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Amino-Claisen Rearrangement of Vinyl Propargylamines and Pyrindane Synthesis from a Divinyl Ketone

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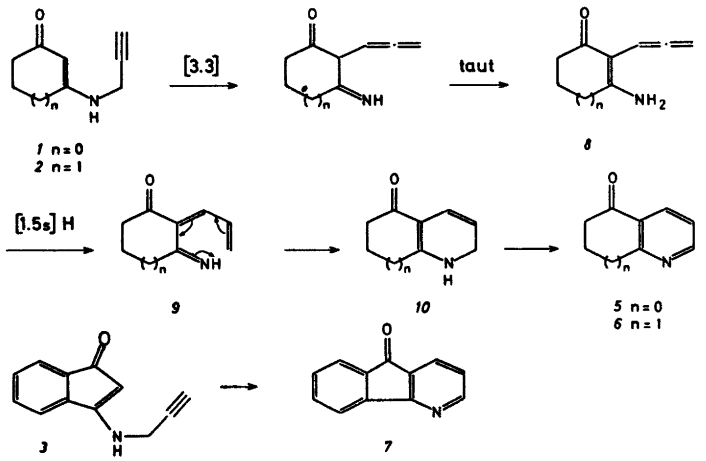
The amino-Claisen rearrangement of 3-(2-propylamino)-2-cyclopenten-1-one, 3-(2-propynylamino)-2-cyclohexen-1-one, and 3-(2-propynylamino)indenone proceeded with electrocyclic ring closure to 6,7-dihydro-1-pyrindin-5-one, 5,6,7,8-tetrahydroquinolin-5-one, and 5*H*-indeno[1,2-*b*]pyridin-5-one, respectively. On the other hand, 3-amino-2-(2-propynyl)-2-cyclohexen-1-one isomerized to 4,5,6,7-tetrahydro-2-methylindol-4-one. 1-(1-Cyclopentenyl)-2-propen-1-one heated with benzylamine afforded 1-benzyl-octahydro-1*H*-1-pyrindin-4-one.

In contrast to phenyl propargyl ether *N*-propargylaniline resists the aromatic amino-Claisen rearrangement when heated to 160 °C; mainly decomposition to aniline occurs.[1] On the other hand, *N*-propargyl-1- and 2-naphthylamine at 250 °C are converted to a mixture of tetrahydrobenzoquinolines and benzoquinolines,[2] and with copper(0) and copper(I) chloride as catalysts, 2,2-dimethyl-1,2-dihydroquinoline was obtained from 3-anilino-3-methyl-1-butyne at room temperature.[3,4] Claisen rearrangement with subsequent electrocyclic ring closure of vinylpropargylamines therefore might be a possible route to fused dihydropyridines.

The desired vinylpropargylamines were obtained from the reaction of propargylamine with cyclopentane-1,3-dione and with cyclohexane-1,3-dione which afforded 3-(2-propynylamino)-2-cyclopenten-1-one (*1*) and 3-(2-propynylamino)-2-cyclohexen-1-one (*2*) in 76 and 74 % yields, respectively. Moreover, 3-(2-propynylamino)indenone (*3*) was obtained from the reaction of propargylamine with indane-1,3-dione. On the other hand, 3-amino-2-cyclohex-



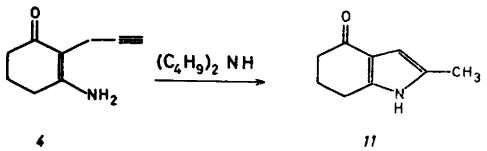
Scheme 1.

en-1-one reacted with propargyl bromide to 3-amino-2-(2-propynyl)-2-cyclohexen-1-one (*4*) in 59 % yield.

In hot nitrobenzene compounds *1*, *2* and *3* underwent amino-Claisen rearrangement and ring closure to 6,7-dihydro-1-pyrindin-5-one (*5*), 5,6,7,8-tetrahydroquinolin-5-one (*6*), and 5*H*-indeno[1,2-*b*]pyridin-5-one (*7*) in 68, 50, and 40 % yields, respectively. Analogous reactions in benzonitrile at 240 °C gave the same products in only 10 – 15 % yields. Other solvents and the use of copper(0) and copper(I) chloride as catalysts resulted in even poorer yields of the desired products. An interpretation of this thermal rearrangement is depicted in Scheme 1.

