Triazolopyridines. Part 27.[1] The preparation of novel 6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridines

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Dedicated to Professor Benito Alcaide on the occasion of his 60th birthday

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Abstract

A very efficient synthesis of the unknown family of 6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridines from [1,2,3]triazolo[1,5-*a*]pyridines have been developed, and a mechanism for their formation has been proposed. Their behaviour with NBS to give 4,5-dibromo substituted-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridines is studied.

Keywords: Nitrogenated heterocycles, triazolopyridines

Introduction

[1,2,3]Triazolo[1,5-*a*]pyridines **1** are fused biheterocyclic ring systems that are readily accessed by mild oxidation of hydrazones of pyridyl ketones and aldehydes.[2] Jones and ourselves, have reported on the synthesis of interesting 2,6-disubstituted pyridines,[3] indolizines,[4] and bipyridines,[5] using [1,2,3]triazolo[1,5-*a*]pyridines as synthons. We have also reported many aspects of the chemistry of [1,2,3]triazolo[1,5-*a*]pyridines, their fluorescent behaviour,[6] the preparation of fluorescent sensors of cations and anions,[7] their coordination chemistry,[8] and their application in the field of magnetic materials.[8d,9] Recent examples are precursors to pyridyl carbenes,[10] reagents for transannulation,[11] or cross-coupling reactions,[6,12,13] and also chiral fluorescent materials.[14]

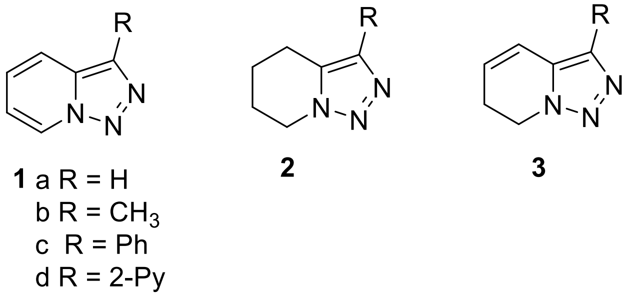
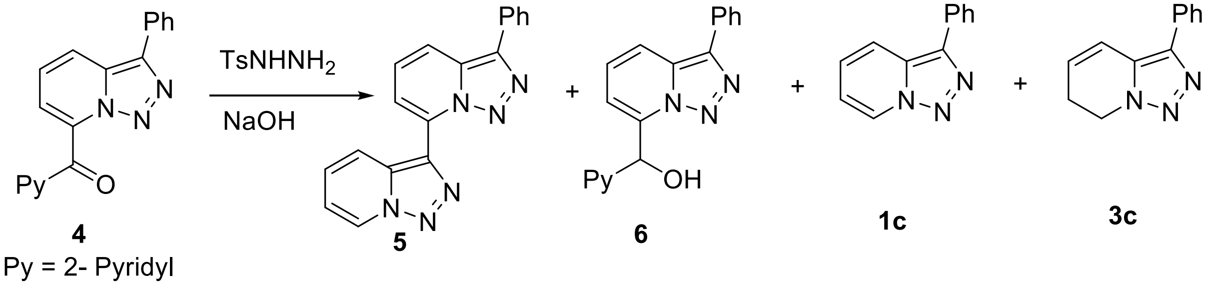


Figure 1

Hydrogenation reactions of some [1,2,3]triazolo[1,5-*a*]pyridines has been studied, under standard conditions (H_2, Pd/C, MeOH, room temperature),[15] to give 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridines **2** in high yield. In general, the pyridine ring is more easily hydrogenated than the triazole or benzene rings. Also, tetrahydrotriazolopyridines have been obtained in some cases by diazo transfer reactions.[16]

The 6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridines **3** are unknown compounds, with one exception described in 2004 in the course of a complex reaction,[17] in which the treatment of 3-phenyl-7-picolinoyl-[1,2,3]triazolo[1,5-*a*]pyridine **4** with $TsNHNH_2$ in aqueous NaOH solution at reflux, gave a mixture of the bitriazolopyridine **5** (2%), the alcohol **6** (45%), the triazolopyridine **1c** (15%), and the surprising 6,7-dihydrotriazolopyridine **3c** (38%) (Scheme 1). We had verified that **3c** is formed from **6** in basic medium.[17]



