Metal-free approach for the L-proline mediated synthesis of nitrones from nitrosobenzene

Minho Choi [a, 1], Mayavan Viji [a, 1], Donghwan Kim [a], Young Hee Lee [a], Jaeuk Sim [a], Young-Shin Kwak [b], Kiho Lee [b], Heesoon Lee [a], Jae-Kyung Jung [a, *]

[a] College of Pharmacy and Medicinal Research Center (MRC), Chungbuk National University, Cheongju 28160, Republic of Korea
[b] College of Pharmacy, Korea University, Sejong 30019, Republic of Korea

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ABSTRACT

An efficient, and metal-free approach for the L-proline mediated synthesis of nitrones from nitrosobenzene and benzaldehydes has been established. The reaction undergoes very efficiently at room temperature in methanol as a solvent. The reaction is assumed to involve that the initial formation of azomethine ylide and [2 + 3] cycloaddition of nitrosobenzene, followed by the subsequent retro [2 + 3] cycloaddition could offer the desired nitrone.

1. Introduction

Nitrone, a 1,3-dipole also called azomethine oxide, is classified as a relatively stable species among the numerous 1,3-dipoles [1]. Synthesis of nitrones have received considerable interest due to their own biological and industrial properties. For example, nitrones are used as anti-oxidants in the rubber industry [2], free radical spin-traps [3], enzyme inhibitors [4], therapeutic agents [5], and etc. Nitrone is a valuable reaction intermediate as well, used to construct various natural products and heterocyclic compounds. [2 + 3] Cycloaddition reaction is one of the most predominant transformations of nitrone. Depending on alkyne or alkene dipolarophiles, it delivers either isoxazoles or isoxazolidines, respectively which are common structural motifs in many biologically important compounds (Fig. 1) [6].

For instance, the copper-mediated Kinugasa reaction of nitrone with alkynes proceeds with [2 + 3] cycloaddition followed by a rearrangement to produce β-lactam [7]. There are other types of cycloaddition reactions, such as [3 + 3] [8], [3 + 4] [9], [4 + 3] [10], [5 + 2] [11], and [2 + 2+3] [12] that were also reported for many 6-membered or larger heterocyclic compounds.

In general, conventional strategies to synthesize nitrones include: (i) oxidation of hydroxylamines by utilizing various oxidizing reagents such as MnO_2 [13g], H_2O_2 [13f], hyper valent iodine reagents [13c], rhodium nanoparticles [13a], microwave conditions [13b], and so on [13d,e,h,i]; (ii) oxidation of amines or imines [14]; (iii) the reaction between either aldehydes or ketone with hydroxyl amine [15], etc [1h,16]. Most of the reported methods suffer from some drawbacks associated with utilizing expensive metal catalyst [16d], or performing at higher [13e,15] or lower temperatures [16e].

Metal-free synthesis has become an appealing method in recent decades for environmental and cost concerns, but it is less explored in nitrone synthesis [14a,15,17]. For instance, recently a pyrrolidine-catalyzed method was reported that it delivered nitrones in high yields [17b]. But, utilizing pyrrolidine is particularly problematic for an environmental point of view because of its toxicity. L-Proline is a common and cost & environmentally friendly amino acid widely employed as a catalyst and a reagent in various organic transformations [18]. Herein, we report a direct synthesis of nitrone from nitrosobenzene and arylaldehydes by utilizing L-proline at room temperature (Scheme 1).
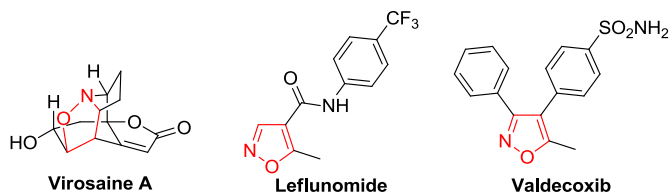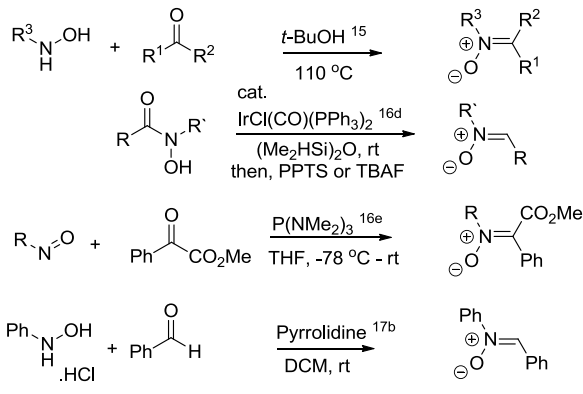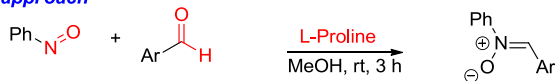

Fig. 1. Isoxazole and isoxazolidine containing natural products.

Previous methods

Our approach


Scheme 1. Representative synthesis of nitrones.

