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## Accepted Article

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COMMUNICATION

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# Synthesis of Nitro Alcohols by Riboflavin Promoted Tandem Nef-Henry Reactions on Nitroalkanes

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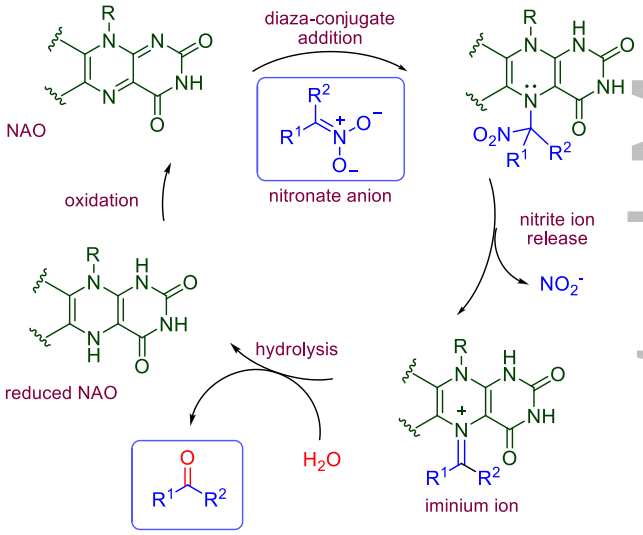
**Abstract.** We disclose a unprecedented riboflavin promoted Nef reaction of primary nitroalkanes coupled with a nitroaldol reaction. This tandem process allows the synthesis of functionalized nitro alcohols under mild reaction conditions. Secondary nitroalkanes fail to give the expected nitroaldol products although they are consumed under the reaction conditions.

**Keywords:** Flavins; Henry reaction; Nef reaction; Nitroalkanes; Tandem reactions.

The flourishing chemistry of nitro compounds is still of notable synthetic interest as evidenced by the large number of processes employing nitro-containing derivatives as pivotal intermediates.[1] The carbanion stabilizing property of the nitro group through the formation of nitronate anions, has been using for a long time to generate new carbon-carbon bonds exploiting the Henry nitroaldol process as well as conjugate additions to electron-poor alkenes.[2] The easy reduction of the nitro moiety is probably one of the most viable and exploited functional group transformations used to access amino derivatives.[3] The nitro to carbonyl conversion, widely known as the Nef reaction, is another process frequently used to install aldehydes, ketones and carboxylic acids in structural frameworks embedding nitro groups.[4] This transformation was originally designed as an hydrolytic cleavage, under strongly acidic conditions, of a preformed nitronate anion.[5] However, along the years the carbon-nitrogen double bond cleavage has been more efficiently achieved under oxidative conditions or by partial reduction of the nitro group using transition metal salts. The original hydrolytic procedure is indeed seldom applied for synthetic purposes because of the harsh conditions required. The ability of some nitroalkane oxidases (NAO) in converting primary and secondary nitroalkanes into the corresponding carbonyls and nitrite anions has been known since the early 1950s.[6] The activity of these enzymes seems associated to the flavoprotein systems which flavin moiety is able to interact with nitroalkanes through a diaza-conjugate addition-elimination step generating nitrite anions and iminium ions which upon hydrolysis afford the parent carbonyl derivatives (Scheme 1).[7] Re-oxidation of the flavin reduced form is usually provided by molecular oxygen restoring the catalyst activity. This approach has been never applied to set up a synthetic methodology for the catalytic or promoted Nef reaction, although various studies open up interesting perspectives for the development of this nitro to carbonyl conversion.[8]




**Scheme 1.** Enzymatic catalytic cycle evidenced for the nitroalkane oxidase (NAO) assisted bio-Nef reactions.

In a very recent paper, various flavinium salts have been proposed as catalysts to generate nitrite anions from nitromethane.[9] The nitrite anions thus formed have been used to support further $NO_x$/TEMPO catalytic cycles for the selective oxidation of alcohols, diols and ethers. The flavinium salts employed in this process, although quite efficient, are not commercially available and must be prepared from a multistep synthesis. In the search for a simple flavin derivative retaining the reactivity features of enzymatic NAO systems our attention was captured by riboflavin, also referred as vitamin $B_2$, a