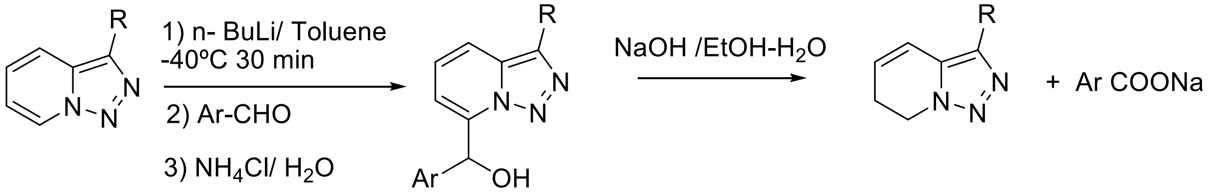
Scheme 1

We describe in this paper the general synthesis of 6,7-dihydro[1,2,3]triazolo[1,5-*a*] pyridines **3** from 7-arylhydroxymethyltriazolopyridines **7** in aqueous NaOH solution at reflux, and we propose a mechanism to explain these results. Also the reaction of 6,7-dihydrotriazolopyridines with NBS is studied.

Results and Discussion

To study the scope of the reaction, we have prepared a series of 7-arylhydroxymethyltriazolopyridines **7a-c** and we have studied their reactions with NaOH in ethanol/ water at reflux.

We had reported that the regioselective metalation of [1,2,3]triazolo[1,5-*a*]pyridines **1a-c** with *n*-BuLi in toluene at -40 ºC gives the corresponding 7-lithioderivatives, which react subsequently with a number of electrophiles to give 7-substituted triazolo-pyridines.[3,17,18] Thus, we have synthesized the 7-arylhydroxymethyltriazolopyridines **7** by direct regioselective metalation of triazolopyridines **1**, followed by treatment with aldehydes. (Scheme 2).



1 a R= H
b R= CH_3
c R = Ph

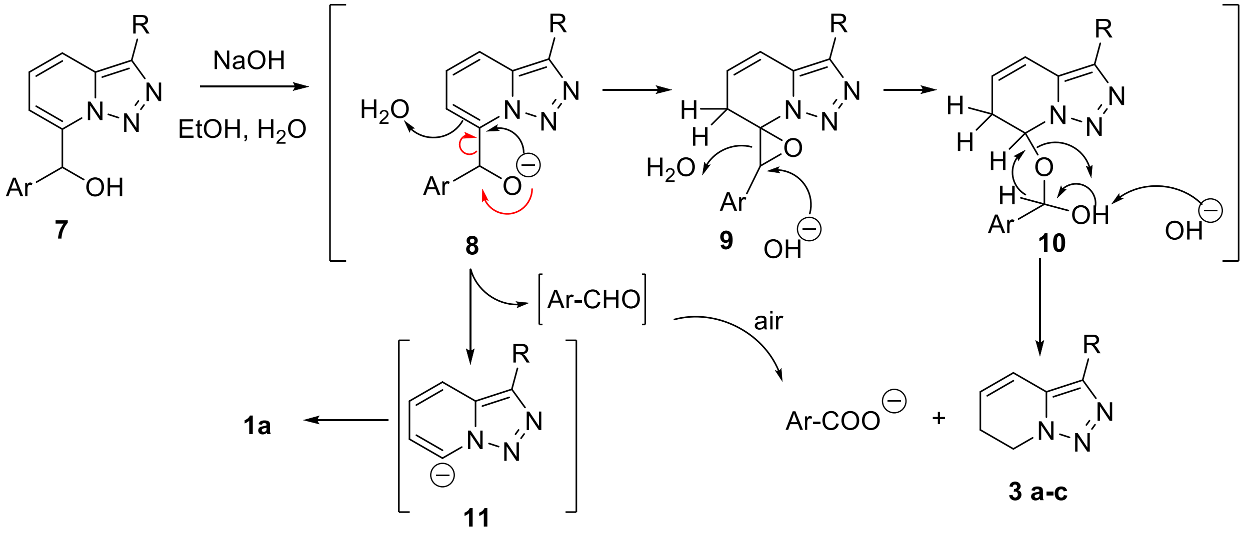
7 a R= H, Ar = Ph
a' R= H, Ar = 4-$NO_2C_6H_4$
b R= CH_3, Ar = Ph
b' R= CH_3, Ar = 2-Py
c R= Ph, Ar = Ph

