CrossMark

# Synthesis of 5-alkyl-5-aryl-1-pyrroline N-oxides from 1-aryl-substituted nitroalkanes and acrolein via Michael addition and nitro reductive cyclization

Jingjing Xu [a], Xingyao Li [a], Jinlong Wu [a,*], Wei-Min Dai [a,b,*,†]

[a] Laboratory of Asymmetric Catalysis and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, China
[b] Laboratory of Advanced Catalysis and Synthesis, Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

## ARTICLE INFO

## ABSTRACT

A general method for accessing 5-alkyl-5-aryl-1-pyrroline N-oxides (AAPOs) has been established using readily available aryl bromides, nitroalkanes, and acrolein as the starting materials. The palladium-catalyzed arylation of nitroalkanes gave the 1-aryl-substituted nitroalkanes, which underwent the Et₃N-catalyzed Michael addition with acrolein at room temperature to afford the 4-aryl-4-nitroaldehydes. The latter were then subjected to the nitro reductive cyclization using Zn–HOAc in EtOH at 0 °C followed by warming the reaction mixture to room temperature for 24 h, furnishing the 5-alkyl-5-aryl-1-pyrroline N-oxides in good overall yields. Selected examples of 1,3-dipolar cycloaddition of the cyclic nitrones with methyl methacrylate were also described.

© 2014 Elsevier Ltd. All rights reserved.

## 1. Introduction

The 1-pyrroline N-oxide (3,4-dihydro-2H-pyrrole 1-oxide) is the core structure of a number of cyclic nitrone spin traps, such as DMPO (**1**),[1] MPPO (**2**),[2] EMPO (**3**),[3] AMPO (**4**),[4] and DEPMPO (**5**)[5] (Fig. 1). These cyclic nitrones and the well known acyclic congeners represented by (Z)-α-phenyl-N-tert-butylnitrone (PBN, **7**)[6] and disodium (Z)-4-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (OKN-007, formerly referred to as NXY-059, **8**)[7] have been extensively studied as therapeutics for oxidative stress-related diseases, such as neurodegeneration, cardiovascular disease, and cancer.[8] Among them, the nitrone **8** has reached to clinical trials for treatment of acute stroke,[7a] and it delivers anticancer activity in animal glioma models[7b–d] and hepatocellular carcinoma.[7c,e] Over the years, acyclic nitrones represented by the general structure **I** (Ar=aryl or heteroaryl) have been synthesized for improved spin trap properties[9a–c] and for stroke treatment.[9d,e] Novel benzoxazinic nitrones **9–11**[10] and other cyclic nitrones[11] have also been reported for studying their reactivity toward oxygen- and
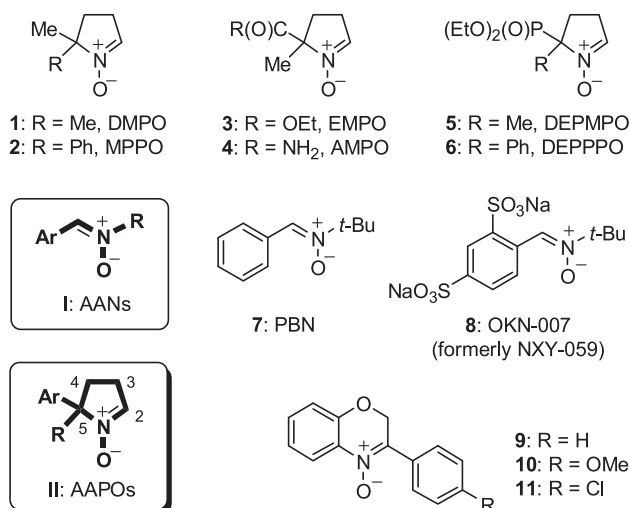


Fig. 1. Structures of cyclic and linear nitrone spin traps **1**–**11**.

carbon-centered radicals and as possible antioxidants in biological systems. Moreover, conjugates of acyclic and cyclic nitrones with cholesterol,[12a,e] β-cyclodextrin,[12b,c] and fluorinated amphiphilic carriers[12d,f] have been synthesized and evaluated for spin-trapping