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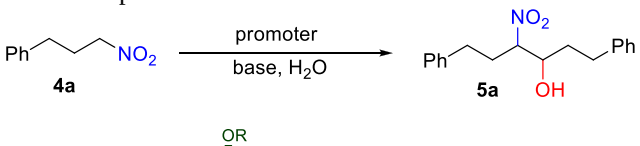
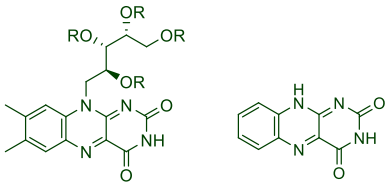
commercially available and relatively inexpensive compound.[10] In this communication we present the preliminary results obtained in the utilization of riboflavin as promoter of the nitro to carbonyl conversion which in our conditions is coupled to a Henry reaction allowing the synthesis of nitro alcohols. To the best of our knowledge, this is the first example in which an efficient biomimetic Nef reaction is realized using commercially available cheap reagents.

The initial goal of our research was to establish a new protocol for the conversion of nitroalkanes into the corresponding carbonyl derivatives. For this purpose we firstly made to react nitroalkane **4a** in the presence of cetyltrimethylammonium hydroxide (CTAOH) and riboflavin **1** in water as solvent. According to the result reported in Table1, entry 1, nitro alcohol **5a** was isolated as single product in low yield after stirring for 4 h at room temperature. The observed nitro alcohol clearly arises from a fast nitroaldol reaction between the initially formed aldehyde and the residual nitroalkane. The combined action of the base and riboflavin is essential for the formation of the nitro alcohol since in absence of one of the two reagents only the unreacted nitroalkane is recovered from the reaction mixture. Considering the nature of the general mechanism portrayed in Scheme 1, it is assumed as a possible cause of the reduced yield observed, a failure in the oxidation step which should regenerate riboflavin from its reduced form. However, repeating the reaction under oxygen atmosphere was unsuccessful in increasing the yield of the nitro alcohol (Table 1, entry 2). Conversely, a notable improvement was observed by increasing the amount of riboflavin, revealing that the catalytic cycle is not operative and that **1** must be considered as an actual reagent (Table 1, entry 3). Since the use of sodium hydroxide was ineffective in this reaction, other quaternary ammonium hydroxides were tested and we finally found in tetrahexylammonium hydroxide (THAOH) the best base for this conversion (Table 1, entry 4). Structurally modified flavin reagents such as acetylated riboflavin **2** and commercially available isoalloxazin **3** have been tested to verify a possible improvement. However compound **2** was less effective than riboflavin and isoalloxazin **3** totally failed in leading to the expected product **5a** (Table 1, entries 5-6). The devised procedure for the Nef reaction occurs under very mild reaction conditions avoiding further oxidation of the intermediate aldehyde which is often observed using oxidative methods.[11] Furthermore, the subsequent nitroaldol process avoids the isolation of the aldehyde increasing the level of efficiency of the whole process. The optimized reaction conditions have been then applied to a series of nitroalkane derivatives **4** leading to nitro alcohols **5** in satisfactory yields (Table 2). Linear nitroalkanes efficiently afford the corresponding nitro alcohols **5a-d** containing simple alkyl chains, phenyl ring and terminal unsaturation.

