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Graphical Abstract

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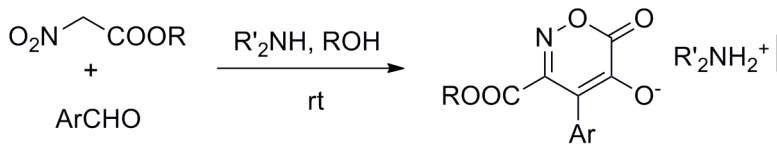

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Novel condensations of nitroacetic esters with aromatic aldehydes leading to 5-hydroxy-1,2-oxazin-6-ones

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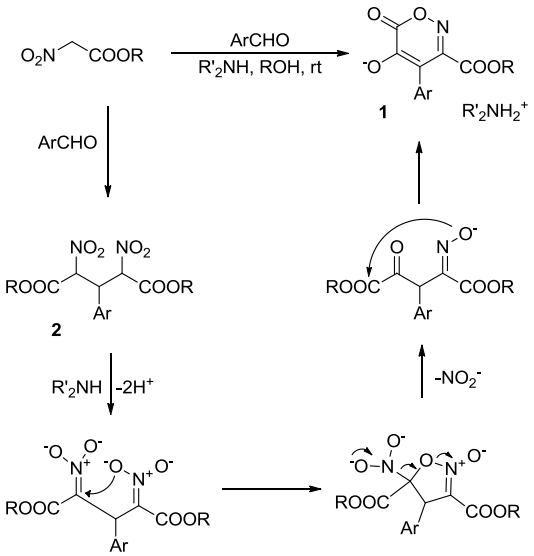
ABSTRACT

Contrary to the early literature [Dornow, A.; Wiehler, G. *Justus Liebigs Ann. Chem*. **1952**, *578*, 113-121], esters of 2,4-dinitro-3-arylglutaric acids **2** could not be obtained by double condensation of aryl aldehydes with alkyl nitroacetates. Instead, under these conditions, we observed formation of novel 4-aryl-5-hydroxy-1,2-oxazin-6-one-3-carboxylates **1**. The roles of the solvent, the reaction conditions and the nature of the reagents in this new condensation were investigated. The data obtained suggest that the heterocyclic products **1** originate from intramolecular oxidation (similar to the Nef reaction) of dinitro derivative **2**, followed by nucleophilic attack of the oxime oxygen at the carboxylate group. The condensation presented provides a novel general synthetic route to these types of heterocycle.

Aliphatic nitro compounds have proven to be valuable intermediates for the synthesis of different classes of organic molecules.[1] Among these, alkyl nitroacetates are of particular utility as versatile synthetic tools.[2] In the course of our research in the field of the chemistry of chromophores of fluorescent proteins[3] we were faced with the necessity of obtaining 2,4-dinitro-3-arylglutarates **2**.

A successful double condensation of nitroacetic esters with aromatic aldehydes leading to the desired dinitroglutaric esters **2** has been reported earlier.[4] However, our attempts to reproduce these results were unsuccessful. Instead, we observed formation of novel 4-aryl-5-hydroxy-1,2-oxazin-6-one-3-carboxylates **1** (Scheme 1).



Scheme 1. Formation of 4-aryl-5-hydroxy-1,2-oxazin-6-one-3-carboxylates **1** from aromatic aldehydes and nitroacetic esters, a proposed mechanism.

We studied various aromatic aldehydes, alkyl nitroacetates and secondary amines in this reaction. Methanol, ethanol or isopropanol were used as solvents corresponding to the alkyl nitroacetate employed, in order to avoid transesterification. In the majority of cases, precipitation of the ammonium salts of oxazinones **1** was observed (Table 1).[5] In the case of 4-

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nitrobenzaldehyde derivatives **1z,** formation of a precipitate did not take place, and the products were isolated in protonated form. However, some aldehydes gave 2,4-dinitroglutarates **2** (also as ammonium salts). We observed gradual transformation of dinitroglutarates **2** into oxazinones **1** during the course of the reaction. Only with 2-pyridinecarboxaldehyde derivative **2c** did this transformation not take place. The nature of the alkyl nitroacetate and amine did not appear to affect the ratio of products **1**:**2**.

Table 1. Oxazinones **1** and dinitroglutarates **2** produced via Scheme 1

Ar	Product, %	Time, (d)	Ar	Product, %	Time,(d)
Ph	**1a(Me)**•Et_2NH, 56%	2	Ph	**1a(Me)**•Cy_2NH, 33%	3
Ph	**1a(Et)**•Et_2NH, 31% or **2a(Et)**•Et_2NH, 56%[a]	2 or 1	Ph	**1a(Me)**•piperidine, 13%	3
Ph	**1a(i Pr)**•Et_2NH, 43% or **1a(i Pr)**•Et_2NH + **2a(iPr)** •Et_2NH[a,b]	3 or 1	Ph	**1a(Me)**•pyrrolidine, 39%	3
4-MeO-Ph	**1b(Me)**•Et_2NH, 27%	3	thiophen-2-yl	**1e(Me)**•Et_2NH, 36%	3
4-MeO-Ph	**1b(Et)**•Et_2NH, 54%	3	3-MeO-C_6H_4	**1f(Me)**•Et_2NH, 46%	2
4-MeO-Ph	**1b(i Pr)**•Et_2NH, 23%	3	4-^{i}Pr-C_6H_4	**1g(Me)**•Et_2NH, 35%	2
4-NO_2-Ph	**1z(Me)**,[c] 22%	3	4-Br-C_6H_4	**1h(Me)**•Et_2NH, 43%	2
4-NO_2-Ph	**1z(i Pr)**,[c] 15%	3	3,4-(MeO)-C_6H_3	**1i(Me)**•Et_2NH, 32%	3
4-HO-Ph	**1d(Me)**•Et_2NH, 45%	2	4-$N(Et)_2$-C_6H_4	**1j(Me)**•Et_2NH, 47%	3
4-HO-Ph	**1d(Et)**•Et_2NH, 44%	2	2-F-C_6H_4	**1k(Me)**•Et_2NH, 37%	3
4-HO-Ph	**1d(i Pr)**•Et_2NH, 53%	2	4-F-C_6H_4	**1l(Me)**•Et_2NH, 36%	3
pyridin-2-yl	**2c(Et)**•Et_2NH, 58%	1	2-Br-C_6H_4	**1m(Me) + 2m(Me)**[b]	3
pyridin-2-yl	**2c(i Pr)**•Et_2NH, 33%	1	2-HO-C_6H_4	**1n(Me) + 2n(Me)**[b]	3