---

* Corresponding authors. Tel./fax: +86 571 87953128; e-mail addresses: wyz@zju.edu.cn (J. Wu), chdai@zju.edu.cn, chdai@ust.hk (W.-M. Dai).
† Tel.: +852 23587365; fax: +852 23581594.

behavior[12a–d] and antioxidant properties in biomimetic membranes,[12f] and as antioxidants against light-induced retinal degeneration.[12e]

Substituent effect on the spin-trapping behavior of 1-pyrroline N-oxides has been examined. Replacement of one C5-methyl group in DMPO (**1**) by a phenyl group as in MPPO (**2**) improved its stability to have an excellent shelf life.[2a] Moreover, longer lifetimes of the spin adducts of MPPO were observed while similar spin-trapping rate constants as compared to those of DMPO were achieved. The unique stereochemistry of the spin adducts of MPPO rendered easy detection of the spin-adduct spectra. In some cases one major *trans* (with respect to the phenyl group) and one minor *cis* adducts were formed in addition reactions with the carbon-centered radicals while the reverse selectivity was observed for the superoxide/peroxyl radical adducts. For the hydroxyl radical adduct of MPPO, only one EPR spectrum was detected. In contrast, substitution of the C5-methyl group in DEPMPO (**5**) by a phenyl group gave DEPPPO (**6**)[13] with a significant decrease of the spin-trapping properties, such as non-stereoselective addition of free radicals on the nitronyl moiety due to less steric bias among the two substituents on the C5 position. It seems interesting to investigate the spin-trapping properties of the general structure **II** (Fig. 1) on the basis of MPPO (**2**).

There are two general methods for synthesis of nitrones, i.e., condensation of hydroxylamines with carbonyl compounds[14] and oxidation of hydroxylamines or secondary amines.[15] In the former cases, the hydroxylamines could be formed from reduction of nitro compounds, providing an efficient synthesis of cyclic nitrones from reductive cyclization of nitro carbonyl precursors.[16,17] Janzen and co-workers[2c] synthesized MPPO (**2**) by a four-step sequence (Fig. 2a), consisting of the Michael addition of nitromethane with methyl vinyl ketone,[16d,e] the nitro reductive cyclization, the Grignard addition with 2-methyl-1-pyrroline N-oxide, and finally the oxidation of the cyclic hydroxylamine. Merino and co-workers[18] prepared a similar nitrone **12** designed for studying neutral 2-aza-Cope rearrangement (Fig. 2b). Starting from the parent 1-pyrroline N-oxide, two iterative Grignard addition and hydroxylamine oxidation cycles were used and the overall yield of **12** was excellent. In our recent work, we established a general synthesis of 5-alkyl-5-aryl-γ-lactams from 1-aryl-substituted nitroalkanes.[19,20] We envisioned that 5-alkyl-5-aryl-1-pyrroline N-oxides (AAPOs) of the general structure **II** (Fig. 1) could be synthesized from the readily available 1-aryl-substituted nitroalkanes **13** via the Michael addition with acrolein followed by the reductive cyclization of the nitro aldehydes **14** to give the nitrones **15**
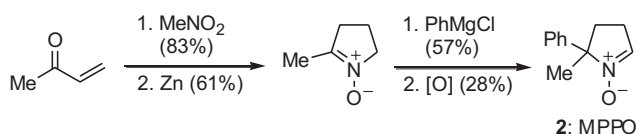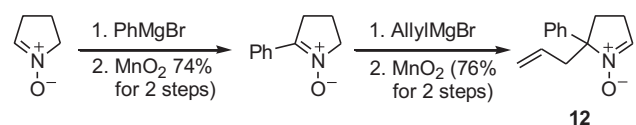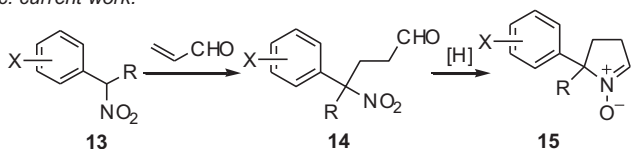
(Fig. 2c).[16d–g] This synthetic sequence is advantageous not only for its generality but also for its tolerance of the functional groups, such as carboxylic esters, which could not survive under the Grignard addition conditions as employed in Janzen and Merino's preparations, respectively (Fig. 2a and b). The functional group X on the phenyl ring of **15** should enable formation of conjugates for achieving enhanced spin-trapping properties as demonstrated in the prior work mentioned above.[12]

## 2. Results and discussion

1-Aryl-substituted nitroalkanes **13a–g** and **13n** (entries 1–7 and 14, Table 1) were obtained by the Pd-catalyzed α-arylation of nitroalkanes under the optimized conditions in our previous work.[19] The compounds **13h–m** were newly synthesized by following the same procedure in good to excellent yields.