**Table 1.** Optimization of the reaction conditions.[a]

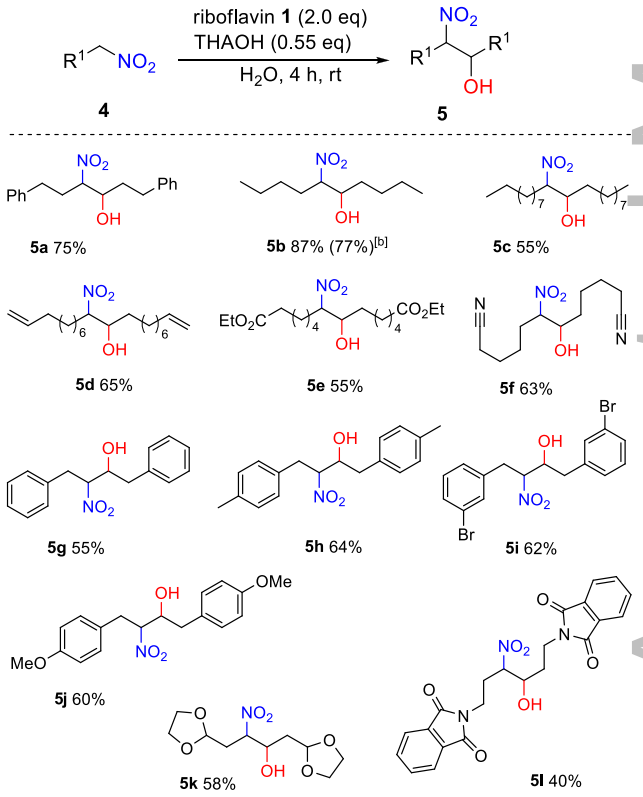



| Entry | Base (eq) | Promoter (eq) | Yield (%) |
|---|---|---|---|
| 1 | CTAOH (0.55) | **1** (1.0) | 26 |
| 2 | CTAOH (0.55), $O_2$ (1 bar) | **1** (1.0) | 26 |
| 3 | CTAOH (0.55) | **1** (2.0) | 61 |
| 4 | THAOH (0.55) | **1** (2.0) | 75 |
| 5 | THAOH (0.55) | **2** (2.0) | 53 |
| 6 | THAOH (0.55) | **3** (2.0) | n.r. |

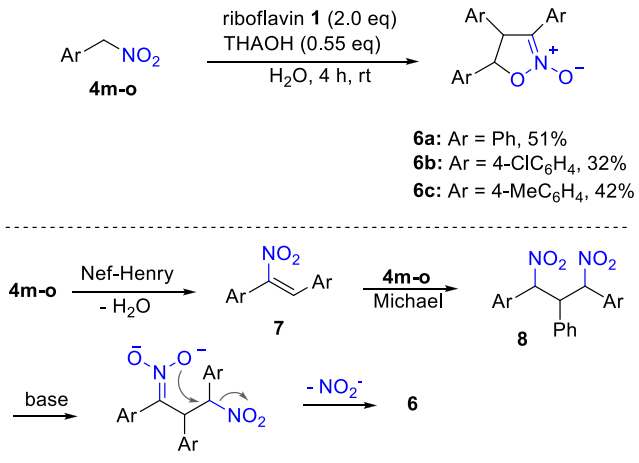
[a] Reaction conditions: **4a** (0.6 mmol), base, promoter in water (1 mL), room temperature, 4 h. CTAOH: cetyltrimethylammonium hydroxide. THAOH: tetrahexyl-ammonium hydroxide.

**Table 2.** Scope of the reaction.[a]



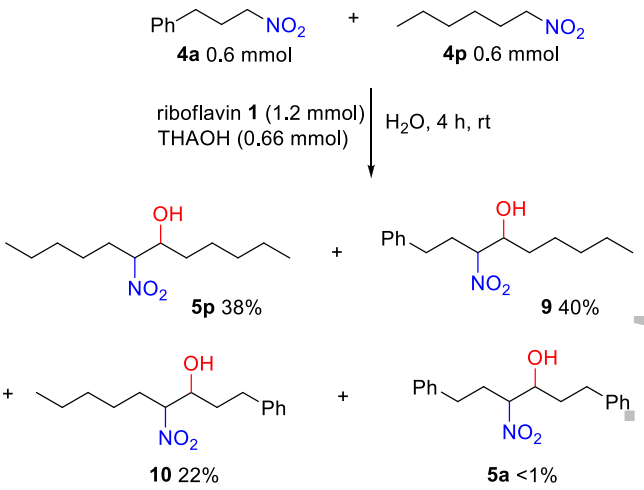

[a] Reaction conditions: nitroalkane **4** (0.6 mmol), riboflavin (0.6 mmol), THAOH (0.33 mmol) in water (1 mL) at rt for 4 h. Nitro alcohols have been isolated as an almost equimolar amount of diastereoisomers. [b] Reaction carried out on a 3 mmol of substrate.

