Pergamon

Tetrahedron 55 (1999) 12881–12884

TETRAHEDRON

Triazolopyridines 20.[1] Hydrogenation Reactions#

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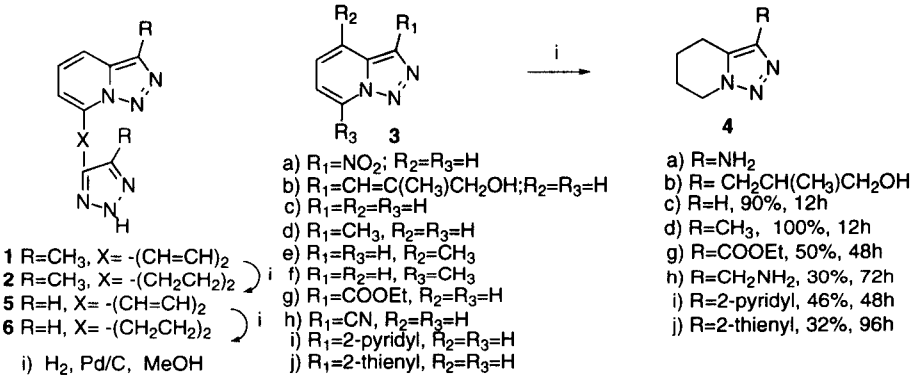
Received 21 June 1999; revised 6 August 1999; accepted 26 August 1999

Abstract: Hydrogenation reactions of some [1,2,3]triazolo[1,5-*a*]pyridines and their benzo derivatives, [1,2,3]-triazolo[1,5-*a*]quinoline and [1,2,3]triazolo[5,1-*a*]isoquinoline are studied. In general, the pyridine ring is more easily hydrogenated than the triazole or benzene rings.

Keywords: Bicyclic heterocyclic compounds, rearrangements, hydrogenation.

Introduction

In the course of our work on triazolopyridine lithiation reactions,[2] the compound **1** was obtained as a by-product, which was hydrogenated giving compound **2** in high yield; no reduction of the heterocyclic rings was found. However, it had been reported that hydrogenation reaction of two [1,2,3]triazolo[1,5-*a*]pyridines (**3a** and **3b**) gives **4a**[3] (as the major product) and **4b**[4] respectively. Due to the different behaviour shown by **1** we decided to study hydrogenation reactions in a number of triazolopyridine derivatives with different patterns of substitution. We report our results here.



Results and discussion

We have used standard conditions for hydrogenation reactions, palladium on activated carbon, methanol as solvent at room temperature and atmospheric pressure. The parent compound **3c** was easily hydrogenated giving tetrahydrotriazolopyridine **4c** in high yield. This result is similar to that described in the hydrogenation reactions of indolizines[5] and [1,2,4]triazolopyridines.[6] Nevertheless, the hydrogenation of compound **5** gives **6** just as we have found in the reaction with **1**. When the triazolopyridine has a methyl group as substituent, the hydrogenation reaction strongly depends on the position of the substituent. Compound **3d** gives **4d** in

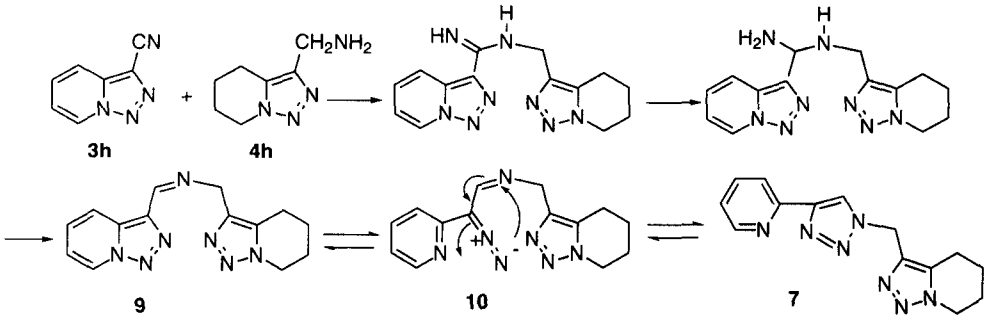
This paper is dedicated to our *magister* and friend Professor Gurnos Jones on his 70th birthday.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00761-9

quantitative yield, however, when the methyl group is at C4 (**3e**) or C7 (**3f**), no hydrogenated products were observed and starting materials were recovered. Under the conditions used the alkyl and alkenyl substituents inhibit the reduction on the pyridine ring.

