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Clay-catalyzed Conversion of 2,2-Disubstituted Malononitriles to 2-Oxazolines[†]: Towards Unnatural Amino Acids

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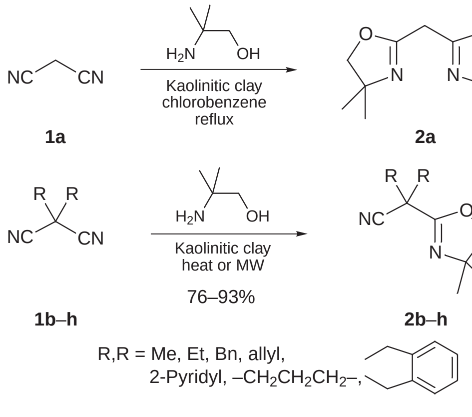
Acidic clay catalyzed reaction of malononitrile derivatives with an excess of 1,2-aminoalcohol furnishes mono-oxazolines selectively; a simple strategy to prepare 2,2-dialkyl-3-aminopropionic acid derivatives is presented.

Heterogeneous catalysis of organic reactions by various inorganic solids has gained importance in recent years.[1] These materials are inexpensive, environmentally friendly, easily recoverable, reusable and often show good selectivity.

Racemic and chiral oxazolines are an important class of compounds in synthetic organic chemistry as they form a versatile class of protecting group[8] and a valuable chiral auxiliary in asymmetric synthesis.[9] We have recently reported[5] a kaolinitic clay catalyzed efficient conversion of nitriles to 2-oxazolines.

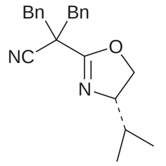
The reaction of malononitrile with an excess of 1,2-aminoalcohol under the catalytic action of kaolinitic clay furnished the bis-oxazoline in high yield[5] (Scheme A). With an aim to prepare chiral bis-oxazolines a series of disubstituted malononitrile derivatives, **1b**–**h** was exposed with excess of 1,2-aminoalcohol in the presence of kaolonitic clay. It was interesting to note the formation of only the mono-oxazoline even under strong reaction conditions and higher quantities of the catalyst.



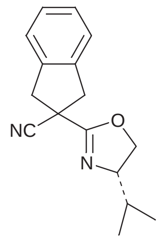
Scheme A

The same transformation was also investigated with commercially available montmorillonite K10 clay as the catalyst. We observed the selective formation of mono-oxazoline with this catalyst as well, with equal efficiency. The reaction was further studied under more powerful microwave irradiation where too we could observe the same pattern. The formation of the mono-oxazoline in all these cases could be due to the steric hindrance of the neopentyl-type center of the disubstituted malononitrile derivatives, as has also been observed by Davies *et al.*[11] However, in their synthesis a mixture of mono- and bis-bisoxazolines was formed compared to our protocol which is very selective.

Optically active mono-oxazolines **2i** and **2j** have been synthesized from the corresponding malononitrile derivatives and L-valinol using kaolinitic clay as the catalyst.

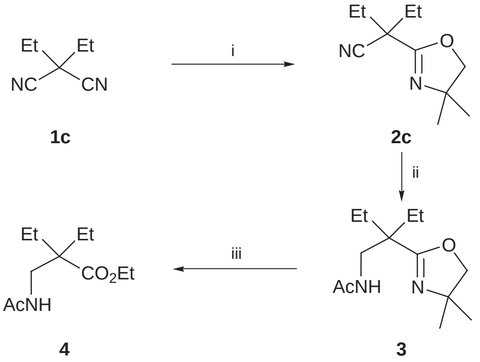


2i



2j

Non-α-amino acids constitute an important part of unnatural amino acids and their chemistry has been reviewed recently.[12] We wish to present a simple strategy for the general synthesis of 2,2-dialkyl-3-aminopropionic acids as an extension of the present finding (Scheme B). This type of compound has been used[13] as intermediates to β-lactams and other biologically useful compounds. We have synthesized the protected 2,2-diethyl-3-aminopropionic acid **4** as an example starting from 2,2-diethylmalononitrile **1c**.



Scheme B *Reagents and conditions*: i, 2-amino-2-methylpropan-1-ol, kaolinitic clay, 160–165 °C, 90%; ii, Raney Ni, Ac_2O, NaOAc, 50 psi, r.t., 80%; iii, H_2SO_4, EtOH, reflux, 55%.

In conclusion we have presented our findings on the natural kaolinitic clay catalyzed selective conversion of dialkylmalononitriles to mono-oxazolines and its application towards the synthesis of unnatural amino acids.

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Techniques used: ^{1}H NMR, MS, IR, microwave irradiation

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[†] IUPAC-recommended name: 4,5-dihydro-1,3-oxazoles.

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Table 1: Conversion of malononitriles to 2-oxazolines (10 examples)

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