A slight erosion in the chemical yield has been observed increasing the scale of the process to 3 mmol in the preparation of compound **5b.** The reaction of functionalized 2-nitroethylbenzenes, also nicely proceeds toward the formation of nitro alcohols **5g-j**. In this specific case the tandem process prevents from the direct utilization of arylacetaldehydes, the products of the Nef reaction of 2-nitroethylbenzenes, which are quite sensitive compounds.[12] Of particular interest is the reaction of nitroalkanes bearing electrophilic fuctionalities such as ester or cyano groups which in our conditions afford polyfunctionalized derivatives **5e,f.** Both these nitro alcohols are amenable of further synthetic manipulation involving selective functional group transformations. Finally, nitroethyl-1,3-dioxolane and 3-phthalimido-1-nitropropane can be converted into nitro alcohols **5k,l** embedding masked carbonyl and amino functions. The nitro alcohols **5** prepared by this procedure are obtained as an equimolar mixture of the two possible diastereoisomers. This trend has been previously observed in the Henry reaction involving nitroalkanes and alkanals using quaternary ammonium salts.[13] Interestingly, the reaction of arylnitromethanes **4m-o** under our reaction conditions led to the exclusive formation of isoxazolidine *N*-oxides **6** under unoptimized conditions (Scheme 2). This result is probably due to the preliminary formation of nitroalkene **7** which upon conjugate addition of phenylnitromethane gives 1,3-dinitro compound **8**.[14] The latter intermediate under basic conditions affords **6** through an intramolecular displacement of the nitrite anion by the nitronate group.[15]



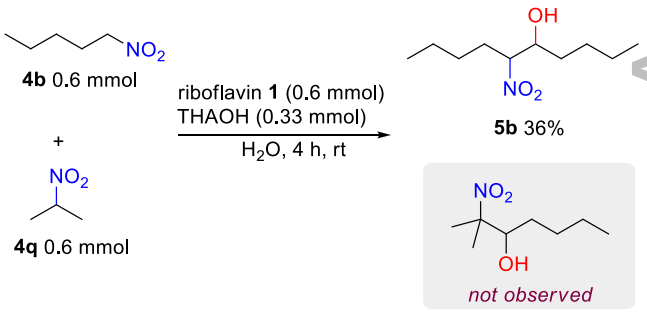

**Scheme 2.** Synthesis of isoxazoline *N*-oxides **6** from arylnitromethanes **4m-o**.

A crossed reaction has been also attempted between primary nitroalkanes **4a** and **4p** evidencing the formation of a mixture of three of the four possible products. Interestingly, product **5a** arising from the homo reaction of **4a** was not observed (Scheme 3). The absence of nitro alcohol **5a** in the reaction mixture may reflect the lower reactivity of 3-phenylpropanal compared to hexanal in the competitive nitroaldol reaction with **4a** and **4p**. Secondary nitroalkanes, although reactive in the devised reaction conditions, do not provide neither the ketone derivatives nor the nitroaldol products.