**Table 1**
Results of Pd-catalyzed arylation of nitroalkanes[a]
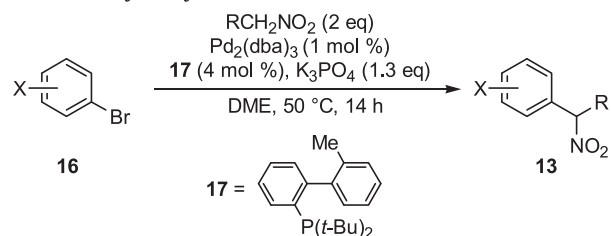


| Entry | 16: X | R | t (h) | 13: Yield[b] (%) |
|---|---|---|---|---|
| 1[c] | **16a**: 2-(1,3-Dioxolan-2-yl) | Me | 24 | **13a**: 71[d] |
| 2 | **16b**: 3-Me | Me | 14 | **13b**: 90[d] |
| 3 | **16c**: 4-Me | Me | 14 | **13c**: 78[d] |
| 4[e] | **16d**: 2-MeO | Me | 18 | **13d**: 91[d] |
| 5 | **16e**: 4-MeO | Me | 14 | **13e**: 74[d] |
| 6 | **16f**: 4-Cl | Me | 14 | **13f**: 84[d] |
| 7 | **16g**: 4-MeO₂C | Me | 14 | **13g**: 88[d] |
| 8 | **16h**: 4-(1,3-Dioxolan-2-yl) | Et | 14 | **13h**: 75 |
| 9[e] | **16i**: 2-Me | Et | 18 | **13i**: 72 |
| 10 | **16b**: 3-Me | Et | 14 | **13j**: 89 |
| 11 | **16c**: 4-Me | Et | 14 | **13k**: 88 |
| 12[e] | **16d**: 2-MeO | Et | 18 | **13l**: 91 |
| 13 | **16f**: 4-Cl | Et | 14 | **13m**: 80 |
| 14 | **16g**: 4-MeO₂C | Et | 14 | **13n**: 87[d] |

[a] Reaction conditions: 1 mol % Pd₂(dba)₃, 4 mol % **17**, 2 equiv of RCH₂NO₂, and 1.3 equiv of K₃PO₄, DME, 50 °C for 14 h.
[b] Isolated yields.
[c] Using 5 mol % Pd₂(dba)₃ and 20 mol % **17** in 1,4-dioxane at 110 °C.
[d] Data are taken from Ref. 19 for comparison.
[e] Using 5 mol % Pd₂(dba)₃ and 10 mol % **17** at 50 °C for 18 h.

In general, the *ortho*-substituent in the aryl bromides **16** rendered the arylation much more difficult to occur. For example, much higher temperature and catalyst loading should be applied for the arylation of **16a** as compared to **16h** (entry 1 vs entry 8, Table 1). Also, the reactions of **16d** and **16i** required higher catalyst loading and longer reaction time (entries 4, 9, and 12, Table 1). On the other hand, the R group in nitroalkanes, i.e., Me (entries 2–4, 6, and 7, Table 1) versus Et (entries 10–14, Table 1) did not show notable influence on the arylation results.

In our previous work on the Michael addition of the 1-aryl-substituted nitroalkanes **13** with methyl acrylate, it was found that Et₃N was not an efficient base to promote formation of the Michael adducts. Instead, DBU (0.5–1.0 equiv) should be used to facilitate the Michael addition in MeCN at room temperature for 2.5 h to furnish the adducts in excellent yields.[19] For the Michael addition of **13** with acrolein,[16f,g] we found that only 0.1 equiv of Et₃N was sufficient to catalyze the formation of the adducts **14** at room temperature. For the substrates **13b–d** and **13f** (R=Me) possessing



Fig. 2. Synthetic approaches toward 5-alkyl-5-aryl-1-pyrroline N-oxides.