With electron withdrawing substituents in the triazole ring, compounds **3g-i**, hydrogenation gives the corresponding tetrahydro derivatives, but the much lower reactivity of these compounds was reflected in much longer reaction times, and compounds **4g-i** were obtained only in moderate yields. In the case of an electron donor group as substituent, compound **3j**, no reaction was observed under standard conditions. Using a double amount of the catalyst and reaction time six times longer, a small amount of hydrogenated compound **4j** was observed.

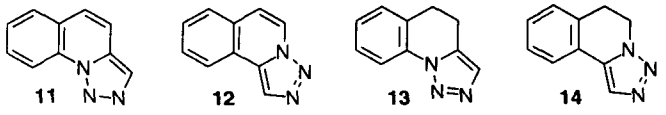
In the case of the hydrogenation reaction of compound **3h** two products were obtained. As well as 3-aminomethyl tetrahydrotriazolopyridine **4h**, formed by reduction of the pyridine ring and the nitrile group, a second compound was isolated. This compound shows a molecular ion of 281.1387 corresponding to a molecular formula of $C_{14}H_{15}N_7$. A careful study of its ^1H and ^{13}C NMR spectral data suggested the presence of a 2-pyridyltriazole, due to a doublet at 8.44 ppm with a coupling constant of 4.7Hz in the ^1H NMR spectrum and a CH at 148.76 ppm in the ^{13}C NMR spectrum, significant signals for a 2-substituted pyridine, as well as a singlet at 8.12 ppm and a CH at 136.36 ppm in the ^1H and ^{13}C NMR spectra, respectively, for a 4-substituted triazole as have been described for a 4-(2-pyridyl) triazole.[7] There are also signals corresponding to a tetrahydrotriazolopyridine. We propose the structure **7** for this compound, which can be formed as is summarized in Scheme 1.



Scheme 1

A nucleophilic addition of **4h** to the starting material **3h** gives the imine intermediate **8** which is further hydrogenated, losing ammonia to give triazolopyridineimine **9** in equilibrium with the diazo tautomer **10**. This intermediate may undergo a new ring-chain tautomerism,[8] giving a 1,4-disubstituted-1,2,3-triazole. This type of rearrangement has no precedent in the chemistry of [1,2,3]triazolo[1,5-*a*]pyridines.

As an extension of our study, we have hydrogenated [1,2,3]triazolo[1,5-*a*]quinoline **11** and [1,2,3]triazolo[5,1-*a*]isoquinoline **12**, giving 4,5-dihydro[1,2,3]triazolo[1,5-*a*]quinoline **13** and 5,6-dihydro [1,2,3]triazolo[5,1-*a*]isoquinoline **14**, respectively, in high yield. In both cases, the pyridine was also the preferred ring to be reduced.



Experimental

Mps were determined on a Kofler heated stage. NMR spectra were determined on a Bruker AC250MHz instrument. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). Chromatography was performed on a Flash 40 column using silica. Infrared spectra were recorded in KBr discs on a Bio-Rad FTS-7.

[1,2,3]Triazolo[1,5-a]pyridines **3**

3c,d,[9] **3e**,[10] **3f**,[11] **3g**,[12] **3h**,[7] **3i,j**[13] were prepared as described in the references cited.

General procedure for hydrogenation reactions.

