Triazolopyridines. Part 30.[1] Hydrogen transfer reactions; pyridylcarbene formation

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Dedicated to Professor Rosa Maria Claramunt on the occasion of her 65th birthday

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Abstract

The transfer hydrogenation reaction of [1,2,3]triazolo[1,5-*a*]pyridines with Pd/C/Zn or $Pd(OH)_2$/C/Zn in water, ethanol or water/ethanol mixture has been explored. 4,5,6,7-Tetrahydro-triazolopyridines were obtained in good to medium yields. In addition, under the same conditions 2-substituted pyridines were also formed as a result of intermediate pyridylcarbene formation, by triazole ring opening and loss of nitrogen.

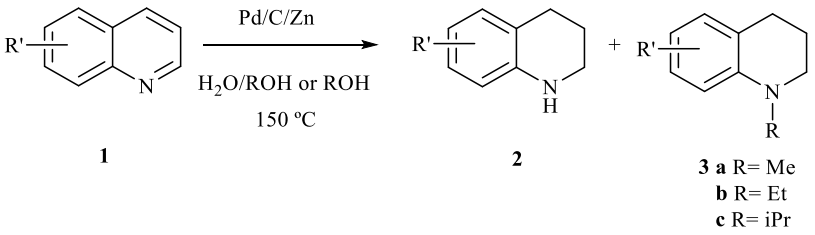
Keywords: Nitrogen heterocycles, triazolopyridines, hydrogen transfer reactions, carbenes

Introduction

Hydrogenation of organic molecules under homogeneous[2,3] or heterogeneous[4,5] catalysis is a process very widely used in industrial synthetic organic chemistry. However, despite its being a reaction of proven efficiency, it presents a significant drawback related with the handling of hydrogen gas (flammable and explosive). For this reason, the scientific community has been directing considerable research effort into catalytic transfer hydrogenation,[6-8] which favors use of hydrogen donors (alcohols, diimides, amines, hydrocarbons or formic acid) and avoids molecular hydrogen. Ruthenium,[9-11] rhodium,[12-15] iridium,[16-19] and nickel [20] are the metals most frequently used as catalysts. Organocatalytic transfer hydrogenation using dihydropyridines as hydride donors and Brönsted acid catalysis has also been intensively investigated.[21,22]

Sasson *et al*. reported in 2000 that Pd/C, Zn combination in water in presence of organic hydrogen acceptors (benzaldehyde, nitrobenzene or 4-nitroanisole) acts as a direct hydrogen transfer from water to an organic substrate, giving the reduction product.[23] However, this methodology had not been explored in any depth using other hydrogen donors and substrates.

Recently we reported the use of the Pd/C, Zn combination in hydrogenation of quinolines **1** (Scheme 1).[24] Various alcohols or mixtures of alcohol and water were employed as hydrogen donors and solvents to obtain 1,2,3,4-tetrahydroquinolines **2**. Furthermore, the Pd/C, Zn mixture was shown to be a good catalyst to activate alcohols as N-alkylating agents in a hydrogen autotransfer process yielding *N*-alkylated tetrahydroquinolines **3** from quinolines, under moderately vigorous conditions, in an one pot process.



Scheme 1

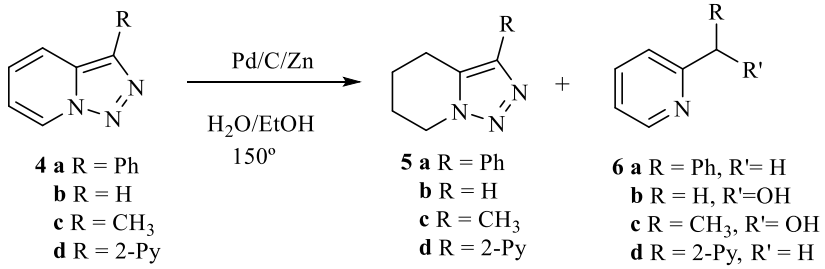
[1,2,3]Triazolo[1,5-*a*]pyridines **4** are simple fused heterocycles in which the triazole ring is in equilibrium with its open form, a diazo compound.[25-27] Hydrogenation of these heterocycles have been studied under standard conditions (H_2, Pd/C) to give rise to 4,5,6,7-tetrahydrotriazolo-pyridines **5** in high yield.[28] On another hand, the behaviour of triazolopyridines with metals such as palladium has been showed to produce, under certain conditions, the triazole ring opening reaction with subsequent loss of nitrogen.[1] We report here the chemistry of [1,2,3]triazolo-[1,5-*a*]pyridines with Pd/Zn mixtures in the presence of hydrogen donors. Both transfer hydrogenation reactions and pyridylcarbene formation were found.

