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Tetrahedron Letters 47 (2006) 2337–2340
Tetrahedron Letters

A cascade process toward the synthesis of fused polycyclic dihydropyridines

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Received 16 January 2006; revised 27 January 2006; accepted 1 February 2006
Available online 20 February 2006

Abstract—The synthesis of fused polycyclic dihydropyridines was achieved using a cascade process comprising a Suzuki coupling, a nucleophilic cyclization and a hydrogen migration. Several functional groups are tolerated in this reaction and the methodology could be applied with success to quinoline and isoquinoline derivatives.

Pyridine containing polycyclic heterocycles represent a large class of compounds having applications in several fields comprising asymmetric catalysis,[1] material science[2,3] and biology.[4,5] In this context, the development of cascade reactions leading to nitrogen containing polycyclic heterocycles represents a major challenge in organic synthesis.[6]

Recently, we disclosed a three-step synthesis of ferroceno-(iso)quinolines based on a Negishi coupling and an aldolization–crotonization reaction promoted by *t*-BuOK (Fig. 1).[7]

In order to minimize the step number in this efficient synthesis, we wondered if the basic conditions of the Suzuki coupling[8] could allow the reaction to proceed in a one-pot process, the base present in the media playing the role of *t*-BuOK and generating the central ring. This improved procedure could also be applied to access in a simple way to benzo-(iso)quinolines and our first attempt was carried out with 2-bromo-3-methylpyridine **1** and 2-formylphenylboronic acid **2**. Surprisingly, by using the standard basic conditions for the Suzuki coupling, no benzo[*h*]quinoline was formed but instead the pyrido[2,1-*a*]isoindolone **3** was produced in 43% yield (Scheme 1).

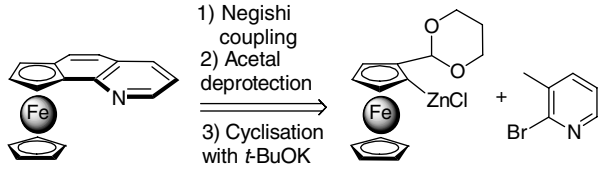
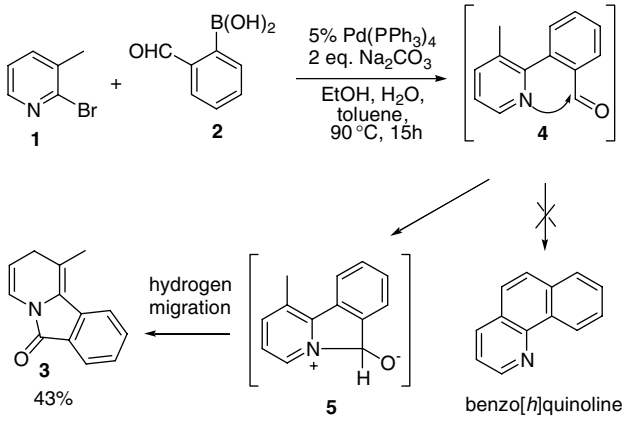


Figure 1. Three-step synthesis of ferroceno[*h*]quinoline.

Presumably, the cross-coupling product **4** generated during the reaction undergoes an internal nucleophilic attack of the aldehyde by the pyridine nitrogen followed



Scheme 1. Isoindolo[2,1-*a*]quinoline formation under Suzuki conditions.

Keywords: Cascade reaction; Polycyclic compounds; Dihydropyridines; Suzuki coupling.
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doi:10.1016/j.tetlet.2006.02.010

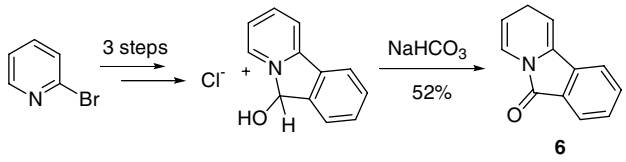


Figure 2. Precedent work by Igeta and co-workers.

by a hydrogen migration to form the dihydropyridine core and the amide. We though that intermediate **5** was probably involved in this reaction since Igeta and co-workers showed that a similar compound obtained in a multistep process as an hydrochloride salt led under basic conditions to the pyrido[2,1-*a*]isoindolone **6** (Fig. 2).[9]

The synthesis of such polycyclic systems is not well documented in the literature. The most representative examples have been described using Heck reaction,[10] anionic cyclization,[11] radical cascade[12] and through *N*-acyl iminium intermediate.[13]

Since Igeta's contribution this reaction did not receive attention probably due to the long synthesis sequence and the instability of intermediates as **4**. In the present letter, both problems are resolved by performing the reaction in one pot from readily available starting materials.