An amino-Claisen reaction followed by tautomerization provides the allenic enamine *8*. This rearranges by a [1,5] sigmatropic hydrogen shift to the intermediate *9* which undergoes ring closure to the intermediate *10*; dehydrogenation yields the observed products *5*, *6*, and *7*. The intermediate *10* is most probably unstable at high temperatures since it could not be isolated from any of the reaction mixtures. When nitrobenzene is used as a solvent it also acts as a dehydrogenating reagent in the last step and the yields are four to seven times higher than in other solvents. Aniline is formed as a byproduct; the reaction was followed by gas chromatography which revealed an increase of the aniline concentration during the reaction.

Base-catalyzed isomerization of compound *4* could lead to the allenic enamine *8* and thus provide an alternative route to compound *6*. However, when compound *4* in dibutylamine was heated to 160 °C for 4 h 4,5,6,7-tetrahydro-2-methylindol-4-one (*11*) was isolated as the sole product in 75 % yield. This compound has previously been prepared in 21.5 % yield only by heating compound *4* in ethanol with copper(I) chloride as a catalyst.[5] In our reaction dibutylamine probably abstracts the relatively acidic amine proton from compound



4 11

Scheme 2.

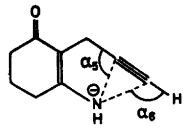


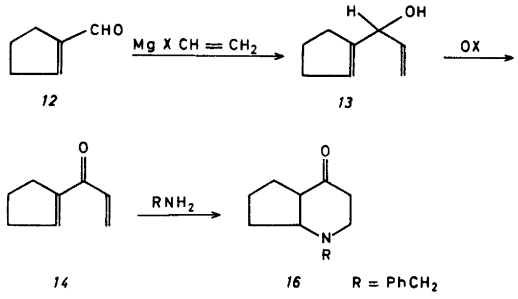
Fig. 1.

4; subsequent reaction of the amide anion with the acetylenic bond explains the formation of the observed indole derivative *11*.

According to the rules for ring closure put forward by Baldwin [6] formation of both five- and six-membered rings is favoured provided the angles α_5 and α_6 between the digonal carbon atoms and the approaching nucleophile are the same in both cases and preferably close to 120° (see Fig. 1).

Molecular models show that an angle α_5 closest to this value is obtained in a planar conformation, but in this conformation the angle α_6 is quite similar in size; usually the *Endo-Dig* cyclization leading to a six-membered ring is preferred in contrast to the result in the present case.

When cyclohexenylvinyl ketones react with primary amines formation of decahydroquinolin-4-ones takes place.[7] Another possible synthetic route to fused dihydropyridines therefore could be as outlined in Scheme 3.



12 13 14 16 R = PhCH2

Scheme 3.

1-Cyclohexenecarbaldehyde can be prepared from 1-nitromethyl-1-cyclohexene by treatment with titanium(III) chloride.[8] However, no 1-cyclopentenecarbaldehyde (*12*) could be detected from the reaction of 1-nitromethyl-1-cyclopentene under the same reaction conditions. Substance *12* therefore was prepared by a known method.[9] It reacted with vinylmagnesium bromide to give 79 % yield of 1-(1-

cyclopentenyl)-2-propen-1-ol (*13*) which was easily oxidized by active manganese dioxide [10] to 1-(1-cyclopentenyl)-2-propen-1-one (*14*) in 90 % yield. The preparation of the 2,4-dinitrophenylhydrazone derivative (*15*) proceeded with addition of ethanol to the terminal double bond which took place either before or after hydrazone formation.

When the ketone *14* was heated with 25 % aqueous ammonia a viscous mixture resulted from which no pure substance could be obtained. Heating at 90 – 100 °C with benzylamine, however, afforded a small amount of 1-benzyl-octahydro-1*H*-1-pyrindin-4-one (*16*). In its NMR spectrum the benzylic methylene protons appear as an AB quartet due to the chirality of the molecule.

EXPERIMENTAL

Melting points were determined on a micro hot-stage. NMR spectra were recorded on Varian A-60 and HA 100 spectrometers with TMS as internal standard. IR spectra were obtained on a Perkin-Elmer 457 Grating Infrared Spectrophotometer and the mass spectra on an AEI/EC MS 902 instrument. Elemental analyses were performed by I. Beetz, West Germany.

