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Pseudonitrosites as masked nitroalkenes in the Barton–Zard pyrrole synthesis

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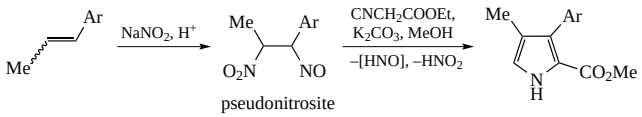
3-Aryl-4-methylpyrrole-2-carboxylates were prepared *via* the Barton–Zard reaction using pseudonitrosites as a source of the corresponding nitroalkenes. The starting pseudonitrosites were, in turn, obtained *via* addition of N_2O_3 to propenylbenzenes available from the natural plant essential oils.



Keywords: Barton–Zard reaction, pseudonitrosites, propenylbenzenes, isomerization, pyrroles, lamellarins.

The Barton–Zard synthesis (a reaction of nitroalkenes with alkyl isocyanoacetates in the presence of a base) is an important method for the preparation of 3,4-disubstituted pyrrole-2-carboxylates.[1] Sometimes, sulfonyl- and cyano-substituted alkenes are used in the reaction instead of nitroalkenes[1(*c*),2] (usually, in these cases more drastic conditions and stronger bases are required).

This reaction has drawn our attention[3] since it enabled the preparation of pyrrole-2-carboxylates with (polyalkoxy)aryl substituents in positions 3 and/or 4 as a structural core of lamellarins (Figure 1), marine natural compounds possessing high biological activities.[4]

For the synthesis of 3-aryl-4-R-substituted pyrrole-2-carboxylates**,** availability of the starting β-R-β-nitrostyrenes is essential. Here we present an approach based on utilization of so called pseudonitrosites,[5] products resulting from addition of N_2O_3 across C=C bond of propenylbenzenes **1** available from plant essential oils.[6] An addition of N_2O_3 to aryl-substituted alkenes is known to occur regioselectively affording 1-aryl-2-nitro-1-nitroso derivatives (see reviews[7] and references therein). Pseudonitrosites are known to undergo base-induced elimination of hyponitrous acid thus affording nitroalkenes.[5(*b*),8] Meanwhile, the Barton–Zard reaction occurs under basic conditions as well, thus prompting to carry out this reaction using pseudonitrosites **2** as starting compounds generating nitroalkenes **3** *in situ* upon treatment with an excess base [some examples of the *in situ* generation of nitroalkenes in the Barton–Zard reaction from *vic*-nitroacetates are known, see lit.[1(*a*),(*b*),9]].

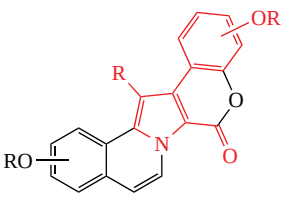


Figure 1 General structure of lamellarins.

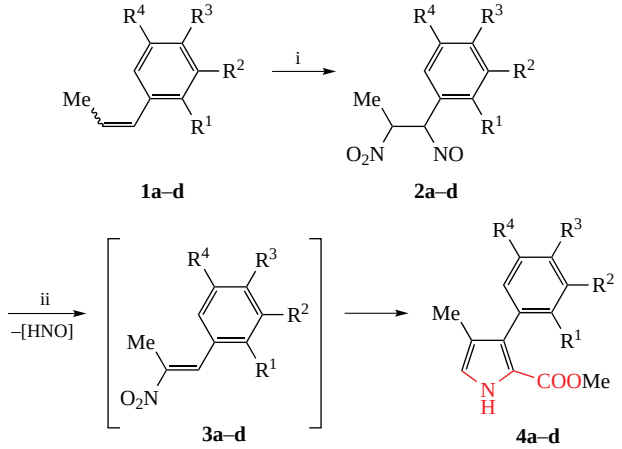
Indeed, the reaction of pseudonitrosites **2a–d** with ethyl isocyanoacetate in MeOH in the presence of 3 equiv. K_2CO_3 afforded 3-aryl-4-methylpyrrole-2-carboxylates **4a–d** in moderate to good yields (the reaction is accompanied with transesterification, methyl esters having been produced, Scheme 1).[†] The compounds **2a–d** are, in turn, readily formed upon adding H_2SO_4 to a stirred two-phase system aq. $NaNO_2$/ethereal solution of propenylbenzene **1a–d** at 5–10 °C and isolated by a simple filtration.

