

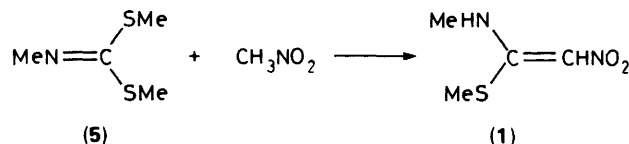
## Zeolites in Organic Syntheses: A Novel Route to Functionalised Ketene *S,N*-Acetals

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Active methylene compounds react with bis(methylthio)alkaneimines in the presence of a zeolite catalyst to give functionalised ketene *S,N*-acetals in good yields.

Ranitidine, a H<sub>2</sub>-receptor antagonist,<sup>1</sup> is a powerful inhibitor of gastric acid secretion and is extensively used in peptic ulcer therapy. 1-Methylamino-1-methylthio-2-nitroethylene (1) is an important intermediate in the synthesis of ranitidine.<sup>2</sup> The reported method for the preparation of (1) involves amination of 1,1-bismethylthio-2-nitroethylene (2) or of the corresponding monosulphoxide (3) with methylamine.<sup>2,3</sup> The sequence thus involves in essence the combination of nitromethane with carbon disulphide first, followed by displacement of one of the sulphur atoms by methylamine. A serious drawback in this method is the formation of 1,1-bismethylamino-2-nitroethylene (4), by further reaction of (1) with a second molecule of methylamine.

We were looking for a viable alternative method for the preparation of (1). Specifically, we were interested in a synthetic route in which the highly nucleophilic methylamine is given no chance to displace both the methylthio groups of the substrate. In principle, the reaction of nitromethane with bis(methylthio)methaneimine (5) (prepared from methylamine and carbon disulphide, followed by methylation) can directly lead to the desired compound (1) (Scheme). The reaction of highly active methylene compounds such as malononitrile with (5) has been reported in the literature.<sup>4</sup> However, reaction of nitromethane with (5) under similar conditions failed to give the desired product (1). The reaction could not be induced to proceed in the desired sense, either by base catalysis (DBU, Et<sub>3</sub>N, K<sub>2</sub>CO<sub>3</sub> in DMSO, NaH, *etc.*) or by acid catalysis (toluene-*p*-sulphonic acid, BF<sub>3</sub>·OEt<sub>2</sub>, ZnCl<sub>2</sub>, *etc.*).



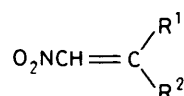
We report here, for the first time, the use of zeolite catalysts in the reaction of nitromethane and other active methylene compounds with bis(methylthio)methaneimine (5), leading to the functionalised ketene *S,N*-acetals (1), (6), (7), (8), and (9).

The reaction of methylamine with carbon disulphide in the presence of aqueous sodium hydroxide and a phase transfer catalyst, *e.g.* tetrabutylammonium bromide, followed by methylation with dimethyl sulphate afforded compound (5)<sup>5</sup> (90%). This ester (5) was refluxed with an excess nitromethane in

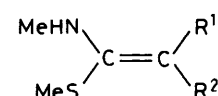
**Table.** Reaction of the active methylene compound with (5) in the presence of zeolite (rare earth exchanged NaY)

Expt. no.	Active methylene compound used <sup>a</sup>	Product <sup>b</sup>	Yield <sup>c</sup> (%)	M.p. (°C)
1	Nitromethane	(1)	50	113
2	Ethyl cyanoacetate	(6) <sup>d</sup>	85	93
3	Acetyl acetone	(7) <sup>e,9</sup>	70	65
4	Meldrum's acid	(8)	78	119
5	Dimedone	(9)	60	142

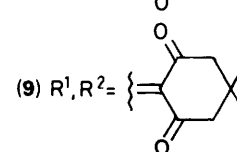
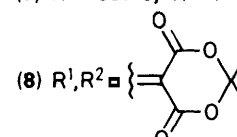
<sup>a</sup> For entry i, nitromethane was taken in excess, for all other reactions compound (5) was in excess. All reactions were carried out at 110–120 °C for 24–48 h. <sup>b</sup> All compounds were characterised by spectral data and gave satisfactory elemental analyses. <sup>c</sup> Isolated yields based on active methylene compounds used. <sup>d</sup> The reported yield for this compound (6) is 42%.<sup>4</sup> <sup>e</sup> One of the acetyl groups was removed under the reaction conditions to give (7) as the sole product.