3-(2-Propynylamino)-2-cyclopenten-1-one (1). A mixture of propargylamine hydrochloride (5.3 g, 50 mmol) in water (5 ml), sodium hydroxide (2.0 g, 50 mmol) in water (2 ml) and cyclopentane-1,3-dione (4.0 g, 40 mmol) in benzene (50 ml) was refluxed with a water separator for 6 h. The reaction mixture was decanted, cooled, and benzene removed at low pressure to give 4.1 g (76 %) of compound *1* as pale yellow needles, m.p. 125 – 127 °C (from chloroform and cyclohexane). Anal. C_8H_9NO: C, H. MS [*m/e* (% rel. int.)]: 135 (29.9, M), 107 (47.0), 106 (100), 79 (23.8), 78 (21.7), 68 (41.6), 53 (24.0), 52 (35.8), 39 (51.3). ^{1}H NMR ($CDCl_3$): δ 2.45 (2 H, t, J 2.3 Hz), ~2.45 (2 H, complex), ~2.75 (2 H, complex), 3.97 (2 H, dd, J 2.3 and 5.5 Hz), 5.15 (1 H, s), 7.65 – 7.15 (1 H, broad). IR (KBr): 3220 (s), 3190 (s), 3040 (s), 2910 (m), 2125 (m), 1648 (s), 1575 (s, broad), 1440 (s), 1281 (s), 1208 (s) cm^{-1}.

3-(2-Propynylamino)-2-cyclohexen-1-one (2). To propargylamine hydrochloride (1.0 g, 10 mmol) in hot ethanol (10 ml) was added sodium hydroxide (0.4 g, 10 mmol) in water (1 ml). After cooling the precipitate was filtered off and cyclohexane-1,3-dione (1.1 g, 10 mmol) was added with stirring until completely dissolved. After 1 h at room temperature the ethanol was removed to give 1.0 g (74 %) of compound *2* as pale yellow crystals, m.p. 142.5 – 143.5 °C (from ethyl acetate and benzene). Anal. $C_9H_{11}NO$: C, H. MS [*m/e* (% rel. int.)]: 149 (39.1, M), 120 (44.8), 93 (100), 66 (24.6), 42 (31.6), 41 (24.9), 39 (51.4). ^{1}H NMR ($CDCl_3$): δ ~2.30 (7 H, complex), 3.92 (2 H, dd, J 2.2 and 5.5 Hz), 5.22 (1 H, s), 6.34 (1 H, broad s). IR (KBr): 3225 (s), 3040 (s), 2110 (w) cm^{-1}.

3-(2-Propynylamino)indenone (3). To propargylamine hydrochloride (1.0 g, 10 mmol) in hot ethanol (10 ml) was added sodium hydroxide (0.4 g, 10 mmol) in water (1 ml). After cooling the precipitate was filtered off and indane-1,3-dione (1.4 g, 10 mmol) was added to the solution. The mixture was heated at 80 °C for 3 h before the solvent was removed to give 0.9 g (49 %) of compound *3* as dark yellow needles, m.p. 170 – 172 °C (from toluene). Anal. $C_{12}H_9ON$: C, H. MS [*m/e* (% rel. int.)]: 183 (29.3, M), 182 (100), 181 (36.1), 155 (23.3), 154 (29.1), 127 (20.0), 102 (20.1), 76 (20.3). ^{1}H NMR (acetone-d_6): 2.79 (1 H, t, J 3 Hz), 4.20 (2 H, d, J 3 Hz), 4.94 (1 H, s), 7.28 – 7.60 (4 H, complex). IR (KBr): 3220 (s), 2100 (w), 1650 (m), 1570 (s) cm^{-1}.

3-Amino-2-(2-propynyl)-2-cyclohexen-1-one (4). A mixture of 3-amino-2-cyclohexen-1-one [11] (6.0 g, 50 mmol), sodium bicarbonate (4.2 g, 50 mmol) and propargyl bromide (6.0 g, 50 mmol) in abs. ethanol (100 ml) was refluxed for 24 h. The solvent was removed and the resulting solid chromatographed on a column of silica gel with chloroform as eluent to give 4.4 g (59 %) of compound *4* m.p. 104 – 106 °C (from benzene).

6,7-Dihydro-1-pyrindin-5-one (5). Compound *1* (0.4 g, 3 mmol) was heated to 195 °C in nitrobenzene (25 ml) for 1.5 h. After cooling the mixture was extracted with 2 N HCl (50 ml) and the extract washed with ether (50 ml × 3). After cautious neutralization with 50 % NaOH to pH 10 – 11 the water layer was extracted with ether (50 ml × 3) and the ether removed to give 0.30 g (68 %) of compound *5*, b.p. 125 °C/9 mmHg, m.p. 64 – 66 °C (lit:[11] b.p. 130 °C/12 mmHg, m.p. 62 – 64 °C). Repeating experiments sometimes gave lower yield due to polymerization.

