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Synthesis and properties of the salts of 1-nitropropan-2-one and 1-nitrobutan-2-one

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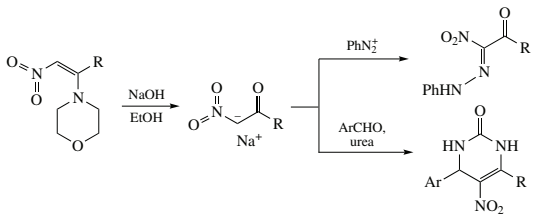
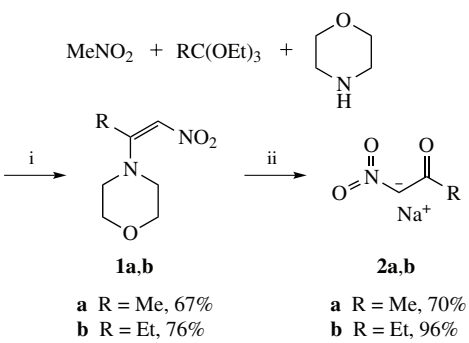
A new safe synthesis of α-nitro ketone salts *via* alkaline hydrolysis of 2-morpholino-1-nitroalkenes has been developed. The salts were introduced into the reactions of diazotization and heterocyclization. Crystal structures of new 2-morpholino-1-nitrobut-1-ene and 6-ethyl-5-nitro-4-phenyl-3,4-dihydropyrimidin-2-one have been determined.



Keywords: nitro compounds, ketones, nitroazine systems, nitroacetone, enamines, diazonium salts, pyrimidinones, hydrazones.

α-Nitro ketones are highly reactive compounds with a wide synthetic potential because they contain both nucleophilic and electrophilic reaction centers. For the same reason, they are unstable and difficult to prepare, which limits their use in organic synthesis. Previously developed methods for the synthesis of α-nitro ketones have significant disadvantages. Their preparation from imidazoles, benzimidazoles or benzotriazoles acylated at the nitrogen atom requires the use of an explosive nitromethane salt.[1–3] The synthesis of nitro ketones from 2-dimethylamino-1-nitroprop-1-ene[4] or from halo ketones[5] typically results in low yields of the target products. Nitration of acetylacetone followed by deacylation leads to nitroacetone with a total yield of 15%.[6] Oxidation of nitroprop-1-ene proceeds with a 37% yield,[7] whereas the preparation of α-nitroacetone from dimethylbutadiene requires unstable toxic nitrous anhydride and ozone, and the total yield for the two steps is 11%.[8] High yields (up to 80%) of nitro ketones can be achieved upon oxidation of nitro alcohols,[9–12] however, free nitro ketones themselves are generally unstable and can be unpredictably destroyed in the course of isolation and storage.[13]

Despite their poor accessibility, α-nitro ketones found an application in the synthesis of relevant organic compounds. Thus, nitroacetone was converted into 4-indolyl-3-nitrobutan-2-one,[14] nitrophenylbutadienes,[15] oxazoles,[16,17] nitropyrroles and their uncyclic precursors, enamines,[18] dihydropyranes[15] as well as nitropyridines.[19–21] 1-Nitrobutan-2-one was used for the synthesis of nitropyridines,[22] aryl nitromethyl ketones,[23] α-amino ketone hydrochlorides[24] and *N*-hydroxy-2-oxoalkanimidothioates.[1]



1a,**b** **2a**,**b**

a R = Me, 67% **a** R = Me, 70%
b R = Et, 76% **b** R = Et, 96%

Scheme 1 *Reagents and conditions*: i, TsOH, 140 °C, 3 h; ii, NaOH, EtOH, room temperature, 30 min.

Therefore, development of a simple, safe and effective method for the synthesis of nitro ketones in their stable form seems an urgent task for organic chemistry. In this work, a new efficient synthesis of stable salts of 1-nitroacetone and 1-nitrobutan-2-one has been proposed, and the possibility of their application in the reactions known for free nitro ketones has been proved.

As precursors of α-nitro ketones, we used readily available 2-morpholino-1-nitroprop-1-ene **1a** and 2-morpholino-1-nitrobut-1-ene **1b**. Compound **1a** had been previously obtained by the condensation of morpholine, nitromethane and diethyl ethoxyethylidenemalonate in a yield of 40%,[25] in turn the preparation of diethyl ethoxyethylidenemalonate in a 66% yield represented an additional stage.[26] Herein, we obtained 2-morpholino-1-nitroalkenes **1a**,**b** by the three-component condensation of commercially available morpholine, nitromethane and the corresponding ortho esters (Scheme 1) similarly to the described preparation of 1-morpholino-2-nitroethylene.[27] The yields of compounds **1a** and **1b** were 67 and 76%, respectively.

2-Morpholino-1-nitrobut-1-ene **1b** represented a new compound, its structure was confirmed by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, elemental analysis and X-ray data (Figure 1).†

† *Crystal data for* **1b**. $C_8H_{14}N_2O_3$ (M = 186.21), space group $P1$, a = 8.7836(6), b = 9.6570(6) and c = 11.6615(8) Å, α = 77.781(6), β = 87.651(5) and γ = 78.959(6)°, V = 948.86(11) Å^3, Z = 4, μ(MoKα) = 0.100 mm^{-1}. At the angles 3.52° < 2θ < 30.84°, total of 8842 reflections were measured, including 5137 unique reflections (R_{int} = 0.0391) and 2117 reflections with $I > 2\sigma(I)$, which were used in all calculations. The final R_1 = 0.1492, wR_2 = 0.2317 (all data) and R_1 =

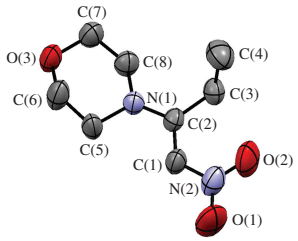


Figure 1 Molecular structure of compound **1b** drawn with 50% probability displacement ellipsoids.