Results and Discussion

We performed reactions under similar conditions to those previously used with quinolines,[24] with different triazolopyridines **4**, Zn powder, Pd/C catalyst and H_2O, H_2O/EtOH or EtOH, as solvents and as hydrogen donors, in an autoclave at 150 ºC over 24 hours (Scheme 2). When the reaction was performed with triazolopyridine **4a** (Table 1, entries 1-3), transfer hydrogenation took place and 3-phenyl-4,5,6,7-tetrahydrotriazolopyridine **5a** was obtained, in low yield. However, it was not the only reaction to take place, and an interesting 2-substituted pyridine **6a**, was also obtained, in variable yields depending on the solvent used.

With the aim of improving the yield of hydrogenated product, the reaction was carried out with $Pd(OH)_2/C$, Zn in H_2O/EtOH mixture, water, or ethanol (Table 1, entries 4-6). We were pleased to find that the reaction of triazolopyridine **4a** proceeded in high yield to provide the hydrogenation product **5a** (85%) when H_2O/EtOH was used (Table 1, entry 4). In this reaction the 2-substituted pyridine **6a,** was also obtained, but in low yield.

Blank reactions using only Zn as catalyst were performed, and no reaction took place.



Scheme 2

Table 1. Reactions of triazolopyridines **4** with [Pd]/C/Zn

Entry	Substrate	Solvent	Catalyst [a]	Products, yield [b] (%)	
				5	**6**
1	**4a**	H_2O/ EtOH	Pd/C, Zn	**5a** (25)	**6a** (71)
2	**4a**	H_2O	Pd/C, Zn	**5a** (24)	**6a** (18) [c]
3	**4a**	EtOH	Pd/C, Zn	**5a** (9)	**6a** (70)
4	**4a**	H_2O/ EtOH	$Pd(OH)_2$/C,Zn	**5a** (85)	**6a** (13)
5	**4a**	H_2O	$Pd(OH)_2$/C,Zn	**5a** (14)	**6a** (16)
6	**4a**	EtOH	$Pd(OH)_2$/C,Zn	-	**6a** (34)
7	**4b**	H_2O/ EtOH	Pd/C, Zn	-	**6b** (82) [d]
8	**4c**	H_2O/ EtOH	Pd/C, Zn	**5c** (47)	**6c** (37)
9	**4d**	H_2O/ EtOH	Pd/C, Zn	**5d** (35)	**6d** (42)
10	**4b**	H_2O/ EtOH	$Pd(OH)_2$/C,Zn	**5b** (13) [d]	-
11	**4c**	H_2O/ EtOH	$Pd(OH)_2$/C,Zn	**5c** (70)	-
12	**4d**	H_2O/ EtOH	$Pd(OH)_2$/C,Zn	**5d** (traces)	**6d** (44)
13	**4b**	H_2O	$Pd(OH)_2$/C,Zn	**5b** (30) [d]	-
14	**4c**	H_2O	$Pd(OH)_2$/C,Zn	**5c** (23)	-
15	**4b**	EtOH	Pd/C, Zn	-	-
16	**4c**	EtOH	Pd/C, Zn	**5c** (traces)	-
17	**4d**	EtOH	Pd/C, Zn	**5d** (traces)	**6d** (72)

[a] Standard conditions: Triazolopyridine 100mg, Zn 1.5 eq, 10% Pd/C (7 mol%) or 5% $Pd(OH)_2$/C, 150 ºC, 6 ml total reaction volume of appropriate solvent (in case of mixtures 3 ml EtOH/ 3 ml H_2O); [b] isolated yield; [c] phenyl (pyridin-2-yl) methanone was also obtained in 5% yield; [d] 1,2-di-(2-pyridyl)ethane was also obtained in 6% (entry 7), 8% (entry 10) and 9% yields (entry 13).

