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Sonochemical Reaction of Cyanoacetamide with $Mn(OAc)_3$ and $Cu(OAc)_2$ in Presence of Alkenes: a Novel Route to α-Cyano-γ,δ-Unsaturated Amines

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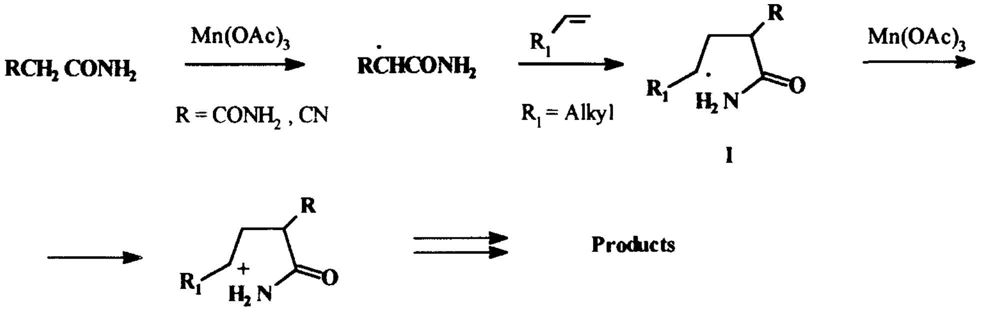
Abstract: Cyanoacetamide reacted with alkyl substituted olefins, $Mn(OAc)_3$ and $Cu(OAc)_2$ in glacial acetic acid affording γ,δ-unsaturated amides. Ultrasound irradiation caused a significant yield enhancement.

We have recently reported on the ultrasound effect on the Mn(III)-promoted lactonization of olefins with activated carboxylic acids.[1] In sonochemical conditions, α-cyano and α-carbomethoxy-γ-lactones were obtained at room temperature in good to high yields and in short reaction times from a great number of olefins. These results prompted us to investigate also the reactivity of "activated" amides (such as malonamide and cyanoacetamide) towards manganese(III) acetate dihydrate ($Mn(OAc)_3 \cdot 2H_2O$) in presence of alkenes.

Reaction of malonamide in glacial acetic acid with manganic acetate dihydrate and alkenes at high temperatures was already reported in literature.[2] In those conditions only phenyl substituted olefins reacted effectively, leading in most cases to mixtures of α,β-unsaturated γ-lactones and γ-lactams in low yields, principally due to side oxidation processes favoured by high temperatures.

Thus, to verify the sonochemical reactivity of amides at room temperature we began to study reaction of simple alkyl olefins with $Mn(OAc)_3$ and malonamide or cyanoacetamide in glacial acetic acid under high intensity ultrasound irradiation.[3]

Scheme 1



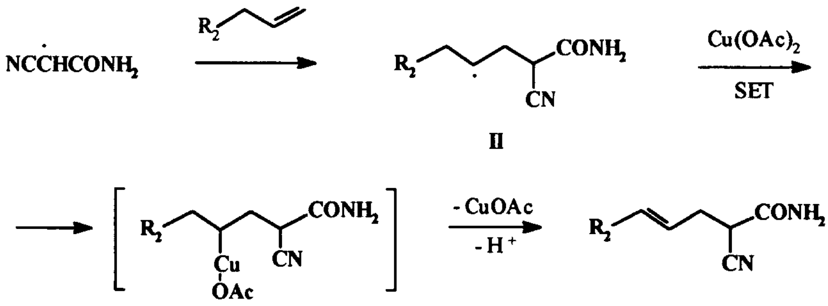
The reaction was carried out also under simple mechanical stirring at the same temperature used in the sonochemical procedure to better compare the experimental results. Alkyl olefins showed to be quite unreactive towards both amides either in sonochemical or in "silent"[4] conditions, or at best gave mixture of many products in very low yields.

An explanation of this unsatisfactory reactivity of simple alkenes could be probably found in the slowness of amidyl radicals addition to olefinic double bond and, in addition, in the scarce effectiveness of $Mn(OAc)_3$ as oxidant of intermediate **I** and the low nucleophilicity of the amidic nitrogen (see Scheme 1).

To overcome this difficulties, we added also cupric acetate to reaction mixture; in fact Cu(II) is known to be a really good oxidant of radicals "via" a single electron transfer (SET) mechanism[5a,b] and, moreover, $Cu(OAc)_2$ oxidizes secondary alkyl radicals 350 times faster than $Mn(OAc)_3$.[6]

In these conditions alkyl olefins reacted to give γ,δ-unsaturated amides as prevalent products. The formation of these unsaturated compounds was not surprising because oxidation with $Cu(OAc)_2$ in most cases proceeds through an alkylcopper as the intermediate,[7] that subsequently undergoes an elimination leading to the formation of a double bond (see Scheme 2). Cyanoacetamide showed to be more reactive than malonamide, then we chose to use exclusively the former in our research.