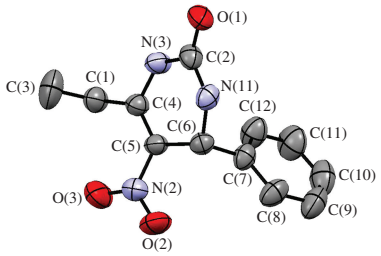
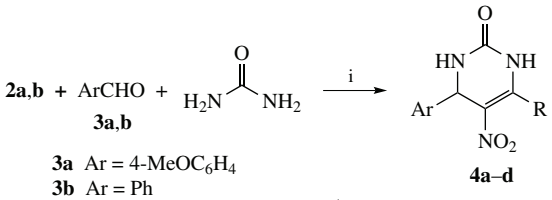


Figure 2 Molecular structure of compound **4b** drawn with 50% probability displacement ellipsoids.

Stirring 2-morpholino-1-nitroalk-1-enes **1a**,**b** in alcoholic solution of NaOH (or KOH) led to sodium (or potassium) salts of nitroacetone and 1-nitrobutan-2-one in 70 and 96% yields, respectively (see Scheme 1). They were isolated and characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. When an aqueous alkali solution was used, hydrolysis of 2-morpholino-1-nitroalkenes also occurred, however the salts of nitro ketones did not precipitate and could be used in further reactions *in situ*.

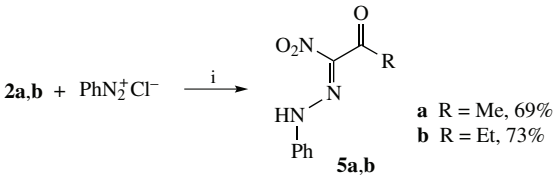
The synthesized salts of α-nitro ketones were found to be able to enter triple condensation with aromatic aldehydes and urea. The resulting substituted pyrimidines **4a–d** were obtained in yields of 81–89% (Scheme 2). The similar transformation was reported for free α-nitro ketones.[28]

The physicochemical characteristics of the synthesized products **4** correlate well with the known data. The structure of new 6-ethyl-5-nitro-4-phenyl-3,4-dihydropyrimidinone **4b** was confirmed by X-ray analysis (Figure 2).†



	R	Ar	Yield (%)
4a	Me	Ph	86
4b	Et	Ph	87
4c	Me	4-MeOC$_6$H$_4$	81
4d	Et	4-MeOC$_6$H$_4$	89

Scheme 2 *Reagents and conditions*: i, HCl, EtOH, reflux, 7 h.



Scheme 3 *Reagents and conditions*: i, AcONa, H_2O, room temperature, 30 min.

The synthesized salts of nitro ketones can be used as well for the preparation of α-nitro-α-phenylhydrazono ketones **5a**,**b** (Scheme 3) upon treatment with phenyldiazonium chloride. The obtained compounds **5a**,**b** were identical to those described.[29]

In summary, a new safe and efficient synthesis of sodium or potassium salts of α-nitro ketones has been developed. These salts can be used in the reactions known for free unstable α-nitro ketones. The results obtained can promote the intensive use of nitro ketones for the synthesis of promising organic compounds. As an example, due to the high rate of hydrolysis of 2-morpholino-1-nitroalkenes, the freshly prepared solutions of α-nitro ketone salts can be used *in situ* for azo coupling reactions, however, the presence of morpholine as the hydrolysis product should be taken into account.

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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.2020.03.015.

= 0.0644, wR_2 = 0.1666 [$I > 2\sigma(I)$], GOOF = 1.002. Largest diff. peak/hole 0.424 and –0.195 e Å^{-3}.

Crystal data for **4b**. $C_{12}H_{13}N_3O_3$ (M = 247.25), space group $P2_1$, a = 7.2666(11), b = 29.257(3) and c = 11.8861(17) Å, β = 103.296(14)°, V = 2459.3(6) Å^3, Z = 8, μ(MoKα) = 0.098 mm^{-1}. At the angles 3.56° < 2θ < 28.28°, total of 16126 reflections were measured, uncluding 6170 unique reflections (R_{int} = 0.0549) and 3059 reflections with $I > 2\sigma(I)$, which were used in all calculations. The final R_1 = 0.1429, wR_2 = 0.2248 (all data) and R_1 = 0.0699, wR_2 = 0.1685 [$I > 2\sigma(I)$], GOOF = 1.005. Largest diff. peak/hole 0.275 and –0.239 e Å^{-3}.

The XRD analysis was accomplished on an Xcalibur 3 diffractometer using standard procedure [MoKα-irradiation, graphite monochromator, λ = 0.71073 Å, ω-scans with 1° step, 295(2) K]. Using Olex2, the structure was solved with a ShelXS structure solution program using Direct Methods and refined using a ShelXL refinement package with the Least Squares minimization in anisotropic approximation for nonhydrogen atoms. The H-atoms were added in the calculated positions and refined using the riding model in isotropic approximation.

CCDC 1948033 and 1948034 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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