To investigate the scope of the transfer hydrogenation reaction, we studied the behaviour of triazolopyridines **4b-d**, (entries 7-12).

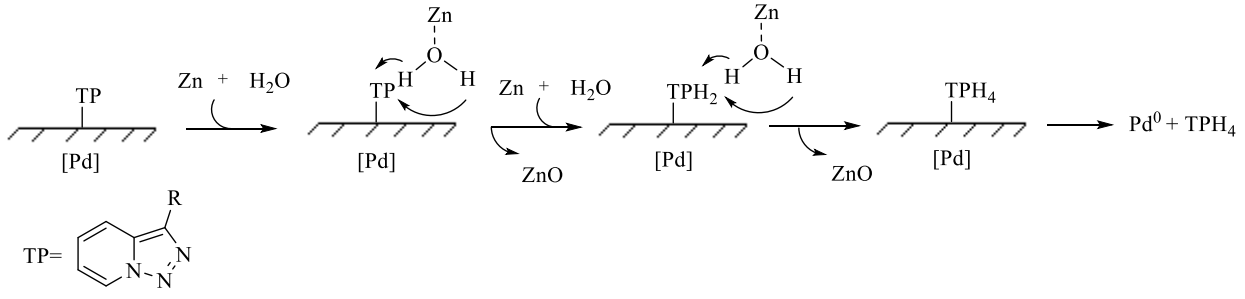
With triazolopyridine **4b** and Pd/C, Zn, only compound **6b** was obtained in good yield (82%, entry 7), but with $Pd(OH)_2/C$, Zn only the hydrogenated product **5b** was formed, in low yield (entry 10). With both palladium catalysts, traces of a secondary product, 1,2-di-(2-pyridyl)ethane, were detected. Also the reaction with $Pd(OH)_2/C$, Zn in H_2O was performed and the hydrogenated product **5b** was obtained in moderate yield (30%, entry 13).

In the case of triazolopyridine **4c**, with Pd/C, Zn as catalyst a mixture of **5c** (47%) and **6c** (37%) was obtained (entry 8). When the catalyst was $Pd(OH)_2/C$, Zn, the hydrogenated product **5c** was the only product, with high yield, when the hydrogen donor was a mixture of H_2O/ EtOH (70%, entry 11), and in moderate yield with H_2O (23%, entry 14).

With regard to triazolopyridine **4d**, with Pd/C, Zn mixture, the tetrahydrotriazolopyridine **5d** and the 2-substituted pyridine **6d** were obtained in moderate yields (35%, and 42% respectively, entry 9). Reaction of **4d** with $Pd(OH)_2/C$, Zn afforded **6d** in moderate yield 44% (entry 12). A good yield of **6d** (72%) was found when EtOH was used as solvent (entry 17).

It is important to point out that when EtOH was used as hydrogen donor and Pd/C, Zn as catalyst, the reaction proceeded to form only very low yields of hydrogenated compounds **5** (entries 3, 16 and 17) or none at all (entry 15). Nevertheless, under these conditions the triazolopyridines **4a** and **4d**, with an aromatic group at the C3 position, gave 2-substituted pyridines **6a** and **6d** in high yields (entries 3 and 17).

Hydrogen transfer reaction to triazolopyridines to form compounds **5** can be explained by a mechanism in which water acts as a hydrogen donor in the presence of ethanol as co-solvent and the metal mixture (Scheme 3). In this process water would be activated by the Zn to transfer hydrogen to the adsorbed triazolopyridine, generating ZnO, as Sasson *et al*. proposed.[23] When Pd^{II} is used as catalyst, it could be reduced to Pd^0 under the reaction conditions.