- (2) R<sup>1</sup> = R<sup>2</sup> = SMe  
(3) R<sup>1</sup> = SMe, R<sup>2</sup> = SOMe  
(4) R<sup>1</sup> = R<sup>2</sup> = NHMe



- (6) R<sup>1</sup> = CO<sub>2</sub>Et, R<sup>2</sup> = CN  
(7) R<sup>1</sup> = COMe, R<sup>2</sup> = H



presence of a zeolite catalyst † to give 1-methylamino-1-methylthio-2-nitroethylene (1) (50%). The main advantages of this reaction are: (i) the catalyst can be recovered and re-used; (ii) the product is not contaminated with the unwanted 1,1-bismethylamino-2-nitroethylene (4); (iii) the crude product obtained is >99% pure by GC and HPLC. ‡

Other active methylene compounds have also been successfully condensed with compound (5) using the same zeolite catalyst (see Table). Some of these condensations could not be achieved without zeolite catalysts, or led to products in low yields. The nitromethane condensation could be extended to other bis(methylthio)alkaneimine; thus, for instance, 1-amino-2-propane could be condensed with carbon disulphide, methylated, and the resulting bis(methylthio)propaneimine treated

† Several catalysts such as ZSM-5, H ZSM-5, CaY, NaY, rare earth exchanged NaY, NaX were tried. Among these rare earth exchanged (70%) NaY and CaY were found to be the most suitable for this reaction.

‡ GC: Column OV-101, oven temp. 188 °C, N<sub>2</sub>, 30 ml/min., *t*<sub>r</sub> 2.8–3.2 min.; HPLC: column C-18, MeCN–H<sub>2</sub>O (2:3), UV 313 nm.

with nitromethane in the presence of zeolite to form 1-methylthio-1-propylamino-2-nitroethylene (m.p. 63–64 °C; yield, 24%). The reaction however failed in those cases where the N-substituent was 4-methoxyphenyl, benzyl, or t-butyl. Obviously the size of the cavity in the zeolite would be the limiting factor in defining the scope of the reaction.

Zeolites as catalysts<sup>7,8</sup> have received increasing attention in recent years, and the present example confirms that their special properties (acidity, cavity size, presence of other metal ions) have advantages in synthesis.

### Experimental

The zeolite of the faujasite group (with  $\text{SiO}_2/\text{Al}_2\text{O}_3 \approx 4.6$ ) was ion exchanged by treating it with a 5% (w/v) aqueous solution (pH  $\approx 5.0$ ) of a commercial rare-earth chloride (a mixture of lighter rare earths like La, Pr, Sm along with heavier ones, obtained from M/s Indian Rare Earths Ltd., Kerala) at 95 °C for 4 h. The ion-exchange treatment was repeated till the required concentration of rare-earth in the zeolite was reached (ca. 70% rare-earth exchanged based on the sodium content). The exchanged zeolite was thoroughly washed with water to free it from any occluded rare-earth chloride. It was then dried at 110 °C for 4 h. Prior to the catalytic run, the catalyst was activated at 400 °C for 4 h and cooled *in vacuo*.

A mixture of compound (5) (2 g), nitromethane (4 ml), and the above zeolite (1 g) was stirred under reflux for 48 h, cooled, and the catalyst filtered off. The filtrate was evaporated under reduced pressure and the residual solid recrystallised from

ethanol to yield 1-methylamino-1-methylthio-2-nitroethylene (0.9 g), m.p. 112–113 °C.

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