**)

Under argon, 2-phenylindole-3-carboxamide (1.0 g, 4.2 mmol) was added slowly to a suspension of *LAH* (1.6 g, 42 mmol) in 50 ml of anhydrous *THF* (distilled from sodium/benzophenone). The reaction mixture was then refluxed for 3 h, cooled, and the excess *LAH* destroyed by careful addition of 15% NaOH aq. The aluminate salts were filtered off, and washed with ether. The combined organic phase was washed with water, dried ($MgSO_4$), and then evaporated to give **3** (88%).

Thin layer chromatography (Macherey-Nagel silica gel pre-coated plastic sheets) showed only one component [$R_f = 0.5$, 40% petroleum ether (bp. 30-60°)/60% ether] with R_f value identical with that of recrystallized (alcohol/water) material, mp. 240.5-241.5°. Lit. 240°[10], 236-238°[17], and 243°[18]. IR (KBr, cm^{-1}): 3410-2280 (br, ν_{max} 3230), 2230, 1495, 1455, 1425, 1245, 735, 685. PMR (*DMSO-*d_6, δ): 7.2-8.3 (m). MS (chemical ionization with methane): $M + 1$ (219).

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