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Grignard reagent-promoted 6-*endo*-dig cyclization: instantaneous synthesis of original dipyrido[1,2-*a*:3′,4′-*d*]imidazole

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ABSTRACT

Dipyrido[1,2-*a*:3′,4′-*d*]imidazole derivatives can be readily synthetized from various 3-alkyne-2-cyanoimidazo[1,2-*a*]pyridines via an efficient Grignard reagent-promoted 6-*endo*-dig cyclization of nitrile to alkynes. A previous optimization of the Sonogashira coupling reaction at C(3) of the 2-cyanoimidazo[1,2-*a*]pyridine was necessary as this coupling reaction is known to be largely influenced by the nature of the 2-substituent.

1. Introduction

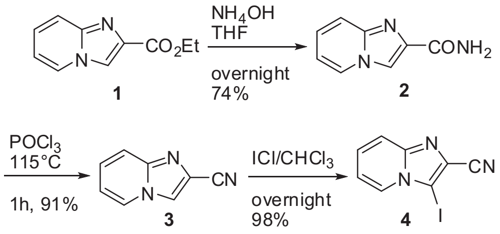
The significant and potential biological activities of compounds sharing the imidazo[1,2-*a*]pyridine moiety have been widely exploited in various pharmacological areas.[1] Consequently, there is a continued demand for the development of analogous heterocyclic systems as part of drug discovery programme.

To our knowledge, dipyrido[1,2-*a*:3′,4′-*d*]imidazole systems have rarely been reported and principally by Teulade group. Mainly three convenient syntheses are proposed for these β-azacarbolines. In 2005, Andaloussi et al. reported the first synthesis of β-azacarbolines by palladium-catalyzed iminoannulation from *tert*-butylimine of 3-haloimidazo[1,2-*a*]pyridine-2-carbaldehyde in the presence of alkynes (around 36% yield).[2] In 2006, Frolov described a photocyclization of 2-chloro-*N*-(pyridin-2-yl)pyridin-3-amine leading to 65% yield of 1-chlorodipyrido[1,2-*a*;3′,4′-*d*]imidazole.[3] More recently, Cartwright et al. reported the annealation reaction between pentafluoropyridine or various tetrafluoropyridine derivatives, and 2-aminopyridine.[4]

We report herein an efficient 6-*endo*-dig cyclization of nitrile to alkynes leading to new dipyrido[1,2-*a*:3′,4′-*d*]imidazole derivatives. To our knowledge, this 6-*endo*-dig cyclization type reaction was not previously described in the literature.

2. Results and discussion

The intramolecular cyclization was performed on the various alkynes **5**. These compounds were obtained in four steps starting from the ethyl imidazo[1,2-*a*]pyridine-2-carboxylate **1** (Scheme 1). Compounds **1**–**3** were prepared according to literature.[5,6] Compound **3** afforded 98% of the expected iodinated carbonitrile **4** using iodide monochloride in chloroform. The original iodinated compound **4** was then submitted to Sonogashira coupling reaction. However, we previously noticed that this cross-coupling procedure applied at C(3) of the imidazo[1,2-*a*]pyridine scaffold, is largely influenced by the nature of the 2-substituent. We then started a rapid optimization study in the case of the carbonitrile **4** to evaluate suitable reaction conditions for the phenylacetylene coupling (Table 1).



Scheme 1. Synthetic route to compound **4**.

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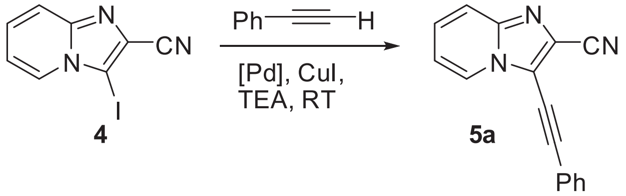
Table 1
Optimization studies on the Sonogashira cross-coupling reaction of **4** with phenylacetylene[a]



4

5a

Entry	[Pd] (mol %)	CuI (mol %)	Solvent	Time	Yield[b] (%)
1	$Pd_2(dba)_3$ (10)	20	DMF	15 h	77
2	$PdCl_2(PPh_3)_2$ (10)	20	DMF	15 h	65
3	$Pd_2(dba)_3$ (10)	20	Dioxane	15 h	65
4	$Pd_2(dba)_3$ (10)	20	Dioxane	5 min	65
5	$Pd_2(dba)_3$ (5)	10	Dioxane	5 min	62

[a] Reaction conditions: **4** (2 mmol), phenylacetylene (4.4 mmol), [Pd] (0.1 or 0.2 mmol), CuI (0.2 or 0.4 mmol), TEA (2 mL), DMF or dioxane (2 mL), rt.

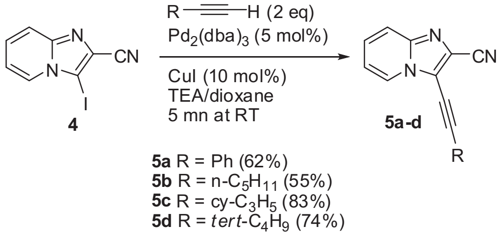
[b] Isolated yields.