2. Results and discussion

At the outset of the research we discovered that when 4-chloro benzaldehyde (**1g**, 1.0 equiv), nitrosobenzene (**2a**, 1.0 equiv) and L-proline (1.0 equiv) were stirred at room temperature in methanol, the nitrone **3g** was formed and isolated in 37% yield (Table 1, entry 1). In order to improve the reaction yield, various parameters like temperature, equivalence of substrates and solvents were examined. Increasing the temperature up to 80 °C caused negative influence to yield. Higher loading of L-proline (3.0 equiv.) promoted the reaction and afforded **3g** in 67% yield (entry 3), however, further increase of the loading did not make a notable impact (entry 7). Varying equivalence of the substrates **1g** and **2a** revealed that the reaction yields were not affected and stayed between 50 and 70% (entries 5–7). When other amino acids were tested in place of L-proline, the reaction yield was negatively influenced (entries 8 and 9). Similarly, lower yield was obtained in the case of L-proline methyl ester, while it was decomposed in pyrrolidine as reagent (entries 10–11).

Next, we undertook an extensive study by examining variables in solvent, but no improvement was observed from the outcome with methanol. Isopropanol, toluene, and THF suppressed the reaction almost completely. Reaction in DMF or MeOH/H$_2$O ended up with poor yields (entries 12–17). Screening additives (up to 20 mol %) and open-to-air conditions delivered **3g** in moderate to good yields (about 30–65%, entries 18–20, 22–26). Interestingly, when we added formic acid as an additive, almost complete conversion occurred and azoxybenzene (**4a**) was isolated in nearly 92% (entry 21) [17b].

Further screening showed that without the addition of 4-chlorobenzaldehyde (**1g**), the reaction proceeded very smoothly and delivered azoxybenzene (Table 2). Complete conversion

Table 1
Optimization of reaction conditions.
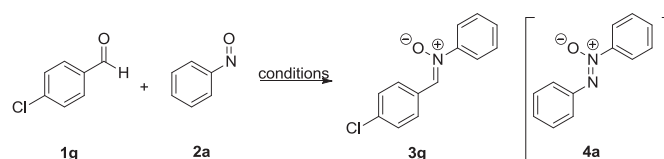
Entry	Reagent (equiv.)	Solvent	Additive	Yield[a](%)
1	L-proline[b]	MeOH	·	37
2[c]	L-proline[b]	MeOH	·	32
3	L-proline	MeOH	·	67
4	L-proline[d]	MeOH	·	62
5[e]	L-proline	MeOH	·	65
6[f]	L-proline	MeOH	·	58
7[g]	L-proline[h]	MeOH	·	48
8	L-alanine	MeOH	·	Trace
9	L-tryptophan	MeOH	·	35
10	L-proline methyl ester	MeOH	·	< 10
11	pyrrolidine	MeOH		decompose
12	L-proline	EtOH	·	18
13	L-proline	i-PrOH	·	Trace
14	L-proline	Toluene	·	Trace
15	L-proline	THF	·	Trace
16	L-proline	DMF	·	17
17	L-proline	MeOH/H$_2$O	·	18
18	L-proline	MeOH	pyrrolidine[i]	59
19	L-proline	MeOH	K$_2$CO$_3$[i]	44
20	L-proline	MeOH	AcOH[i]	31
21	L-proline	MeOH	HCOOH[i]	92 (**4a**)
22	L-proline	MeOH	Zn[i]	57
23	L-proline	MeOH	MgSO$_4$[j]	64
24	L-proline	MeOH	Na$_2$SO$_4$[j]	62
25	L-proline	MeOH	Open Air	38
26	L-proline	MeOH	4 Å MS[j]	63

Reaction conditions: **1g** (0.37 mmol), **2a** (0.37 mmol), and reagent (3.0 equiv.) in solvent (0.61 M) at room temperature for 3 h.
[a] Isolated yield of **3g**.
[b] 1.0 equiv. of L-proline was used.
[c] The reaction was performed at 80 °C.
[d] 5.0 equiv. of L-proline was used.
[e] 2.0 equiv. of **1g** was used.
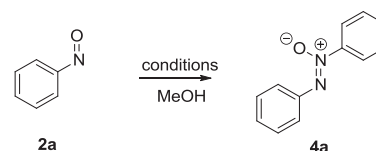[f] 2.0 equiv. of **2a** was used.
[g] 4.0 equiv. of **2a** was used.
[h] 12.0 equiv. of L-proline was used.
[i] 20 mol% additive was used.
[j] 1.0 equiv. of additive was used.

Table 2
Control experiments.3

Entry	L-proline (equiv.)	Temp (°C)	Yield[a] (%)
1	0.1	rt[c]	100[b]
2	0.5	rt	100[b]
3	1.0	rt	100[b]
4	3.0	rt	(92)[a]100[b]
5	3.0	0	NR
6	3.0	−20 or −78	NR
7	3.0	reflux	100[b]

Reaction conditions: **2a** (0.37 mmol), L-proline (as mentioned above.) in MeOH (0.61 M) stirred at room temperature for 3 h.
[a] Isolated yield.
[b] On the basis of TLC analysis.
[c] Reaction time one week.