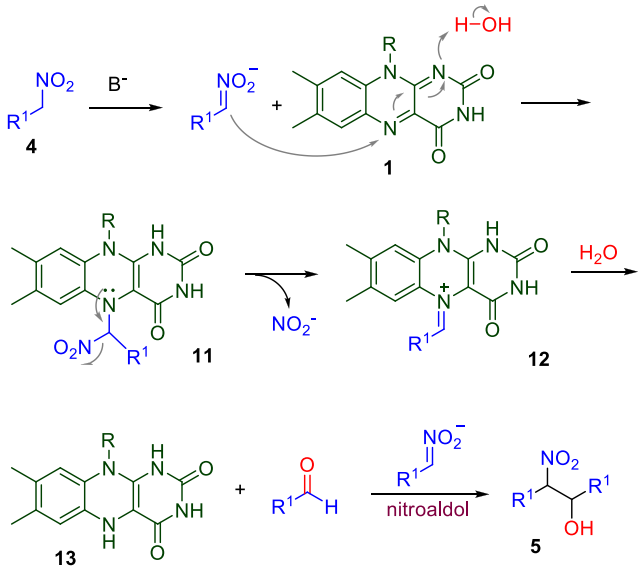

**Scheme 3.** Crossed experiment with 3-phenylnitropropane and 1-nitrohexane

Surprisingly, it was observed disappearance of the starting materials but no compounds arising from the Nef or any other process have been detected. A possible explanation for this behavior lies in the possibility that the Michael adduct of secondary nitroalkanes with the riboflavin is enough stable to prevent loss of the nitrite anion to generate the reactive iminium ion.[16] In order to gain further elements supporting this hypothesis, a mixture of nitropentane and 2-nitropropane were made to react under the usual reaction conditions (Scheme 4). The only product isolated from the reaction mixture was nitro alcohol **5b** arising from the reaction of nitropentane albeit in reduced yield compared to that reported in Table 2. The cross nitroaldol product obtained by the reaction between 2-nitropropane and pentanal, generated from the Nef reaction of 1-nitropentane, was not observed. This finding would apparently support the scavenging of riboflavin by 2-nitropropane limiting the efficiency of the reaction of nitropentane.




**Scheme 4.** Crossed experiment with nitropentane and 2-nitropropane.

However, a LC-MS analysis of the solid portion of the reaction with nitrocyclohexane did not evidence neither the presence of nitroalkane-riboflavine adducts nor the reduced form of riboflavine. An extensive decomposition of reduced riboflavine could explain the failure of the oxidative last step of the catalytic cycle. According to the experimental observations the plausible mechanism is portrayed in Scheme 5. The nitronate anion generated from nitroalkane **4** by basic treatment attacks the riboflavin **1** leading to adduct **11**. This intermediate, upon loss of a nitrite anion, generates the iminium ion **12** which upon hydrolysis affords the reduced form of riboflavin **13** and the aldehyde. Compund **13** is not oxidized to riboflavin maybe because of its decomposition thus disrupting a possible catalytic cycle. Finally, the aldeyde reacts with the nitronate anion present in the reaction mixture leading to the nitro alcohol **5**.




**Scheme 5.** Plausible reaction mechanism for the synthesis of nitro alcohols **5**.

In conclusion, we have disclosed for the first time a riboflavin-promoted Nef reaction on primary nitroalkanes which coupled with a tandem Henry reaction allows the efficient synthesis of nitro alcohols. A wide range of functionalized primary nitroalkanes can be used for this purpose while secondary nitrolakanes, although reactive fail to afford the expected nitro alcohols. Further studies to elucidate the mechanistic aspects of this process are currently underway.

## Experimental Section

### General Procedure for the Preparation of Nitro Alcohols 5.

To nitroalkane **4** (0.6 mmol) in a 5 mL glass vial equipped with magnetic stirring bar, tetrahexylammonium hydroxide (THAOH) was added (0.33 mmol, obtained diluting 0.3 mL of THAOH 40% water solution in 0.7 mL of water). Riboflavin (0.6 mmol, 2 eq.) was then added and the resulting mixture was stirred at room temperature for 4 hours. Upon completion, the mixture was diluted with $CH_2Cl_2$ (4 mL) and washed with brine (3×2 mL). The aqueous phase was further extracted with $CH_2Cl_2$ (4×20 mL), and the combined organic phases were dried over $Na_2SO_4$, filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 9:1).

## Acknowledgements

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