Scheme 3

However the formation of compounds **6** should be explained by another mechanism. The formation of a carbene as intermediate (or a Pd-carbenoid) by loss of nitrogen must be the key of this behaviour. There are examples in the literature of reactions of [1,2,3]triazolo[1,5-*a*]pyridines involving nitrogen extrusion with formation of a carbene intermediate. The first reports of the

formation of this type of reactive intermediates are from Wentrup, describing gas-phase pyrolysis reactions of triazolopyridines.[29] Also, when mass spectrometry studies of triazolopyridines have been made, loss of nitrogen is the principal fragmentation mode.[25,26] More recently, Gevorgyan *et al.* have obtained indolizines and imidazopyridines by reaction of 7-chloro-3-ethoxycarbonyltriazolo-pyridines with alkynes and nitriles *via* a carbenoid species generated by Rh(II) catalysis.[30] Furthermore, we have described the thermal decomposition (100 ºC, 1.7 atm, 5 days) of the 7-bromo-3-methyltriazolopyridine in dry acetonitrile, with formation of several products derived from a carbene intermediate.[31] In the cited references,[30,31] the substrates in general requires halogen substitution at C7 position. In the current work substrates lacking halogen substituents work nicely to generate carbene species.

Whether triazolopyridines react by thermal decomposition or by metal activation to afford the pyridylcarbene is an important point. To clarify this we considered it interesting to study the thermal stability of our compounds in the solid state and in ethanol solution.

Differential Scanning Calorimetry (DSC) and Thermogravimetry (TG) experiments of all triazolopyridines **4** were performed. In Figure 1 we can see DSC and TG of triazolopyridines **4a** and **4b**. In both DSC, the melting point appears as an exothermic band at the expected temperature. Also is observed that decomposition occurs between 200-300 ºC for triazolo-pyridine **4a**, while in the case of triazolopyridine **4b** we detect decomposition between 100 and 200 ºC. The same conclusions can be reached from the TG experiments. When these were performed with triazolopyridine **4c**, the data obtained were analogous to those of **4b**, and the case of triazolopyridine **4d** was very similar to that of triazolopyridine **4a**. Triazolopyridines with aromatic substitution in C3 seem to be more stable against thermolysis.

We now heated triazolopyridines **4a-d** with ethanol at 150 ºC for 24 hours in a sealed tube. Under these conditions no reaction was observed. However, when we heated them in a water/ethanol mixture, the triazolopyridine **4b** afforded 2-pyridylmethanol (67%).[32] The other triazolopyridines gave no reaction.

These results show the thermal stability of compounds **4** in the conditions of solvents and temperatures studied, and the necessity of metal catalysis to obtain compounds **6**.

In Scheme 4 we represent the proposed mechanism for the formation of 2-substituted pyridines **6** in which a carbene is formed, by loss of dinitrogen.

It is also remarkable the difference in the reactivity of the carbene intermediate depending on the C3 substitution. With triazolopyridines with non aromatic substitution, pyridine alcohols **6b,c** are formed, while with the aromatic-substituted substrates the pyridines **6a,d** are obtained. This difference can be explained by the formation of a singlet carbene in the case of triazolopyridines **4b,c**, that reacts with water[33] to afford an ylide, that generates the corresponding alcohol **6b** or **6c**. However, C3 aromatic-substituted triazolopyridines may generate a triplet carbene, stabilised by the aromatic groups, that reacts as a diradical giving place to hydrogen abstraction[34] to afford compounds **6a** or **6d**.