[a] Compound **1** or **2**, or their mixture was isolated depending on the reaction time

[b] Complete conversion of **2** into **1** could not be achieved even after prolonged reaction times

[c] Precipitation of the ammonium salts of **1** and **2** was not observed; **1** was isolated from the reaction mixture in protonated form.

The structures of novel heterocyclic products **1** were confirmed by NMR spectroscopy and X-ray crystallography (Figure 1).[6]

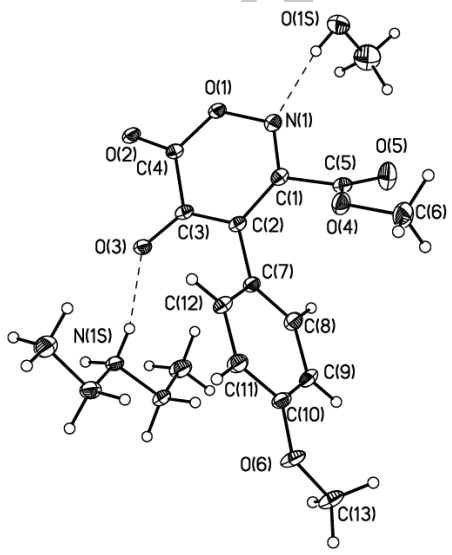

Figure 1. General view of compound **1b(Me)**•Et_2NH. Thermal ellipsoids at the 50% probability level.

Other products (isoxazoles and isoxazoline *N*-oxides) have been reported to arise from condensation of two molecules of an alkyl nitroacetate and one molecule of an aromatic aldehyde.[7-9] Proposed mechanisms[8,9] for these transformations include initial formation of adduct **2** followed by intramolecular cyclization *via* nucleophilic substitution of the nitro group. However, these mechanisms do not explain the formation of the six-membered ring of **1**. Therefore, we speculate that oxazinones **1** may originate from intramolecular oxidation (similar to the Nef reaction) of dinitroglutarates **2** followed by nucleophilic attack of the oxime oxygen at the carboxylate (Scheme 1). It should be noted that our mechanism does not contradict the experimental data reported in the discussed papers.[8,9]

In conclusion, contrary to the earlier literature,[4] esters of 2,4-dinitro-3-arylglutaric acids **2** cannot be isolated by double condensation of aryl aldehydes with alkyl nitroacetates. Generally, compounds **2** are unstable in solution and transform spontaneously into novel 4-aryl-5-hydroxy-1,2-oxazin-6-one-3-carboxylates **1**. To the best of our knowledge, only one example of the synthesis of 5-hydroxylated 1,2-oxazines has been reported in the literature.[10] The present report offers a novel general synthetic route to these heterocycles.

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5. Representative example for the synthesis of **1b(Me)**•Et_2NH: 4-methoxybenzaldehyde (140 mg, 1.0 mmol) and methyl 2-nitroacetate (260 mg, 2.2 mmol) were dissolved in dry MeOH (1 mL) at 0 ^oC. After complete dissolution, diethylamine (160 mg, 2.2 mmol) was added and the mixture was stirred at r.t. for 72 h. The resulting precipitate was filtered, washed with MeOH (1 mL, 0 ^oC) and Et_2O (2x2 mL) and dried *in vacuo*. Yield 95 mg (27%). White solid, mp 171-174 ^oC. ^1H NMR (700 MHz, $CDCl_3$) δ 9.19 (s, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.62 (s, 3H), 2.31 (q, *J* = 7.1 Hz, 4H), 1.00 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.08 (C), 163.60 (C), 159.07 (C), 156.81 (C), 154.05 (C), 130.81 (CH), 126.38 (C), 113.97 (CH), 110.68 (C), 55.37 (CH), 52.68 (CH), 43.07 (CH), 11.76 (CH). HRMS *m/z*: 276.0521 found (calculated for $C_{13}H_{11}NO_6$, $[M-H]^-$ requires 276.0508).
6. Crystals of **1b(Me)**•Et_2NH•MeOH ($C_{18}H_{26}N_2O_7$, M = 382.41) are monoclinic, space group $P2_1/c$, at 100(2) K: , *a* = 9.1912(15) , *b* = 12.701(2) , *c* = 16.895(3) Å, β = 96.130(3)°, V = 1961.0(6) $Å^3$, *Z* = 4 (Z'=1), d_{calc} = 1.295 $g{\cdot}sm^{-3}$, μ=1.00 cm^{-1}, F(000) = 816. Intensities of 16556 reflections were measured with a "Bruker SMART APEX2" CCD diffractometer and 4703 independent reflections [R_{int} = 0.0402] were used in further refinement. The refinement converged to wR2 = 0.0951 and GOF = 1.006 for all independent reflections (R1 = 0.0374 was calculated against F for 3668 observed reflections with $I > 2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0 [Sheldrick, G. M.; *Acta Cryst.*, **2008**, *A64*, 112-122]. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Cent, CCDC 905699.
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