The present approach is superior to the known syntheses of 1-aryl-2-nitroprop-1-enes ArCH=C(NO_2)Me by direct nitration of the corresponding propenylbenzenes ArCH=CHMe since they require the use of rather expensive ($AgNO_2$)[10] or explosive [$C(NO_2)_4$][11] reagents.

In the solid state, pseudonitrosites are known to exist in dimeric form (similarly to other aliphatic nitroso compounds).[12] However, in solution they readily undergo isomerization to the corresponding α-nitro oximes.[13] In our case, ^{1}H NMR spectra of pseudonitrosites **2** in DMSO-d_6, in fact, showed only the signals of nitro oximes MeCH(NO_2)–C(Ar)=N–OH [as mixtures of (*Z*)- and (*E*)-isomers].

[†] *Synthesis of pseudonitrosites* **2a–d** *(general procedure).* To a solution of the starting propenylbenzene **1**[6(*b*)] (5 mmol) in Et_2O (10 ml), $NaNO_2$ (1.5 g, 21.7 mmol) in H_2O (2.5 ml) was added. A solution of H_2SO_4 (0.6 ml) in H_2O (5 ml) was added dropwise to the reaction mixture under vigorous stirring at 5 °C within 20 min. The mixture was stirred at 5–10 °C for 2 h, and placed in a refrigerator overnight. The resulting precipitate was filtered off, washed successively with water, MeOH and diethyl ether, and dried.

Synthesis of methyl 3-aryl-4-methylpyrrole-2-carboxylates **4a–d** *(general procedure).* A mixture of pseudonitrosite **2** (1 mmol), K_2CO_3 (3 mmol, 415 mg) and ethyl isocyanoacetate (1 mmol, 113 mg) in MeOH (3 ml) was vigorously stirred at room temperatute for 2 days, additional portion of ethyl isocyanoacetate (16–17 mg, 15 mol%) being added in 1 day. The reaction course was monitored by TLC. The mixture was diluted with water (15 ml) and extracted with ethyl acetate (3 × 10 ml). The combined extracts were evaporated to dryness, and the residue recrystallized from MeOH (for **4a–c**) or chromatographed (for **4d**).



a $R^1 = R^4 = OMe$, $R^2 + R^3 = OCH_2O$; 59% (**2a**), 46% (**4a**)
b $R^1 = R^2 = OMe$, $R^3 + R^4 = OCH_2O$; 68% (**2b**), 63% (**4b**)
c $R^1 = H$, $R^2 + R^3 = OCH_2O$, $R^4 = OMe$; 86% (**2c**), 44% (**4c**)
d $R^1 = R^2 = R^3 = R^4 = OMe$; 34% (**2d**), 67% (**4d**)

Scheme 1 *Reagents and conditions*: i, $NaNO_2$, H_2SO_4, Et_2O, 5–10 °C; ii, $CNCH_2COOEt$, MeOH, K_2CO_3 (3 equiv.).

Mass spectra (EI) of the pseudonitrosites **2a–d** featured weak peaks of the corresponding molecular ions and abundant peaks of fragment ions [M – 76] (obviously, [M – NO – NO_2]).

It should be noted that 1-aryl-2-nitroprop-1-enes **3** could be really synthesized by the condensation of the corresponding benzaldehydes with nitroethane. However, such benzaldehydes are, in turn, most conveniently prepared[6] by ozonolysis of propenylbenzenes of type **1**. Therefore, from an atom-economy point of view the present approach seems preferable (notwithstanding rather low rate of the Barton–Zard reaction with pseudonitrosites **2**).

In summary, the Barton–Zard reaction of pseudonitrosites as masked nitroalkenes provided a convenient and atom-economical approach to 3-aryl-4-methylpyrrole-2-carboxylates starting from propenylbenzenes available from plant essential oils.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.07.026.

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