3 a R= H
b R= CH_3
c R = Ph

Scheme 2

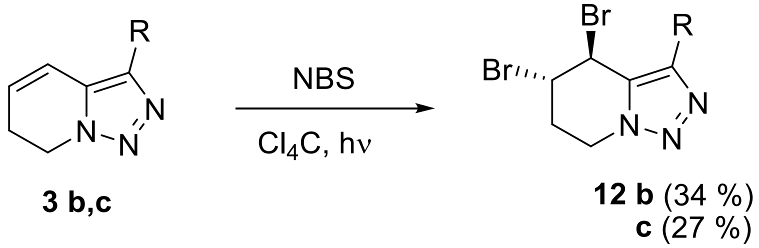
With compounds **7a, 7b, 7b'** and **7c** in basic medium we have obtained the 6,7-dihydrotriazolopyridines **3a-c** in good yield, and sodium benzoate or sodium picolinate as by-products. In the case of the carbinol **7a'** only the triazolopyridine **1a** has been obtained in quantitative yield. To explain this behaviour we propose the mechanism shown in Scheme 3. Deprotonation of alcohols **7** gives the alkoxides **8**. Nucleophilic attack to the activated 7-position towards nucleophiles,[19] and trapping of a proton in C6 position, leads to the intermediates **9** (black arrows). Ring-cleavage reaction with OH^- forms the new hemiacetal intermediates **10**. By deprotonation in basic media followed by hydride shift to C7 position,[20] the 6,7-dihydrotriazolopyridines **3** are obtained with the corresponding arylcarboxylate salts.

The formation of the triazolopyridine **1a** from **7a'**, could be explained by the formation of alkoxide **8a'** and then, a nucleophilic attack of the anion (O^-) to the next C with formation of a new anion **11** and the corresponding aldehyde (red arrows). Protonation of **11** gives **1a**.



Scheme 3

Compounds **3b** and **3c** were treated in standard conditions for allylic bromination.[21] Nevertheless reaction with NBS in carbon tetrachloride and irradiation with visible light gives **12b** and **12c** in low yields, products of addition of bromine to the double bond (CAUTION carbon tetrachloride, which is an ozone depleting compound and suspected carcinogen,[22] can be substituted by less pernicious dichloromethane).[23,24] The corresponding products of allylic bromination were not observed. If two equivalents of NBS and one equivalent of 6,7-dihydrotriazolopyridines were used only polymerization was observed. By this procedure it was able to prepare new 4,5-dibromo-4,5,6,7-tetrahydrotriazolopyridines **12b** and **12c**. (Scheme 4).



Scheme 4

Conclusions

In summary we have developed an efficient synthesis of the unknown family of 6,7-dihydrotriazolopyridines. We have proposed a mechanism for their formation and we have studied their behaviour with NBS to give 4,5-dibromo substituted tetrahydrotriazolopyridines.

Experimental Section

General Procedures. Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC300MHz in $CDCl_3$ as solvent. COSY experiments were done for all compounds. HRMS Electron Impact (EI) or ElectroSpray (ES) determinations were made using a VG Autospec Trio 1000 (Fisons). All the lithiation reactions were done under inert atmosphere and dry solvents.[25]

[1,2,3]Triazolo[1,5-*a*]pyridine **1a**,[26] 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b**,[26] 3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridine **1c**,[26] phenyl [1,2,3]triazolo[1,5-*a*]pyridin-7-yl methanol **7a**,[3] 4-nitrophenyl [1,2,3]triazolo[1,5-*a*]pyridin-7-yl methanol **7a'**,[3] phenyl 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridin-7-yl methanol **7b**, and 2-pyridyl 3-methyl-[1,2,3] triazolo[1,5-*a*]pyridin-7-yl methanol **7b'**,[18] were prepared as described elsewhere.