To a solution of the corresponding triazolopyridine **3** (0.2g) or **5** (50mg, 0.21mmoles), triazoloquinoline[8] **11** (200mg, 1.18mmoles) or triazoloisoquinoline[14] **12** (200mg, 1.18 mmoles) in methanol (50 ml) palladium on activated carbon (0.1g,10%) was added. The mixture was stirred at room temperature under a slight positive pressure of hydrogen maintained by a balloon. The development of the reaction was monitored by tlc. Then it was filtered and the filtrate was evaporated. The isolation and purification procedures are given for each compound.

4,5,6,7-Tetrahydro[1,2,3]triazolo[1,5-a]pyridine ***4c.-***

Compound **4c** was obtained pure after 12h, as a colourless oil (186mg) (90%). HRMS found for M^+ 123.0795; $C_6H_9N_3$ requires 123.0796. ν_{max} (neat) 2953, 1642, 1551,1450, 1237 cm^{-1}. ^1H NMR δ ($CDCl_3$) 1.86-2.04 (m, 2H); 2.05-2.13 (m, 2H); 2.83 (t, J=6.5Hz, 2H); 4.34 (t, J=5.8Hz, 2H); 7.40 (s,1H). ^{13}C NMR δ ($CDCl_3$) 19.51 ($2CH_2$); 22.12 (CH_2); 45.37 (CH_2); 129.96 (CH); 132.80 (C).

3-Methyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-a]pyridine ***4d.-***

Compound **4d** was obtained pure after 12h, as a colourless oil (205mg) (100%). HRMS found for M^+ 137.0947; $C_7H_{11}N_3$ requires 137.0953. ν_{max} (neat) 2950, 1691, 1577, 1449, 1348, 1239 cm^{-1}. ^1H NMR δ ($CDCl_3$) 1.84-1.94 (m, 2H); 1.99-2.20 (m, 2H); 2.21 (s, 3H); 2.69 (t, J=6.2Hz, 2H); 4.28 (t, J=5.8Hz, 2H). ^{13}C NMR δ ($CDCl_3$) 9.34 (CH_3); 19.18 (CH_2); 19.54 (CH_2); 22.01 (CH_2); 45.57 (CH_2); 129.45 (C); 138.15 (C).

Ethyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate ***4g.-***

After 48h the reaction crude was purified by chromatography. Elution with chloroform-methanol (15:1) gave starting material (150mg) and then compound **4g** as a white solid (35mg, 50% based on unrecovered starting material). m.p. 90-92°C (ethyl acetate) (lit.,[15] m.p. 88-90°C, hexane). HRMS found for M^+ 195.1001; $C_9H_{13}N_3O_2$ requires 195.1007. ν_{max} (KBr) 2958, 1706, 1567, 1445, 1231cm^{-1}. ^1H NMR δ ($CDCl_3$) 1.41 (t, J=6.6Hz, 3H); 1.90-1.99 (m, 2H); 2.05-2.12 (m, 2H); 3.10 (t, J=6.2Hz, 2H); 4.35-4.45 (m, 4H). ^{13}C NMR δ ($CDCl_3$) 14.30 (CH_3); 19.26 (CH_2); 21.33 (CH_2); 22.12 (CH_2); 46.30 (CH_2); 60.75 (CH_2); 135.28 (C); 138.82 (C); 161.57 (CO).

4,5,6,7-Tetrahydro[1,2,3]triazolo[1,5-a]pyridin-3-ylmethanamine ***4h*** *and 3-[4-(2-pyridyl-1H-1,2,3-triazol-1-ylmethyl]-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-a]pyridin-3yl)-methane* ***7.-***