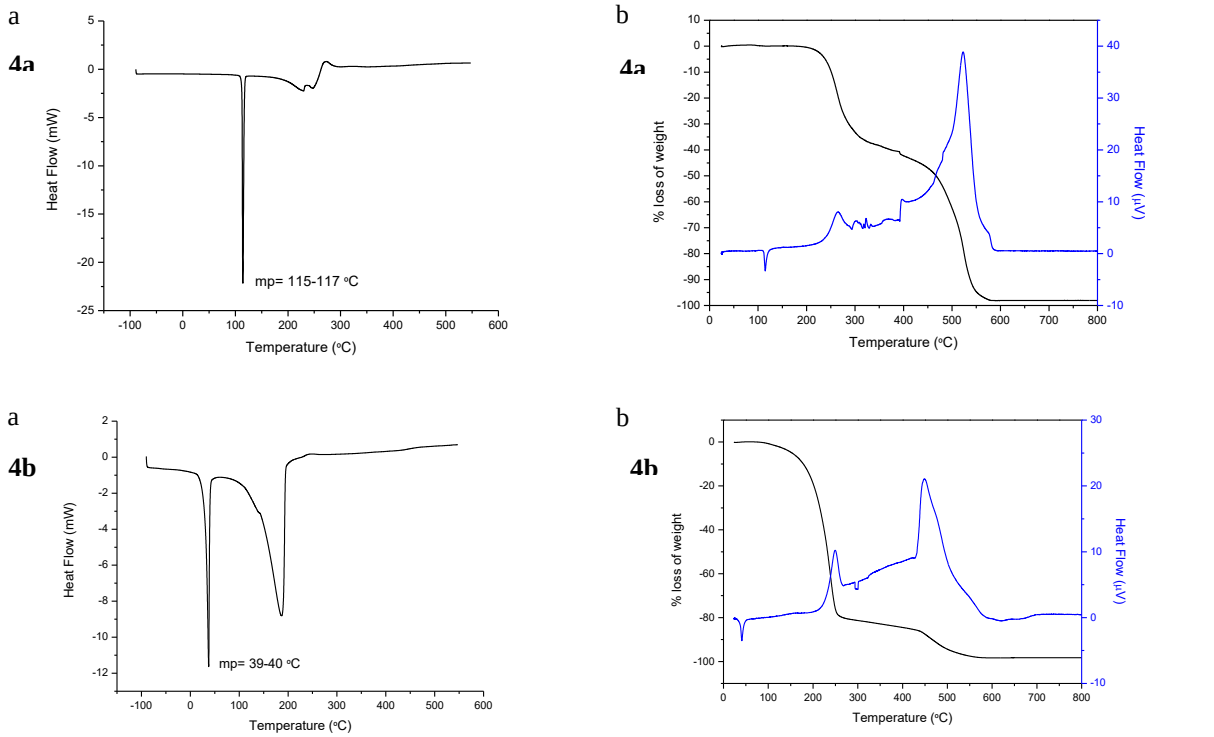
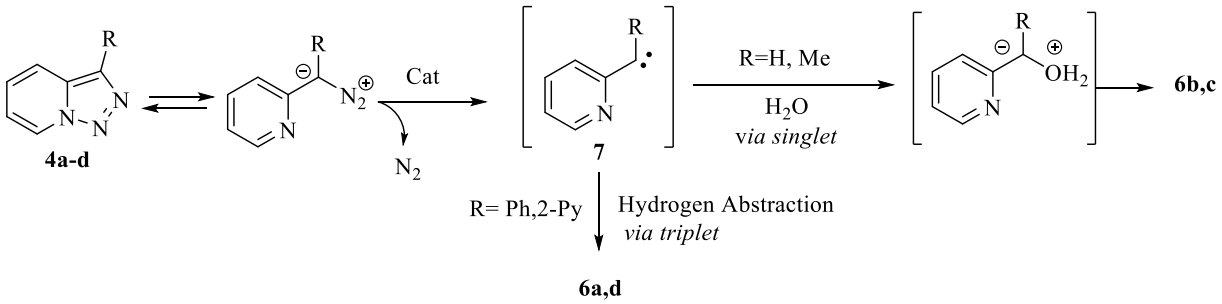


Figure 1. (a) Differential scanning calorimetry (DSC). (b) Thermogravimetry curves (TG) and associated derivative thermogram (DGT) of triazolopyridines **4a** and **4b**.