In order to improve the yield of this reaction, we performed several experiments by changing either the solvent or the nature of the base (Table 1).

With Na_2CO_3 as a base, it turned out rapidly that toluene was a good solvent for this reaction while DME inhibited the cascade process (entries 1 and 2). Using anhydrous conditions with CsF or K_3PO_4 as the base was detrimental for the reaction independently of the solvent (entries 3–6). However, by using aqueous solutions of both bases in toluene led to the product formation albeit in low yields (entries 7 and 8). These results showed the importance of water in this reaction. Since the formation of **6** was described to proceed in the presence of a base (Fig. 2), we decided to vary the amount of Na_2CO_3 in the reaction. Curiously increasing the number of equivalents of Na_2CO_3 led to lower yields (entries 9 and 10).[14] In contrast, the best yield was obtained by using a stoichiometric amount of Na_2CO_3 (entry 12). As expected, the yield dropped by using only 0.5 equiv of base (entry 13). Entry 14 showed that 1 equiv of Na_2CO_3 could be replaced by 2 equiv of the weaker base $NaHCO_3$. Note that an excess of $NaHCO_3$ conducted to a slight decrease of the yield (entry 15).

Table 1. Optimization of the reaction conditions for the formation of **3**[a]

Entry	Solvent	Base[b] (*n* equiv)	Yield[c] (%)
1	Toluene	Na_2CO_3 (2)	43
2	DME	Na_2CO_3 (2)	0
3	Toluene	CsF (2)	0
4	DME	CsF (2)	0
5	Toluene	K_3PO_4 (1)	0
6	DME	K_3PO_4 (1)	0
7	Toluene	CsF (2)[d]	34
8	Toluene	K_3PO_4 (1)[d]	37
9	Toluene	Na_2CO_3 (3)	31
10	Toluene	Na_2CO_3 (4)	30
11	Toluene	Na_2CO_3 (1.5)	54
12	**Toluene**	**Na_2CO_3 (1)**	**65**
13	Toluene	Na_2CO_3 (0.5)	16
14	**Toluene**	**$NaHCO_3$ (2)**	**55**
15	Toluene	$NaHCO_3$ (3)	51

[a] All the reactions were performed at 90 °C using 0.5 mmol **1**, 0.525 mmol **2** (1 M in EtOH) and 5 mol % $Pd(PPh_3)_4$.
[b] Na_2CO_3 and $NaHCO_3$ were used as a 1 M solution in H_2O.
[c] Isolated yield after chromatography on silica gel.
[d] CsF and K_3PO_4 were used as a 1 M solution in H_2O.

The next step was to determine the scope of this reaction by introducing electron-donating (EDG = Me, SMe) or electron-withdrawing groups (EWG = CN, CF_3) on the pyridine ring and by using other heterocycles (quinoline, isoquinoline) (Table 2).[15]

From these studies, it appears that several substrates could be used in this reaction regardless of the electronic nature of the substituents, generating products with modest to good yields.

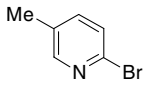
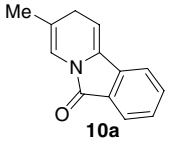
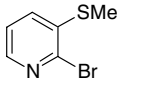
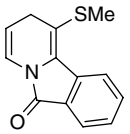
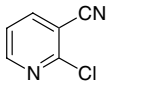
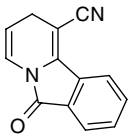
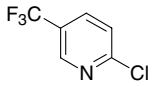
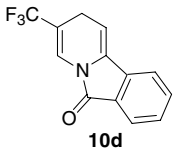
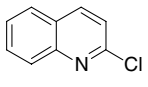
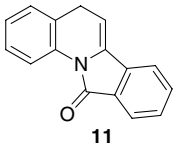
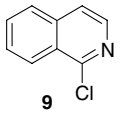
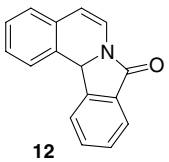
The base effect was difficult to rationalize. One main reason could be the partial or total hydrolysis of the substrate in presence of the base,[16] thus reducing the yield of the reaction. This hypothesis is emphasized in case of substrate **7c**. While no product was observed when Na_2CO_3 was used, a yield of 55% was obtained by employing the less basic $NaHCO_3$. A similar effect was observed with 1-chloroquinoline **9**.

The tetracyclic skeleton of compounds **11** and **12** is of interest[17–19] and several synthesis were described in the literature.[20–27] The method reported in this letter represents a fast and efficient entry to this class of compounds.