The reaction was done with **3h** (500mg, 3.47mmoles, 72h). The crude reaction product was purified by chromatography on alumina (I). Elution with ethyl acetate/hexane (9:1) gave starting material (140mg). Further elution with dichloromethane/methanol (8:2) gave a yellow oil (240mg, 34%) identified as compound **7**. HRMS found for M^+ 281.1394; $C_{14}H_{15}N_7$ requires 281.1387. ν_{max} (neat) 2953, 1600, 1336, 1243 cm^{-1}. ^1H NMR δ ($CDCl_3$) 1.75-1.82 (m, 2H); 1.89-1.96 (m, 2H); 2.66 (t, J=6.2Hz, 2H); 4.25 (t, J=5.8Hz, 2H); 5.59 (s, 2H); 7.14 (dd, J_1 7.7Hz, J_2=4.7Hz, 1H); 7.67 (dd, J_1=7.7Hz, J_2=8.0Hz, 1H); 8.00 (d, J=8.0Hz, 1H); 8.12 (s, 1H); 8.44 (d, J=4.7Hz, 1H). ^{13}C NMR δ ($CDCl_3$) 18.92 ($2CH_2$); 21.60 (CH_2); 44.43 (CH_2); 45.70 (CH_2); 119.46 (CH); 121.67 (CH); 122.33 (CH); 132.38 (C); 136.27 (C); 136.36 (CH); 147.81 (C); 148.76 (CH); 149.37 (C). Elution with methanol, gives compound **4h** as a yellow oil (115mg, 30% based on unrecovered starting material). HRMS found for M^+ 152.1059; $C_7H_{12}N_4$ requires 152.1062. ν_{max} (neat) 3450-3300, 2952, 1696, 1595, 1445, 1238 cm^{-1}. ^1H NMR δ ($CDCl_3$) 1.87-1.90 (m, 2H); 1.91-2.14 (m, 2H); 2.78 (t, J=6.2Hz, 2H); 4.00 (brs, 2H); 4.21 (t, J=5.8Hz, 2H); 4.51 (s, 2H); ^{13}C NMR δ ($CDCl_3$) 19.76 (CH_2); 19.84 (CH_2); 22.41 (CH_2); 42.27 (CH_2); 46.15 (CH_2); 132.36 (C); 139.28 (C).

3-(2-Pyridyl)-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-a]pyridine ***4i.-***

After 48h the crude reaction product was purified by chromatography. Elution with ethyl acetate- hexane (2:1) gave starting material (130mg), further elution gave the compound **4i** as a white solid, m.p. 117-120°C (ethyl acetate/ hexane) (46% based on unrecovered starting material). HRMS found for M^+ 200.1066 ; $C_{11}H_{12}N_4$ requires 200.1062. ν_{max} (KBr) 2948, 1596, 1502, 1424, 1357 cm^{-1}. ^1H NMR δ ($CDCl_3$) 1.87-1.96 (m, 2H); 2.02-2.14 (m, 2H); 3.24 (t, J=6.2Hz, 2H); 4.40 (t, J=5.8Hz, 2H); 7.13 (dd, J_1=5.0Hz, J_2=7.6Hz, 1H); 7.70

(dd, J_1=8.0Hz, J_2=7.6Hz, 1H); 8.14 (d, J=8.0Hz, 1H); 8.54 (d, J=5.0Hz, 1H). ^{13}C NMR δ ($CDCl_3$) 19.98 (CH_2); 22.46 (CH_2); 46.44 (CH_2); 120.49 (CH); 121.65 (CH); 133.09 (C); 136.40 (CH); 142.28 (C); 149.01 (CH); 152.17 (C).

3-(2-Thienyl)-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-a]pyridine ***4j***.-