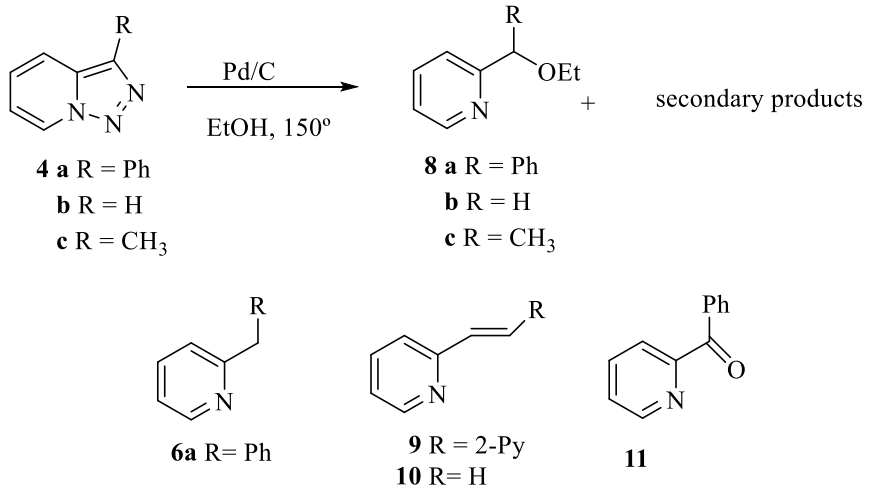


Scheme 4

In the case of triazolopyridine **4b** we also obtained in very low yields 1,2-di-(2-pyridyl)ethane. The formation of this product can be justified by the dimerization of the carbene **7b** [35] to afford 1,2-di-(2-pyridyl)ethene, which can suffer hydrogenation by hydrogen transfer process.

All the results pointed to an important role of the palladium catalyst in the formation of 2-substituted pyridine products, therefore we decided to study reactions of triazolopyridines **4a-c** in EtOH and EtOH/H_2O with only Pd/C or $Pd(OH)_2$/C (Scheme 5, Table 2). When we tested reactions in EtOH we detected the ethers **8a-c** in low yields (Table 2, entries 1-5), as well as

products **6a** (from **4a**), **9** (from **4b**), and **10** (from **4c**). However, when H_2O/EtOH was used, ethers **8** were not formed, and, in the case of triazolopyridine **4a**, ketone **11** was also obtained (Table 2, entry 6).



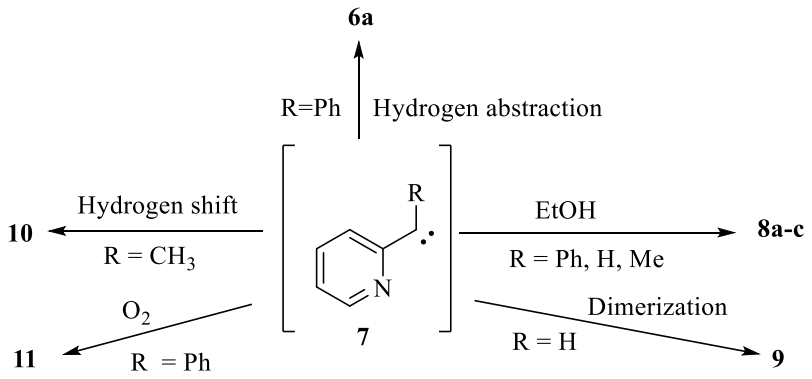
Scheme 5

Table 2. Reactions of triazolopyridines **4a-c** with [Pd]

Entry	Substrate	Solvent	Catalyst [a]	Products (Yield %)[b]
1	**4a**	EtOH	Pd/C	**8a** (7), **6a** (20), **11** (10)
2	**4b**	EtOH	Pd/C	**8b** (7), **9** (7)
3	**4c**	EtOH	Pd/C	**8c**[c] (traces), **10** (23)
4	**4a**	EtOH	$Pd(OH)_2$/C	**8a** (6), **6a** (24)
5	**4b**	EtOH	$Pd(OH)_2$/C	**8b** (7), **9** (8)
6	**4a**	H_2O/ EtOH	Pd/C	**6a** (49),**11** (14)
7	**4b**	H_2O/ EtOH	Pd/C	**9** [c] (traces)
8	**4a**	H_2O/ EtOH	$Pd(OH)_2$/C	**8a**[c] (traces), **6a** (18)
9	**4b**	H_2O/ EtOH	$Pd(OH)_2$/C	**9** (24)

[a] Standard conditions: Triazolopyridine 100mg, Pd/C (7 mol%) or 5% $Pd(OH)_2$/C (7 mol%), 150 ºC, 6 ml total reaction volume of appropriate solvent (in case of mixtures 3 ml EtOH/ 3 ml H_2O), 24 hours; [b] Isolated yield; [c] detected by ^{1}H NMR.