Since the reaction products were formed under palladium catalysis we wondered if a double bond hydrogenation could be performed in the same pot by introducing hydrogen. Compound **9** was then subjected to this one-pot process but no reduced product **13** was observed. However, an addition of a catalytic amount of Pd/C in the mixture at the end of the reaction followed by the introduction of a normal pressure of H_2 allowed the formation of **13** in high yield (Scheme 2).

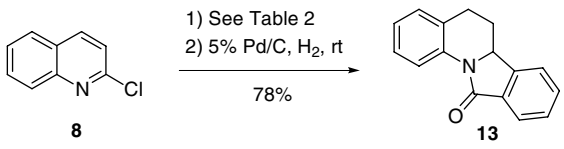
In conclusion, we have described a straightforward access to fused polycyclic dihydropyridines. Several functional groups are tolerated in this cascade reaction rendering it very attractive for the preparation of biologically active compounds. The base effect was shown to have an important outcome. Na_2CO_3 was the base of choice except for electron-poor heterocycles for which $NaHCO_3$ was the best system. A mechanistic study to explain the hydrogen migration as well as the synthesis of a natural product based on this new cascade reaction are underway.

Table 2. Scope of the reaction[a]

Substrate	Base (*n* equiv)	Product	Yield[b] (%)
 **7a**	Na_2CO_3 (1)	 **10a**	52
7a	$NaHCO_3$ (2)	**10a**	44
 **7b**	Na_2CO_3 (1)	 **10b**	40
 **7c**	Na_2CO_3 (1)	 **10c**	0
7c	$NaHCO_3$ (2)	**10c**	55
 **7d**	Na_2CO_3 (1)	 **10d**	79
 **8**	Na_2CO_3 (1)	 **11**	80
 **9**	Na_2CO_3 (1)	 **12**	19
9	$NaHCO_3$ (2)	**12**	69

[a] General conditions: substrate (0.5 mmol), **2** (0.525 mmol, 1 M in EtOH), 5 mol % $Pd(PPh_3)_4$, Na_2CO_3 or $NaHCO_3$ (1 M in H_2O), 90 °C.

[b] Isolated yield after chromatography on silica gel.



8 **13**

Scheme 2. One-pot synthesis of **13**.

Acknowledgements

We gratefully acknowledge the CNRS and the University of Nancy for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.010.

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13. Alsarabi, A.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2004**, *45*, 9003.
14. In order to analyze the base excess effect we have submitted compound **3** to the same reaction conditions (5% $Pd(PPh_3)_4$, ethanol, toluene, 90 °C, 15 h) in the presence of 1 equiv of Na_2CO_3 (1 M in H_2O). The ^1H NMR of the crude mixture showed the presence of the starting material as the major product along with a lot of degradation products. These degradation products were also observed in the crude mixture of entry 1, Table 1. This undesired material could provide from the isomerization of **3** to the other regioisomers and from the oxidation to the pyridinium species.
15. *General experimental procedure*: 2-Chloroquinoline **8** (0.5 mmol) was added to a degazed toluene solution (2 mL) containing $Pd(PPh_3)_4$ (0.025 mmol). To the mixture under N_2 were added successively a degazed solution of boronic acid **2** (0.525 mmol) in ethanol (1 mL) and a degazed solution of Na_2CO_3 (0.5 mmol) in water (0.5 mL). After heating for 15 h at 100 °C, the reaction mixture was cooled to room temperature, extracted with ethyl acetate and dried over $MgSO_4$. After concentration, the residue was purified by chromatography on silica gel (hexanes/ethyl acetate 4:1) to give compound **11** as a pale yellow powder (93 mg, 80%). Mp: 138–140 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.69 (d, $J = 4$ Hz, 2H), 5.92 (t, $J = 4.2$ Hz, 1H), 7.00–7.15 (m, 2H), 7.26 (dt, $J = 6.4$, 3.4, 1H), 7.35–7.65 (m, 3H), 7.83 (d, $J = 7.2$ Hz, 1H), 8.96 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7, 103.7, 117.6, 119.1, 121.9, 123.1, 124.5, 127.3, 128.8, 129.0, 129.9, 131.8, 133.2, 133.7, 134.9, 165.0. MS (EI) *m/z* 233 (M^+, 47%), 232 (100), 203 (13), 102 (22). Anal. Calcd for $C_{16}H_{11}NO$ (233.26): C, 82.38; H, 4.75; N, 6.00. Found: C, 81.87; H, 4.78; N, 5.97. For analytical data of all other compounds, see Supplementary data.
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