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A stereoselective organic base-catalyzed protocol for hydroamination of alkynes under solvent-free conditions

Vadym Kozell[a], Fariba Rahmani[a,b], Oriana Piermatti[a], Daniela Lanari[c,*], Luigi Vaccaro[a,*]

[a] Laboratory of Green Synthetic Organic Chemistry, Dipartimento di Chimica, Biologia e Biotecnologie, Università di Perugia Via Elce di Sotto, 8-06123, Perugia, Italy
[b] Department of Chemistry, Faculty of Science, Vali-e-Asr University of Rafsanjan, Rafsanjan, 77176, Iran
[c] Department of Pharmaceutical Sciences, Università di Perugia, Via del Liceo, 1-06123, Perugia, Italy

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ABSTRACT

The hydroamination of alkynes is a straightforward and atom-economical process for the synthesis of substituted nitrogen-containing alkenes. Herein we report a novel protocol that involves for the first time solvent-free conditions (SolFC) and the use of an organic base, namely 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) to stereoselectively promote the process. The scope of this metal-free protocol has been evaluated through an extensive study that has led to the conclusion that in most cases the yield and stereoselectivity values are very high (14 examples, up to 95% yield, Z/E up to 99%).

1. Introduction

The hydroamination of alkynes is an atom economical process for the preparation of enamines, valuable building blocks for the synthesis of pharmaceuticals, natural products, biomolecules, organometallics and semiconductors [1]. Despite the fact that this reaction is thermodynamically favored, it is generally reported that a catalyst is required in order to efficiently accomplish this transformation [2] (Scheme 1).

Accordingly, hydroamination reactions have been initially performed using transition metal catalysts such as rhodium, mercury, zirconium, ruthenium, titanium [3]. Later, Knochel et al. proposed an effective use of $CsOH{\cdot}H_2O$, as an inorganic basic catalyst for many transformations including the hydroamination reaction in which anilines and heterocyclic amines reacted with phenylacetylene to give the corresponding enamines in very good yields but not always with complete stereoselectivity [4]. Mao proposed inorganic bases as catalyst (i.e potassium phosphate) with good results [5]. Verma extensively studied this process and introduced the use of potassium hydroxide as a simpler and cheaper catalyst for the reaction of imidazole derivatives with alkynes allowing to efficiently access the corresponding imidazolyl enamines [6]. Dodd instead presented the use of sodium *tert*-butoxide as a catalyst for the functionalization of indoles with ynamides [7]. In addition, Trofimov proposed a protocol where potassium hydroxide could be efficiently used as a catalyst for the hydroamination of arylacetylenes with pyrroles allowing to prepare nitrogen-containing stilbene analogs [8]. To the best of our knowledge, only one contribution by Kondo, reported the use of a catalytic amount of an organic base (t-Bu-P4) to promote the alkynylation of nitrogen containing compounds but poor stereoselectivity was observed [9].

Generally, known hydroamination methods allow to access *E*:*Z* isomeric mixtures of enamines that cannot be easily purified to isolate pure single stereoisomers. The main reason for the formation of both *E* and *Z* isomers is related to the strength of the base, that is actually also responsible for the isomerization process that may occur. Another important parameter that influences the regioisomeric outcome is the reaction time [2a].

Our research is mainly devoted on the development of environmentally-friendly and waste-minimized procedures based on metal or organocatalyzed transformations. Preferred reaction conditions involved the use of recoverable catalysts in safer/greener reaction media or the adoption of solvent-free conditions (SolFC) [10]. As part of an on-going project aimed at the preparation of N-heterocyclic based pincer to be used as ligand for metal catalysis we have been searching for a new catalytic protocol to efficiently promote the key-step reaction, namely the hydroamination of alkynes.

2. Experimental

2.1. General information

Unless otherwise stated, all solvents and reagents were used as obtained from Sigma-Aldrich Co. without further purification. GC-EIMS analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 Mass Selective Detector equipped with an

* Corresponding authors.
E-mail address: luigi.vaccaro@unipg.it (L. Vaccaro).

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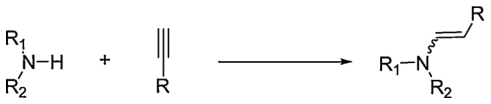


Scheme 1. Hydroamination of alkynes.

electron impact ionizer at 70 eV. NMR spectra were recorded on a Bruker DRX-ADVANCE 400 MHz (^{1}H at 400 MHz, ^{13}C at 100.6 MHz and ^{19}F at 376.4 MHz) in $CDCl_3$ using TMS as the internal standard. Elemental analyses were conducted on a Fisons EA1108CHN. Melting points are not corrected and they were measured on a Büchi 510.

2.2. General procedures

2.2.1. Hydroamination using homogeneous base (BEMP) in SolFC conditions.

In a screw-capped vial equipped with a magnetic stirrer, imidazole (**1a**) (102 mg, 1.5 mmol, 99% purity), phenylacetylene (**2a**) (0.112 µL, 1 mmol, 98% purity), BEMP (15 µL, 0.05 mmol, 98% purity) were consequently added and the resulting mixture was left under stirring at 150 °C. After 16 h the final mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to obtain (*Z*)-1-styryl-1H-imidazole (**3a**) as yellowish oil (126 mg, 74% yield).

2.2.2. Hydroamination under base-free and SolFC conditions.

In a screw-capped vial equipped with a magnetic stirrer, imidazole (**1a**) (102 mg, 1.5 mmol, 99% purity) and phenylacetylene (**2a**) (0.112 µL, 1 mmol, 98% purity) were consequently added and the resulting mixture was left under stirring at 150 °C. After 80 h the final mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to obtain (*Z*)-1-styryl-1*H*-imidazole (**3a**) as yellowish oil (150 mg, 88% yield).