Scheme 2



Since ultrasonic activation is particularly strong in SET processes,[8a,b] we supposed that ultrasound irradiation could effectively stimulate both Mn(III)-promoted generation of amidyl radicals and the subsequent Cu(II)-mediated oxidation of the radical adduct **II**.

As expected, reactions carried out under ultrasound irradiation showed a significant yield enhancement with respect to the analogous "silent" reaction and a shortening of the reaction time. α-Cyano-γ,δ-unsaturated amides were obtained in low to high yields depending upon the reactivity of the particular olefin.

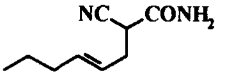
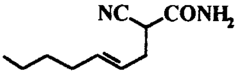
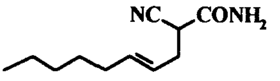
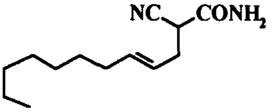
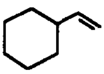
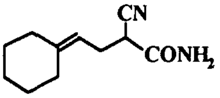
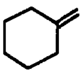
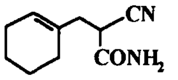
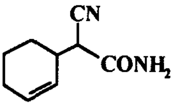
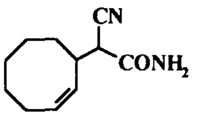
The reaction worked well on terminal acyclic olefins, while a yield lowering was observed with disubstituted or cyclic alkenes. The best yields were obtained using $Mn(OAc)_3$, $Cu(OAc)_2$, cyanoacetamide and alkene in a 2:2:4:1 molar ratio. Attempts to increase yields by prolonging the sonication time were unsuccessful.

Results obtained are summarized in Table 1.

The application of this reaction was restricted to alkyl olefins only, because enol ethers were not reactive in these conditions, and phenyl substituted olefins such as styrene did not give γ,δ-unsaturated amides, but mostly cyclization products.[9]

However, the sonochemical reaction of cyanoacetanide with simple alkenes and Mn(III)-Cu(II) seems to be a really effective method to carry out the allylation of cyanoacetamide.

Table 1. Reaction of Alkenes with Cyanoacetamide, Manganese(III) acetate and Copper(II) Acetate in Glacial Acetic Acid

Alkene	Product	Yields[a] (%) ↻[b]	Time (hr) ↻	Yields[a] (%)))))[c]	Time (hr)))))
1 - Hexene		27	4	47	4
1 - Heptene		25	4	60	2.5
1 - Octene		30	4	73	3
1 - Decene		28	5	64	2.5
		32	5	48	2
		8	4	20	3
Cyclohexene		11	4	21	4
Cyclooctene		30	4	40	4

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a) All reported yields refer to chromatographically isolated, pure products; b) this simbol indicates "silent" reactions; c) this simbol indicates ultrasonic reactions.

In a typical experimental procedure, 2.0 mmoles of alkene and 8.0 mmoles of cyanoacetamide (672 mg) were placed in a cylindrical vessel (h 16 cm, ϕ 3.5 cm) containing 30 ml of glacial acetic acid under an argon atmosphere; then, 4.0 mmoles of manganic acetate dihydrate (1.07 g) were added together with 4.0 mmoles of $Cu(OAc)_2$ monohydrate (0.8 g). A portion of the titanium microtip (1 cm) of ultrasonic transducer was plunged into the mixture and the reaction was sonicated (ultrasound intensity of 180-210 W/cm^2) for several hours at room temperature, until conversion of the alkene stopped (in the "silent" procedure the same reaction mixture was kept under stirring at room temperature under an argon athmosphere). The reaction mixture was subsequently poured into water (100 ml), and then extracted with CH_2Cl_2 (3x50 ml). The organic phase was washed with a $NaHCO_3$ saturated solution to remove acetic acid, then with water, and finally dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure afforded in most cases a solid residue which was chromatographed on silica gel column eluted with CH_2Cl_2 or CH_2Cl_2/Et_2O mixtures to afford pure γ,δ-unsaturated amide.

This procedure could represent the method of choice to carry out the allylation of activated primary and secondary amides, that is really difficult to carry out with "ionic" reactions. Moreover, our results confirm the strong activating effect exerted by ultrasound in transition metal-promoted oxidations of enolizable compounds in glacial acetic acid.[1]

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2. Nishino, H. *Bull.Chem. Soc. Jpn.*, 1985, **58**, 217-222.
3. Sonochemical experiments were carried out in a Vibracell 600 Watt Probe transducer equiped with a titanium microtip (ϕ 6.5mm) directly connected to the horn operating between 180-300 W/cm^2.
4. In this paper we currently define "silent" those reactions carried out under simple mechanical stirring at the same temperature adopted in sonochemical procedure.
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