Phenyl 3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridin-7-yl methanol (7c). To a solution of 3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridine **1c** (1g, 5.12 mg) in anhydrous toluene (57 ml) at -40ºC, a solution of *n*-butyllitium in hexane (3.2 ml, 1.6M) (2.5M) was added with stirring. A deep red colour developed. The mixture was kept at –40ºC (30 min). Treatment with benzaldehyde (0.54 g, 5.12 mmol) produced a colour change to yellow. The reaction mixture was left at room temperature (2 h 30 min), and quenched with a saturated aqueous solution of ammonium chloride. The organic layer was separated and the aqueous layer extracted with dichloromethane. After dried over anhydrous Na_2SO_4 and evaporation of the organic solvents, a residue was obtained. This residue was purified by FLASH + 40^{TM} chromatography (Biotage cartridges) over silica gel with hexane-ethyl acetate to obtain **7c** (500 mg, 32.4%). HMRS found for M^+ 301.1206; $C_{19}H_{15}N_3O$ requires 301.1215. ^1H NMR δ 7.98 – 7.94 (m, 3H), 7.60 (dd, J_1= 8.1Hz, J_2= 1.14Hz, 2H), 7.52 (t, J_1= 7.23Hz, 2H), 7.45 – 7.29 (m, 5H), 6.77 (d, J= 6.87Hz, 1H), 6.58 (s, 1H), 4.67 (s, 1H, <u>OH</u>CH). ^{13}C NMR δ 139.13 (C), 137.14 (C), 137.07 (C), 129.92 (C), 129.62 (C), 127.75 (CH), 127.34 (CH), 127.27 (CH), 126.76 (CH), 125.95 (CH), 125.46 (CH), 124.68 (CH), 116.08 (CH), 112.05 (CH), 70.21 (CH). EM (E.I.): m/z (%) 301 (5.6); 273 (84.5); 244 (100.0); 228 (8.6); 196 (26.6); 182 (5.0); 168 (70.2); 139 (58.6); 105 (71.7); 91 (12.4) ; 77 (99.2).

General procedure for preparation of 6,7-dihydrotriazolopyridines

To a solution of the corresponding 7-arylhydroxymethyltriazolopyridine **7 a, b, b' c** in ethanol was added a solution of aqueous NaOH (conditions in Table 1), and the mixture was heated to reflux (95 ºC) during 24 hours. The ethanol was evaporated, and the aqueous layer was extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and concentrated, giving a crude mixture. The products, yields, and conditions of purification are given for each compound.

Table 1. Conditions for the reaction of 7-arylhydroxymethyltriazolopyridines with NaOH

7-Arylhydroxymethyl triazolopyridine	(mg, mmol)	NaOH aq (ml, M)	EtOH (ml)
7a	(170, 0.75)	(27, 4)	25
7b	(350, 1.44)	(50, 4)	50
7b'	(100, 0.42)	(15, 4)	15
7c	(500, 1.66)	(60, 4)	50

6,7-Dihydro[1,2,3]triazolo[1,5-*a*]pyridine (3a). The crude product from **7a** was purified by chromatotron with ethyl acetate/hexane (51.06 mg, 56.3%, colourless oil). HMRS found for M^+ 121.0642; $C_6H_7N_3$ requires 121.0640. ^{1}H NMR δ 7.35 (s, H3), 6.53 (ddd, J_1=9.8Hz, J_2=J_3=1.8Hz, 1H, H4), 6.11 (ddd, J_1= 9.61Hz, J_2=4.3Hz, J_3=4.5Hz, 1H, H5), 4.48 (t, J_1=7.8Hz, 2H, H7), 2.70 (m, 2H, H6). ^{13}C NMR δ 132.11 (C), 129.48 (CH), 127.17 (CH), 115.48 (CH), 43.65 (CH_2), 24.52 (CH_2). MS (E.I.): m/z (%) 121 (100), 93 (23), 92 (24), 67 (17), 66 (72), 65 (51), 53 (9).

3-Methyl-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridine (3b). The crude product from **7b** was purified by chromatotron with ethyl acetate/hexane (94.6 mg, 50%, colourless oil), and from **7b'** was purified in the same conditions (20 mg, 48%).). HMRS (ES) found for (M^+ + 1) 136.0873; $C_7H_9N_3H$ requires 136.0875. ^{1}H NMR δ 6.36 (ddd, J_1=9.9, J_2=J_3=1.8Hz, 1H, H4), 5.96 (ddd, J_1=9.9, J_2=J_3=4.5Hz, 1H, H5), 4.32 (t, J_1=J_2=7.8Hz, 2H, H7), 2.57 (m, 2H, H6), 2.23 (s, 3H, CH_3). ^{13}C NMR δ 132.20 (C), 128.80 (C), 125.59 (CH), 115.08 (CH), 43.86 (CH_2), 23.90 (CH_2), 9.84 (CH_3). MS (E.I.): m/z (%) 135 (100), 107 (70), 106 (81), 92 (19), 79 (90), 66 (83).

