



ORIGINAL ARTICLE

Nitrosylation of imidazo[1,2-*a*]pyridines in metal free system



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Near quantitative yields

Abstract An efficient nitrosylation of imidazo[1,2-*a*]pyridines has been developed using tert-Butyl nitrite (TBN) as the NO resource. The nitrosylation protocol demonstrates broad compatibilities, with various functional groups such as halogen, Me, OMe, COOMe et al. well tolerated. Near quantitative yields could be obtained within the imidazo[1,2-*a*]pyridine scaffold under the optimized conditions.

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1. Introduction

In recent years, C–H activation has emerged as a powerful strategy for the construction of various small molecules and pharmaceutical intermediates. However, the current protocol focused on the precious metal catalyst, including Pd, Rh, and Ir salts [1]. Alternatively, earth-abundant first-row transition-metal such as Fe, Co, and Ni served as potential replacements with the advancement of synthetic methodology and technology [2]. However, there is still a great need to develop environmentally

benign, operationally convenient and green protocol without the aid of metal catalysis [3]. Meanwhile, imidazo[1,2-*a*]pyridine derivatives have been extensively investigated owing to their pharmaceutical and biological applications [4–6]. Many commercialized drugs containing imidazo[1,2-*a*]pyridine skeleton [7,8], such as alpidem, saripidem and zolpidem et al., have been developed (Fig. 1) [9–15]. The biological activities of imidazo[1,2-*a*]pyridine are dependent on different substituents at its framework. In this context, our group has been interested in exploring new methodologies with regard to established imidazo[1,2-*a*]pyridine derivatives [16–18]. In 2015, we described a Rh(III)-catalyzed annulation of 2-arylimidazo[1,2-*a*]pyridines and alkynes via direct double C–H activation [16]. To avoid the use of catalytic amount of metal catalysis, catalyst-free Friedel–Crafts hydroxyalkylation [17] and alkylation [18] of imidazo[1,2-*a*]pyridine were also reported. Among the imidazo[1,2-*a*]pyridine derivants, 3-nitrosoimidazo[1,2-*a*]pyridine complexes have received wide attention for their

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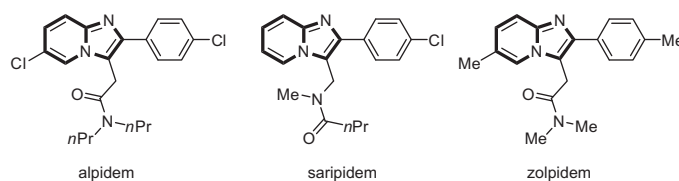


Figure 1 Imidazo[1,2-*a*]pyridine as the framework in drugs.

antiretroviral activities [19]. Although numerous literatures for the direct C3 nitrosylation of imidazo[1,2-*a*]pyridine frameworks have been reported [20–22], most of them adopted HNO₃ or HNO₂ as the NO source. In order to avoid the acidic and harsh conditions, the development of general and efficient methods for the nitrosylation of imidazo[1,2-*a*]pyridine is highly desirable. Herein, we reported a straightforward and general route for the synthesis of 3-nitrosoimidazo[1,2-*a*]pyridines.

2. Methods

2.1. Materials

2-Phenylimidazo[1,2-*a*]pyridines were prepared according to previous literature [23]. All other chemicals including Pd(OAc)₂, RhCl₃, and NiCl₂, as well as NO sources (AgNO₂, NaNO₂, and TBN) were used as purchased without purification unless otherwise stated. The solvent employed to the reaction was dried and freshly distilled before use.

2.2. Instrumentation

¹H and ¹³C NMR spectra were all recorded on a Bruker DPX 400 instrument using TMS as an internal standard. Data are reported as follows: chemical shift (δ ppm), multiplicity (*s* = single, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet), integration, and coupling constants in Hertz (Hz). Melting points were measured on a WC-1 instrument and were uncorrected. HRMS was determined on a Waters Q-ToF Micro MS/MS System ESI spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh).

2.3. General procedure for the synthesis of 3-nitroso-2-phenylimidazo[1,2-*a*]pyridine

In a 10 mL vial were added the requisite 2-arylimidazo[1,2-*a*]pyridine derivatives (1.0 eq.), TBN (2.0 eq.) and DCE (1 mL). The reaction vial was sealed and heated to 90 °C for 30 min. After cooling to room temperature, the product was isolated through silica gel chromatography using CH₂Cl₂ as an eluent to afford the desired product.

3. Results and discussion

Initially, we speculated that the nitrosylation of imidazo[1,2-*a*]pyridine at C3 position would require metal as the catalyst via C–H functionalization. Based on this hypothesis, several metal catalysts have been applied into the reaction. Pd(OAc)₂ was tested firstly owing to its outstanding catalytic activities in C–H activation. However, no target product was obtained under the setting reaction conditions (Table 1, entry 1). Subsequently, RhCl₃ and NiCl₂ were also introduced into

the nitrosylation reaction, respectively (Table 1, entry 2–3). However, there was still no desired product obtained. Using AgNO₂ as the NO source instead of NaNO₂ could achieve slightly better yield (Table 1, entry 4). In view of above unsatisfied results, we attempted to explore the reaction in the presence of other NO source. As the nitrosylation reagent, TBN has been reported in homogeneous catalytic system to successfully access oxindoles and quinoxaline N-oxides [24,25]. We were interested in investigating TBN initialized nitrosylation of imidazo[1,2-*a*]pyridine derivatives. To our delight, a moderate yield was achieved using a mixture of palladium salts and TBN (Table 1, entry 5). Unexpectedly, the yield could reach up to 99% yield in the absence of metal salts in 2 h (Table 1, entry 6). The excellent result could be still reproduced in 0.5 h (Table 1, entry 7), indicating that the reaction could proceed smoothly in the metal free system. With preliminary data in hand, a variety of solvents were screened. As can be

Table 1 Screening of the nitrosylation reaction conditions.

Entry ^a	Catalyst	NO source	Solvent	Temp. [°C]	Yield [%] ^b
1	Pd(OAc) ₂	NaNO ₂	DCE	90	–
2	RhCl ₃	NaNO ₂	DCE	90	–
3	NiCl ₂	NaNO ₂	DCE	90	–
4	Pd(OAc) ₂	AgNO ₂	DCE	90	28
5	Pd(OAc) ₂	TBN	DCE	90	86
6	–	TBN	DCE	90	99
7 ^c	–	TBN	DCE	90	99
8 ^c	–	TBN	CH ₃ CN	90	87
9 ^c	–	TBN	Acetone	90	79
10 ^c	–	TBN	DMF	90	87
11 ^c	–	TBN	THF	90	89
12 ^c	–	TBN	DME	90	55
13 ^c	–	TBN	Xylene	90	Trace
14 ^c	–	TBN	Ethanol	90	Trace
15 ^c	–	TBN	DCE	25	N.R.
16 ^c	–	TBN	DCE	70	51
17 ^c	–	TBN	DCE	110	99

^a Reaction conditions: **1a** (0.2 mmol), NO source (0.4 mmol), catalyst 10 mol%, solvent (1 mL), 2 h.

^b Isolated yield.

^c 30 min.

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