5,6,7,8-Tetrahydroquinolin-5-one (6). The procedure was as described above using compound *2* (1.5 g, 3 mmol) to give 0.8 g (50 %) of compound *6*, b.p. 54 °C/0.04 mmHg, n_D^{20} 1.5630, (lit:[12] 116 – 117 °C/6 mmHg, n_D^{20} 1.5643).

5H-Indeno[1.2-b]pyridin-5-one (7). The procedure was as described above using compound *3* (0.5 g, 3 mmol) to give 0.2 g (40 %) of the product *7*, m.p. 139 – 140 °C (from ethanol), (lit:[13] m.p. 139.5 – 141.5 °C). The IR spectrum was consistent with that previously reported.[13]

4,5,6,7-Tetrahydro-2-methylindol-4-one (11). Compound *4* (0.2 g, 1.3 mmol) was heated to 170 °C in dibutylamine (25 ml) for 4 h. The solvent was removed to give 0.15 g (75 %) of compound *11* as white crystals, m.p. 207 – 208 °C (from benzene), (lit:[5] m.p. 210 – 211 °C).

1-(1-Cyclopentenyl)-2-propen-1-ol (13). To a slurry of magnesium (27.0 g, 1.1 mol) and a

crystal of iodine in tetrahydrofuran (500 ml) under nitrogen with stirring and a Stoke condenser was added vinylbromide (160 g, 1.5 mol) in dry tetrahydrofuran (100 ml) during 3 h while the temperature in the mixture was kept at 45 – 50 °C. After heating for 1 h at 80 °C the mixture was cooled to room temperature and 1-cyclopentenecarbaldehyde [9] (*12*) (21.0 g, 0.2 mol) was slowly added with some cooling. After 1 h the reaction mixture was hydrolyzed with saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted 3 times with chloroform. The combined organic layers were dried, the solvent evaporated and the residue distilled to give 21.5 g (79 %) of compound *13*, b.p. 39 °C/0.02 mmHg, n_D^{22} 1.4848 (lit:[14] b.p. 43 °C/0.5 mmHg, n_D^{22} 1.4890).

1-(1-Cyclopentenyl)-2-propen-1-one (*14*). Compound *13* (21.5 g, 173 mmol) and active manganese dioxide [10] (400 g) were stirred in pentane (300 ml) for 30 min, filtered and the solvent removed. The residue was distilled to give 19.0 g (90 %) of compound *14*, b.p. 34 – 38 °C/0.04 mmHg. MS [*m/e* (% rel. int.)]: 122 (62.5, M), 95 (100), 79 (30), 67 (86), 66 (19), 65 (22). ^{1}H NMR ($CDCl_3$): 1.93 (2 H, qw, *J* 7 Hz), 2.63 (4 H, t, *J* 7 Hz), 5.68 (1 H, dd, *J* 2.3 and 10.0 Hz), 6.25 (1 H, dd, *J* 2.3 and 17.0 Hz), 6.81 (1 H, t, *J* 1.5 Hz), 6.95 (1 H, dd, *J* 10.0 and 17.0 Hz). IR (film): 3508 (m), 1665 (s), 1658 (s), 1614 (s), 1608 (m) cm^{-1}.

1-Benzyl-octahydro-1H-1-pyrindin-4-one (*16*). A mixture of benzylamine (2.1 g, 20 mmol) and the ketone *12* (2.5 g, 20 mmol) was kept at 90 – 100 °C for 1 h and then distilled through a 2 cm column, b.p. 135 °C/0.01 mmHg. The destillate was dissolved in 2 N HCl (5 ml) and washed with chloroform; the solution was made basic with NH_3 and extracted with chloroform. Repetition of this purification procedure gave 0.3 g (13 %) of compound *16*. MS [*m/e* (% rel. int)]: 229 (25.0, M), 200 (61.4), 91 (100), 65 (10.9). Mol. wt., obs. 229.1468, calc. for $C_{15}H_{19}NO$ 229.1466. ^{1}H NMR ($CDCl_3$): δ 1.50 – 3.34 (12 H, complex), 3.34 (1 H) and 3.92 (1 H) (*AB* quartet, *J* 13.8 Hz), 7.30 (4 H, complex). IR (film): 3030 (m), 2950 (s), 2872 (m), 2800 (s), 1715 (s), 1455 (s), 1350 (s), 740 (s), 698 (s) cm^{-1}.

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