2.2.3. Isomerization protocol of (Z)-1-styryl-1H-imidazole *3a*

In a screw-capped vial equipped with a magnetic stirrer (*Z*)-1-styryl-1H-imidazole (**3a**) (170 mg, 1 mmol), $CsOH{\cdot}H_2O$ (34 mg, 0.2 mmol) and 2 mL of NMP were consequently added and the resulting mixture was left under stirring at 120 °C. The isomerization ratio was analyzed by GC. After 220 h the final mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to obtain (*E*)-1-styryl-1*H*-imidazole (**3a**) as a white solid (80 mg, 47% yield).

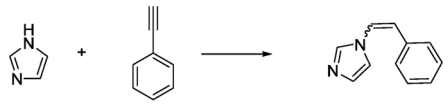
3. Results and discussion

While common hydroamination procedures relied on the catalysis of an inorganic base or a transition metal salt, herein we report the use of commercially available BEMP in SolFC to efficiently promote the reaction between several alkynes (**2a-2g**) with N-heterocycles (**1a-1e**). The representative hydroamination of imidazole (**1a**) and phenylacetylene (**2a**) was investigated and used as a model to optimize the reaction conditions (Table 1).

Initially, we tested the reaction under solvent-free conditions (SolFC) without any catalyst and we observed that hydroamination of **2a** proceeded with a 90% conversion at 150 °C after 80 h and with a remarkable 99% *Z*-stereoselectivity (Table 1, entry 2). According to literature, we attempted uncatalyzed processes in different reaction media (for instance NMP, 1.8 M or DMSO, 0.5 M) but in all the cases they resulted in no product (Table 1, entries 10 and 11). These preliminary results although not fully satisfactory, showed that SolFC had beneficial effect on the hydroamination outcome.

In order to optimize the process we investigated the effect of the base catalyst on the conversion, reaction time and stereoselectivity (Z/E ratio). We focused on BEMP and MTBD (7-methyl-1,5,7-triazabicyclo [4.4.0]dec-5-ene) that have previously promoted in a very effective way a large variety of organic transformations [11].

Table 1
Optimization of reaction conditions between imidazole (**1a**) and phenylacetylene (**2a**).[a]



1a **2a** **3a**

Entry	Medium	Catalyst	T (°C)	t (h)	C (%)[b]	*Z/E* ratio[b]
1	–	–	120	24	< 1	–
2	–	–	150	80	90	99/1
3	–	BEMP (5 mol%)	120	40	95	98/2
4	–	BEMP (5 mol%)	150	16	100	96/4
5	–	MTBD (5 mol%)	120	24	36	98/2
6	–	MTBD (5 mol%)	150	60	100	97/3
7	–	BEMP (20 mol%)	120	24	90	99/1
8	–	BEMP (20 mol%)	150	7	100	95/5
9	–	BEMP (50 mol%)	150	5	100	93/7
10	DMSO	–	150	24	–	–
11	NMP	–	150	24	–	–

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (if indicated), medium (if indicated) were consequently added in a 4 mL screw capped vial equipped with a magnetic stirrer. The resulting mixture was left under heating and stirring.

[b] Conversion and isomer ratio of **3a** were determined by GC analysis without purification.

We examined the influence of different amounts of base and temperatures on the formation of **3a**. We found out that when 5 mol% of BEMP were employed at 120 °C the process was very slow (Table 1, entry 3) but with excellent stereoselectivity, a good compromise has been reached by increasing the reaction temperature up to 150 °C using the same amount of BEMP, infact full conversion in a reasonable time (16 h) and with 96% *Z*-stereoselectivity was observed (Table 1, entry 4). The use of an higher amount of BEMP (20–50 mol%) instead led to worse results in terms of yield (Table 1, entry 7) and stereoselectivity (Table 1, entries 8–9). When 5 mol% of MTBD were used, complete conversion to **3a** was achieved only after 60 h with a stereoselectivity comparable with that observed with BEMP.

Since isomerization of hydroamination products may occur during prolonged reaction times, we investigated the isomerization reaction of (*Z*)-1-styryl-1*H*-imidazole (**3a**) under SolFC in the presence of BEMP and under different experimental conditions (the data obtained are reported in the Supporting Info). We compared the use of i) 20 mol% of $CsOH{\cdot}H_2O$ in NMP at 120 °C [3] ii) 20 mol% of KOH in DMSO [5] and iii) 5 mol% of BEMP under SolFC. The use of $CsOH{\cdot}H_2O$ in NMP slowly promoted the isomerization and a 1:1 mixture was obtained after 120 h. The use of KOH in DMSO led to a 1:1 mixture of *Z/E* isomers in 50 h, with an increasing formation of the *E* isomer by prolonging the reaction time. The isomerization rate was significantly lower when BEMP was employed as catalyst yielding only ca. 1.5% of the *E*-isomer after 48 h at 150 °C. These results confirmed that the use of BEMP under SolFC can significantly reduce isomerization of the final product in the reaction between phenylacetylene and imidazole, therefore its use is compatible with substrates that need long reaction time.

We extended then our protocol to different substrates and found out that when alkynes with electron with-drawing groups were used (Table 2, entries 2, 3 and 9), the reaction occurred efficiently without catalyst under SolFC conditions with very good conversion values and almost complete stereoselectivity in less than 24 h. All the other substrates reported in Table 2 yielded the desired products only when BEMP was used as catalyst. Unfortunately when pyrrole was used as substrate for the hydroamination reaction with activated and non-activated alkynes in the presence of BEMP under SolFC the desired products were not observed.