These results can be explained also by the formation of a carbene by loss of nitrogen. In the absence of Zn, ethanol can act as a nucleophile and react with the carbene to generate ethers **8a-c** in low yields. Product **9** can be explained by dimerization,[35] and 2-vinylpyridine **10** by a concerted shift of one hydrogen of the methyl group.[31] For formation of product **11** we postulate that carbene reacts with atmospheric oxygen[36] (Scheme 6).



Scheme 6

Conclusions

In conclusion, we have performed hydrogenation of [1,2,3]triazolo[1,5-*a*]pyridines **4a-d** through a green approach, as it is hydrogen transfer reaction. We have demonstrated that the combination of [Pd]/Zn as catalyst is necessary to produce hydrogen transfer from a mixture of EtOH/H_2O. The best results were obtained with the triazolopyridines **4a** and **4c**, giving good yields of hydrogenated products **5**. Alongside these reactions, the formation of 2-substituted pyridines, derived from carbene formation through nitrogen loss from the triazole ring, occurred. The effects of temperature and catalyst were explored, concluding that [Pd] catalyst has an important role in carbene formation. We are currently working in the applications of this type of reaction.

Experimental Section

General. Melting points were determined on a Kofler heated stage apparatus. NMR spectra were recorded on a Bruker AC 300 MHz in $CDCl_3$ as solvent. HRMS Electron Impact (EI) Quadrupole time of flight (QqTOF) 5600 system (Applied Biosystems-MDS Sciex). Mode positive. Conditions: Gas1 35 psi, GS2: 35, CUR: 25, temperature: 450 ºC, ion spray voltage: 5500 V Collision energy (CE): 25-35 V. IR spectra were recorded using a Thermoscientific Nicolet FT IR iS10 ATR. Differential scanning calorimeter Thermo Q20. Thermobalance Setaram Setsys 16/18. Simultaneous TGA-ATD. All reagents used were from a commercial source (Aldrich). [1,2,3]Triazolo[1,5-*a*]pyridine **4b**,[37] 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **4c**,[37] 3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridine **4a**,[38] and 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine **4d**,[39] were prepared as described elsewhere.

General procedure. To a solution of the corresponding triazolopyridine **4a-d** (100 mg) in ethanol (1.5mL) and distilled water (1.5mL), Pd/C (7 mol%) or $Pd(OH)_2$/C (7mol%) and Zn

(10%) were added. The mixture was charged in an autoclave and was maintained at 150 ºC during 24 hours. After cooling to room temperature the reaction mixture was filtered and the solid washed with dichloromethane. The filtrates were mixed, dried, and evaporated giving a crude material which was purified by chromatotron, eluting firstly with hexane and then with mixtures of ethyl acetate/ hexane of increasing polarity. By this procedure the following compounds described in the literature were prepared: 4,5,6,7-Tetrahydro-[1.2,3]triazolo[1,5-*a*]pyridine **5b**,[28] 3-methyl-4,5,6,7-tetrahydro[1.2,3]triazolo[1,5-*a*]pyridine **5c**,[28] 3-(2-pyridyl)-4,5,6,7-tetrahydro-[l,2,3]triazolo[l,5-*a*]pyridine **5d**,[28] 2-benzylpyridine **6a**,[40] pyridin-2-ylmethanol **6b**,[40] 1-(pyridin-2-yl)ethanol **6c**,[40] di-(pyridin-2-yl)methane **6d**,[41] (*E*)-1,2-di(pyridin-2-yl)ethane,[42] (*E*)-1,2-di(pyridin-2-yl)ethene **9**,[43] 2-vinylpyridine **10**,[40] 2-benzoylpyridine **11**.[40]