From the literature, only few studies related examples of Sonogashira coupling reactions to the 3-halogenoimidazo[1,2-*a*]pyridines. In 2007, our group presented a general study on the convenient synthesis of alkenyl-, alkynyl- and allenyl-substituted imidazo[1,2-*a*]pyridines.[7] It appeared that the presence of an ester group in position 2 of the heterocyclic system reduced its reactivity towards the Sonogashira reaction. We then proposed the following coupling procedure in the case of the 2-ester compound: $Pd_2(dba)_3$ (10 mol %), CuI (10 mol %), TEA in DMF for 24 h at room temperature (64% yield). In 2007, the cross-coupling of phenylacetylene to the 3-bromo-2-esterimidazo[1,2-*a*]pyridine was performed by Hellal et al. using $PdCl_2(PPh_3)_2$ as catalyst (5 mol %) in the presence of CuI (4 mol %), TEA in acetonitrile under microwaves irradiation for 20 min at 120 °C (90% yield).[8] These drastic conditions confirm the poor reactivity of the 2-ester derivative. Only one example of 3-alkyne-2-cyanoimidazo[1,2-*a*]pyridine was reported in the literature. In this case, the nitrile was introduced after the alkyne group starting from a 2-bromo-3-iodoimidazo[1,2-*a*]pyridine derivatives.[9]

In a first approach, the Sonogashira coupling conditions applied to **4** was inspired from the protocol we previously determined in the case of the ethyl 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylate: $Pd_2(dba)_3$ (10 mol %), CuI (20 mol %), TEA (1 mL/mmol) overnight at room temperature in DMF (Table 1, entry 1). The yield of phenylacetylene coupling was slightly better in the case of the 2-carbonitrile **4** (77%) than starting from the 2-ester (64%). This can be explained by the amount of alkyne and copper iodide that was increased to 2.2 equiv and 20 mol %, respectively, in the present work (compared to 1.2 equiv and 10 mol % in the previous publication).

We also decided to evaluate $PdCl_2(PPh_3)_2$ as catalyst (entry 2). The coupling product was obtained with a slightly lowered yield (65%). We thus decided to hold $Pd_2(dba)_3$ as catalyst but to switch to dioxane as solvent in place of DMF, leading to **5a** in 65% yield (entry 3). Working on the reaction time, it appeared that the conversion in these conditions was completed in 5 min compared to the 15 h of the previous methods (entry 4). This represents an important advantage of this methodology. In a last attempt, we tried to lower the palladium catalyst and copper iodide amounts (entry 5) to 5 mol % and 10 mol %, respectively. The attempted **5a** was obtained in 62% yield.

We then exemplified the optimized coupling conditions to various alkynes (hept-1-yne, ethynylcyclopropane and 3,3-dimethylbut-1-yne) with moderate to good yields (55–83%) (Scheme 2).



Scheme 2. Sonogashira cross-coupling of **4** with various alkynes.

The direct anionic cyclization was then performed by treatment with Grignard reagents of the various 3-ethynylimidazo[1,2-*a*]pyridine-2-carbonitrile derivatives **5**. In a first attempt, the addition of the organomagnesium to **5** proceeded smoothly in diethylether (Table 2). After overnight stirring at room temperature, moderate yields of compounds **6**–**9** were obtained (10–45% yields) along with starting material. Two different heteroaromatic rings were expected from the 6-*endo*-dig cyclization or the 5-*exo*-dig ring closure. Actually, only the 6-*endo*-dig cyclization was detected. We then changed the solvent to cyclopropylmethylether (Table 3) and thus increasingly improved the cyclization yield from 45 to 80% for **9**. We also noticed that the conversion was completed after 5 min of stirring, that is, an interesting feature of the protocol. With the optimal conditions in hand, the scope of the cyclization was next explored. Various dipyridoimidazoles **9**–**15** were thus obtained in good yields (60–89%) (Table 3). This protocol allows the introduction of alkyl or aryl groups in both positions 1 and 3 of the tricyclic compounds. The nature of these groups does not influence the efficacy of the 6-*endo*-dig cyclization. Only compound **12** was obtained in a lower yield of 60% but this result was not optimized. The tricyclic structure of compound **14** was confirmed by X-ray crystallographic analysis[10] (Fig. 1).

In the case of compound **12**, we determined the presence of a by-product along with the attempted tricyclic compound. The structural determination of this by-product was based on the NMR spectroscopy and ascertained by X-ray crystallographic analysis.[10] The ^{13}C NMR spectrum presented a signal around 195 ppm attributed to a carbonyl function present in position 2 of the imidazo[1,2-*a*]pyridine. This 2-acetyl-3-(2-cyclopropylethyn-1-yl)imidazo[1,2-*a*]pyridine derivative **16** was formed from the organomagnesium attack of the carbonitrile, followed by the hydrolysis of the imine intermediate, thus preventing the cyclization step to occur.

In summary, an efficient approach has been developed to assemble dipyrido[1,2-*a*;3′4′-*d*]imidazole by employing a Grignard reagent-promoted 6-*endo*-dig cyclization of a nitrile to an alkyl group. The protocol features mild conditions and allows the functionalization of the positions 1 and 3 of the tricyclic compounds with alkyl or aryl groups with the same efficacy. The two steps of Sonogashira coupling reaction and heterocyclization present the advantage to be performed in a very short reaction time and in good yields.

3. Experimental section

3.1. General

^1H and ^{13}C NMR spectra were recorded on a 200 MHz, 300 MHz or 500 MHz spectrometer in $CDCl_3$. Mass spectra were determined on a Hewlett Packard 5988A spectrometer or on a Shimadzy QP 2010 spectrometer by direct inlet at 70 eV. All products were identified by ^1H and ^{13}C NMR, MS, and Element Analysis. The melting points were determined in a capillary apparatus and are uncorrected. Commercial reagents were used as received without additional purification.