After 96h the crude reaction product was purified by chromatography using dichloromethane/ethyl acetate (9:1), firstly starting material was recovered (140mg), further product **4j** was obtained as a white solid (19mg, 46% based on unrecovered starting material), m.p.105-107°C (dichloromethane). HRMS found for M^+ 205.0666; $C_{10}H_{11}N_3S$ requires 205.0673. ν_{max} (KBr) 2954, 1526, 1439, 1356 cm^{-1} . ^{1}H NMR δ ($CDCl_3$) 1.96-2.00 (m, 2H); 2.03-2.10 (m, 2H); 2.97 (t, J= 6.2Hz, 2H); 4.39 (t, J= 5.8Hz, 2H); 7.09 (dd, J_1= 3.6Hz, J_2= 4.7Hz, 1H); 7.28 (d, J= 3.6Hz, 1H); 7.29 (d, J= 4.7Hz, 1H). ^{13}C NMR δ ($CDCl_3$) 19.97 (CH_2); 21.17 (CH_2); 22.36 (CH_2); 46.40 (CH_2); 123.16 (CH); 124.33 (CH); 127.45 (CH); 129.13 (C); 133.95 (C); 138.38 (C).

1-([1,2,3]Triazolo[1,5-a]pyridin-7-yl)-4-(5-methyl-1H-[1,2,3]triazol-4-yl)butane ***6***.-

Compound **6** was obtained pure after 2h, as a white solid (48mg) (95%). m.p. 123-125°C (MeOH). HRMS found for M^+ 242.1281; $C_{12}H_{14}N_6$ requires 242.1280. ν_{max} 3600-2400 cm^{-1}. ^{1}H NMR δ (DMSO) 1.68-1.81 (m, 2H); 1.84-1.90 (m, 2H); 2.72 (t, J=7.3Hz, 2H); 3.25 (t, J=6.9Hz, 2H); 3.79 (brs, 1H); 7.02 (d, J=6.6Hz, 1H); 7.36 (dd, J_1=8.8, J_2=6.6Hz, 1H); 7.60 (s, 1H); 7.85 (d, J=8.8Hz, 1H); 8.23 (s, 1H). ^{13}C NMR δ (DMSO) 24.10 (CH_2); 25.50 (CH_2); 28.73 (CH_2); 30.04 (CH_2); 113.72 (CH); 115.93 (CH); 126.01 (CH); 133.97 (C); 138.88 (C).

4,5-Dihydro[1,2,3]triazolo[1,5-a]quinoline ***13*** .-

The mixture was stirred 72h. Purification by chromatography, elution with ethyl acetate/ hexane (3:2), gives starting material (46mg), further product **13** was eluted (140mg, 90% from recovered starting material) as a colourless oil. HRMS found for M^+ 171.0794; $C_{10}H_9N_3$ requires 171.0796. ν_{max} (neat) 2954, 1589, 1500, 760 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 2.97-3.12 (m, 4H); 7.27-7.43 (m, 3H); 7.59 (s, 1H); 8.11 (d, J=7.7Hz, 1H). ^{13}C NMR δ ($CDCl_3$) 19.00 (CH_2); 25.45 (CH_2); 117.04 (CH); 126.92 (C); 127.49 (CH); 128.12 (CH); 128.71 (CH); 130.71 (CH); 132.34 (C).

5,6-Dihydro[1,2,3]triazolo[5,1-a]isoquinoline ***14***

The mixture was stirred 96h. Purification by chromatography, elution with ethyl acetate/ hexane (3:2), gives product **14** as a white solid (180mg, 72%). m.p. 62-63°C (Hexane/ethyl acetate) (5:1). HRMS found for M^+ 171.0797; $C_{10}H_9N_3$ requires 171.0796. ν_{max} (KBr) 2975, 1487, 1425, 775 cm^{-1}. ^{1}H NMR δ 3.10 (t, J=6.6Hz, 2H); 4.44 (t, J=6.6Hz, 2H); 7.20-7.21 (m, 3H); 7.41-7.45 (m, 1H); 7.81 (s, 1H). ^{13}C NMR δ 28.25 (CH_2); 44.11 (CH_2); 124.19 (CH); 127.42 (CH); 128.11 (CH); 128.95 (CH); 131.61 (C); 133.39 (C); 144.63 (C).

Acknowledgements: Our thanks to the Comisión Interministerial de Ciencia y Tecnología (CICYT, project PB94-0959) for its financial support.

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