3-Phenyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine (**5a**). Oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.57 (m, 2H), 7.46-7.27 (m, 2H), 7.26-7.10 (m, 1H), 4.31 (t, J = 6.1 Hz, 2H), 2.92 (t, J = 6.1 Hz, 2H), 2.10-1.92 (m, 2H), 1.91-1.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.55 (C), 131.86 (C), 130.01 (C), 128.77 (2CH), 127.44 (CH), 126.29 (2CH), 46.54 (CH_2), 22.45 (CH_2), 21.96 (CH_2), 20.36 (CH_2). HRMS found 199.1106, $C_{12}H_{13}N_3$ requires 199.1109.

2-[(Ethoxy)(phenyl)methyl]pyridine (**8a**). Oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (ddd, J_1 = 4.9 Hz, J_2 = 1.8 Hz, J_3 = 0.9 Hz, 1H), 7.59 (ddd, J_1 = J_2 = 7.7 Hz, J_3 = 1.8 Hz 1H), 7.45 (ddd, J_1 = 7.9 Hz, J_2 = J_3 = 0.9 Hz 1H), 7.39-7.31 (m, 2H), 7.29-7,11 (m, 3H), 7.06 (ddd, J_1 = 7.4 Hz, J_2 = 4.9 Hz, J_3 = 1.2 Hz, 1H), 5.42 (s, 1H), 3.58-3.40 (m, 2H), 1.21 (dd, J_1 = 8.2, J_2 = 5.9 Hz, 3H). ^{13}C NMR (75 M Hz, $CDCl_3$) δ 162.20 (C), 149.11 (CH), 141.49 (C), 136.94 (CH), 128.56 (CH), 127.70 (CH), 127.03 (CH), 122.42 (CH), 120.72 (CH), 84.83 (CH), 64.91 (CH_2), 15.49 (CH_3). HRMS found for [M^++1] 214.1218, $C_{14}H_{16}NO$ requires 214.1226.

2-(Ethoxymethyl)pyridine (**8b**).[44] Oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (ddd, J_1 = 4.9 Hz, J_2 = 1.8 Hz, J_3 = 0.9 Hz, 1H), 7.66 (ddd, J_1 = J_2 = 7.7 Hz, J_3 = 1.8 Hz 1H), 7.30 (d, J = 7.7 Hz, 1H) 7.19 (ddd, J_1 = 7.9 Hz, J_2 = 4.9 Hz, J_3 = 0.9 Hz 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.85 (s, 1H), 1.26 (t, J_1 = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 162.10 (C), 149.89 (CH), 137.03 (CH), 124.25 (CH), 122.47 (CH), 61.44 (CH_2), 44.40 (CH_2), 14.57 (CH_3).

2-(1-Ethoxyethyl)pyridine (**8c**).[45] Oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (ddd, J_1 = 4.9 Hz, J_2 = 1.8 Hz, J_3 = 0.9 Hz, 1H), 7.65 (ddd, J_1 = J_2 = 7.7 Hz, J_3 = 1.8 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H) 7.17 (ddd, J_1 = 7.9 Hz, J_2 = 4.9 Hz, J_3 = 0.9 Hz, 1H), 4.19-4.11 (m, 2H), 3.93 (q, J = 7.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H), 1.20 (t, J_1 = 7.1 Hz, 3H).

(*E*)-1,2-Di(pyridin-2-yl)ethene (**9**).[43] **O**il, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (ddd, J_1 = 4.8 Hz, J_2 = 1.8 Hz, J_3 = 0.9 Hz, 2H), 7.70 (s, 2H), 7.69 (ddd, J_1 = J_2 = 7.9 Hz, J_3 = 0.9 Hz 2H), 7.43 (ddd, J_1 = 7.9 Hz, J_2 = 1 Hz, J_3 = 0.9 Hz 2H), 7.21-7.17 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.43 (CH), 150.18 (C), 137.17 (CH), 132.44 (CH), 123.75 (CH), 123.06 (CH). HRMS found for [M^++1] 183.0918, $C_{12}H_{11}N_2$ requires 183.0917.

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