3-Phenyl-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridine (3c). The crude product from **7c** was purified by chromatotron with ethyl acetate/hexane (90.4 mg, 28%, yellow solid). Mp 100-102 ºC (hexane). HMRS (ES) found for (M^+ + 1) 198.1029; $C_{12}H_{11}N_3H$ requires 198.1031. ^{1}H NMR δ 7.75 (dd, J_1=7.14Hz, J_2=1.5Hz, 2H, H*o*), 7.45 (dd, J_1=J_2=7.14Hz, 2H, H*m*), 7.36 (dd, J_1=7.14Hz, J_2=1.5Hz, 1H, H*p*), 6.78 (ddd, J_1=9.99Hz, J_2=J_3=1.89Hz, 1H, H4), 6.19 (ddd, J_1=9.99Hz, J_2=J_3=4.35Hz, 1H, H5), 4.45 (t, J=7.74Hz, 2H, H7, H7'), 2.67 (m, 2H, H6, H6'). ^{13}C NMR δ 142.06 (C), 131.23 (C), 128.85 (2CH), 127.97 (CH), 127.58 (CH), 126.93 (2CH), 126.17 (C), 116.25 (CH), 44.09 (CH_2), 23.92 (CH_2).

General procedure for preparation of 4,5-dibromo-4,5,6,7-tetrahydrotriazolopyridines

To a solution of the corresponding 6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyridine **3b, c** in CCl_4 (10 ml) was added NBS (1 eq). The mixture was heated to reflux and irradiated with visible light (conditions showed in table 2). Formation of succinimide was observed, which floated on the surface of the CCl_4. The solution was cooled to room temperature and the succinimide was removed by filtration and washed with CCl_4. The combined filtrates were concentrated under reduced pressure giving a crude mixture. The products, yields and conditions of purification are given for each compound.

Table 2. Conditions for the reaction of 6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridine with NBS

6,7-Dihydro-[1,2,3]triazolo[1,5-a]pyridine (mg, mmol)	NBS (mg, mmol)	time
3b (112, 0.83)	(144, 0.83)	5 h
3c (90.4, 0.46)	(79.8, 0.46)	6 h

4,5-Dibromo-3-methyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine (12b). The crude product was purified by chromatotron with ethyl acetate/hexane (73.6 mg, 34%, yellow oil). HMRS found for M^+ 292.9162; $C_7H_9Br_2N_3$ requires 292.9163. ^1H NMR δ 5.54 (m, 1H, H4), 4.85 (m, 1H, H5), 4.73 (ddd, J_1=13.7Hz, J_2=6.2Hz, J_3=1.4Hz, 1H, H7), 4.57 (ddd, J_1=13.6Hz, J_2=12.2Hz, J_3=4.7Hz, 1H, H7), 2.99 (m, 1H, H6), 2.40 (m, 1H, H6), 2.30 (s, 3H, CH_3). ^{13}C NMR 142.68 (C), 127.61 (C), 46.29 (CH), 42.52 (CH_2), 39.18 (CH), 25.58 (CH_2), 10.28 (CH_3). MS (E.I.): m/z (%) 292 (3.5); 214 (63.8); 186 (23.5); 135 (100); 107 (88.4); 79 (31.5); 168 (70.2); 139 (58.6); 105 (71.7); 91 (12.4); 77 (99.2).

4,5-Dibromo-3-phenyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine (12c). The crude product was purified by chromatotron with ethyl acetate/hexane (43.4 mg, 27%, yellow solid). Mp 138-142 ºC (AcOEt/hexane). HMRS found for M^+ 354.9314; $C_{12}H_{11}Br_2N_3$ requires 354.9320. ^1H NMR δ 7.92 (dd, J_1=8.2Hz, J_2=1.5Hz, 2H, H1’, H5’), 7.50 (ddd, J_1=7.6, J_2=6.1Hz, J_3=1.4Hz, 2H, H2’, H4’), 7.41 (ddd, J_1=J_2=6.4Hz, J_3=1.3Hz, 1H, H3’), 5.79 (m, 1H, H4), 4.93 (m, 1H, H5), 4.87 (ddd, J_1=13.7Hz, J_2=6.6Hz, J_3=1.2Hz, 1H, H7), 4.69 (ddd, J_1=13.7Hz, J_2=12.4Hz, J_3=5.2Hz, 1H, H7), 3.20 (m, 1H, H6), 2.46 (m, J=14Hz, 1H, H6). ^{13}C NMR δ 145.28 (C), 137.45 (C), 130.58 (C), 129.36 (CH), 128.91 (CH), 127.45 (CH), 46.41 (CH), 43.29 (CH_2), 41.17 (CH), 25.70 (CH_2). MS (E.I.): m/z (%) 197 (9.5); 276 (3.3); 169 (100); 154 (17.0); 141 (20.4); 128 (9.2); 115 (27.2); 104 (11.8); 102 (4.9).

Acknowledgements

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