

IN SITU GENERATION OF DIAZOMETHANE

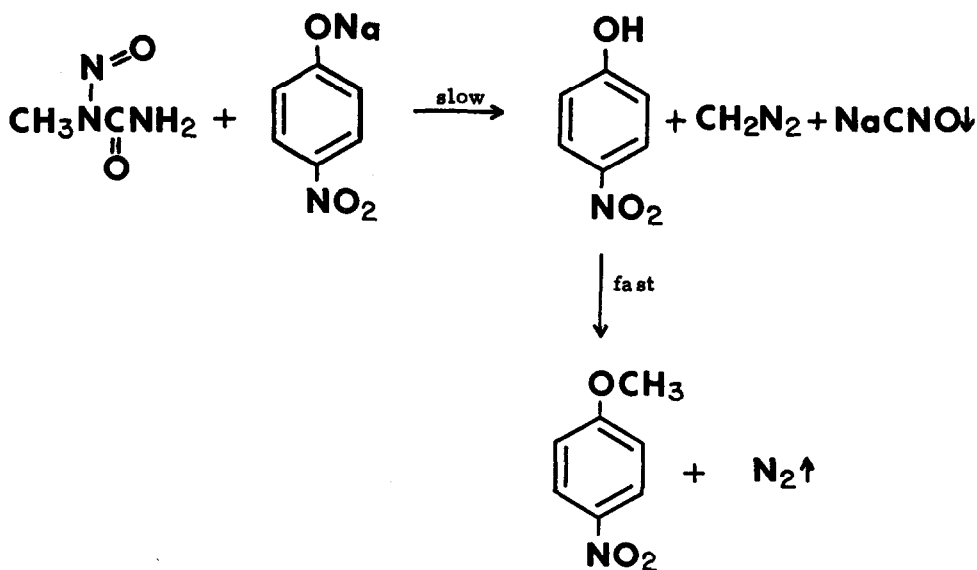
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(Received in USA 29 January 1973; received in UK for publication 13 March 1973)

Diazomethane is toxic, prone to cause the development of specific sensitivity and potentially explosive. Recommended precautions during its utilization include the use of heavy gloves and goggles, a safety shield and fire-polished glassware, and the avoidance of ground glass equipment, sharp surfaces, or exposure to strong light.¹ In spite of the considerable inconvenience associated with its utilization, especially with regard to large scale preparations, CH_2N_2 is the reagent of choice for many organic transformations. A few methods are available for the in situ generation of CH_2N_2 ,^{2,3} although these typically require attention to the rate of generation of the reagent and afford by-products in the reaction mixture. We report here on a convenient method for the in situ generation of diazomethane at a moderate rate, thus obviating the need for its presence in appreciable concentration during the course of methylation.

The generation of diazomethane from N-nitroso-N-methylurea by the action of potassium hydroxide solution affords CH_2N_2 contaminated only by potassium cyanate.⁴ During the course of a study on the utilization of diazomethane,^{5,6} it became apparent that a wide variety of bases and solvents could equally as well be employed in its generation from N-nitroso-N-methylurea. In particular for compounds of moderate pKa, such as p-nitrophenol, it was found that the conjugate base of the acid to be methylated could itself effect the decomposition of the urea. Thus sodium p-nitrophenolate was used to decompose N-nitrosomethylurea, generating diazomethane, sodium cyanate and p-nitrophenol. The phenol immediately reacted with CH_2N_2 to form the desired product. Since the generation of diazomethane was the slow step, no appreciable concentration of this species was present during the course of the methylation. Experi-



mentally, the procedure involved stirring a suspension of sodium *p*-nitrophenolate (5 mmoles) and *N*-nitroso-*N*-methylurea (5 mmoles) in 25 ml of 1,2-dimethoxyethane for 1 hr at 0°C, then for 6 hr at room temperature. Filtration of the cyanate, followed by workup of the solution, afforded *p*-nitroanisole in 90+% yield, mp 52-53°. Similar results were obtained with sodium *m*-nitrophenolate. More acidic compounds, such as *p*-nitrobenzoic acid, were methylated starting from the protonated species by inclusion in the reaction mixture of triethylamine. Thus a stirred suspension of *p*-nitrobenzoic acid (5 mmoles), triethylamine (15 mmoles) and *N*-nitroso-*N*-methylurea (15 mmoles) in 25 ml of 1,2-dimethoxyethane was stirred at 0° for 1 hr, then at room temperature for 6 hr. Workup afforded methyl-*p*-nitrobenzoate in quantitative yield, mp 93-95°.

The methylations were also effected by the *in situ* generation of diazomethane in aqueous media. This permitted the methylation in good yield of very polar compounds such as guanosine,² without prior blocking of the reactants to increase solubility in the reaction medium, and without the vigorous agitation often required for reactions in two-phase systems. The procedure involved the generation of diazomethane from *N*-nitrosomethylurea in a 1,2-dimethoxyethane-water solution by the dropwise addition of a solution of potassium hydroxide. The reactant was present in the *N*-nitroso-*N*-

methylurea solution and reacted with diazomethane (liberating nitrogen) as the latter was formed. Therefore, no significant concentration of diazomethane was ever achieved. Although the diazomethane also reacted with the aqueous phase, which was present in considerable molar excess relative to the intended reactant, the much lower pKa of the compound to be methylated, as compared with that of water, facilitated its methylation. The only side product formed in the reaction, aside from methanol, was potassium cyanate. This was conveniently separated from the desired product by extraction of the latter into an organic solvent or by treatment of the aqueous solution containing the product and KCNO with a cation exchange resin (H⁺ form) which resulted in the generation of CO₂ and NH₃ from the cyanate.

In a typical experiment, p-nitrobenzoic acid (6 mmoles) and N-nitrosomethylurea (24 mmoles) were dissolved in 25 ml of 1,2-dimethoxyethane-water (5:1). The solution was maintained at ice bath temperature and treated dropwise with a potassium hydroxide solution (40 ml, 0.6 N). The solution was concentrated under diminished pressure and the aqueous solution was extracted with ether. The ether layer was dried (MgSO₄) and evaporated to afford methyl p-nitrobenzoate. Acidification of the aqueous layer afforded unreacted starting material. The yield of methyl p-nitrobenzoate was 0.77 g (74% conversion, 97% yield based on recovered starting material). Similar results were obtained with m-nitrobenzoic acid.

The utilization of this technique with compounds of higher pKa resulted, as expected, in negligible levels of methylation due to inefficient competition of these species for diazomethane in the presence of the large molar excess of water. Mixtures of p-nitrobenzoic acid and p-nitrophenol, e. g., were methylated in aqueous solution largely to afford the ester of the carboxylic acid regardless of the amount of diazomethane utilized, suggesting the possible utility of this procedure in selective methylations. Although selective methylations may be achieved at present by the use of a precisely measured amount of diazomethane in a non-aqueous medium, the need for such measurement in aqueous solution is eliminated by the competition for CH₂N₂ by each of the reactive groups and water.

ACKNOWLEDGEMENT

We thank the National Science Foundation (GB-31212) for financial support of this work.

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