Tetrahedron Letters,Vol.23,No.27,pp 2789-2792,1982 0040-4039/82/272789-04$03.00/0
Printed in Great Britain

# NITROETHYLENE: NITROETHYLATION OF AMINES

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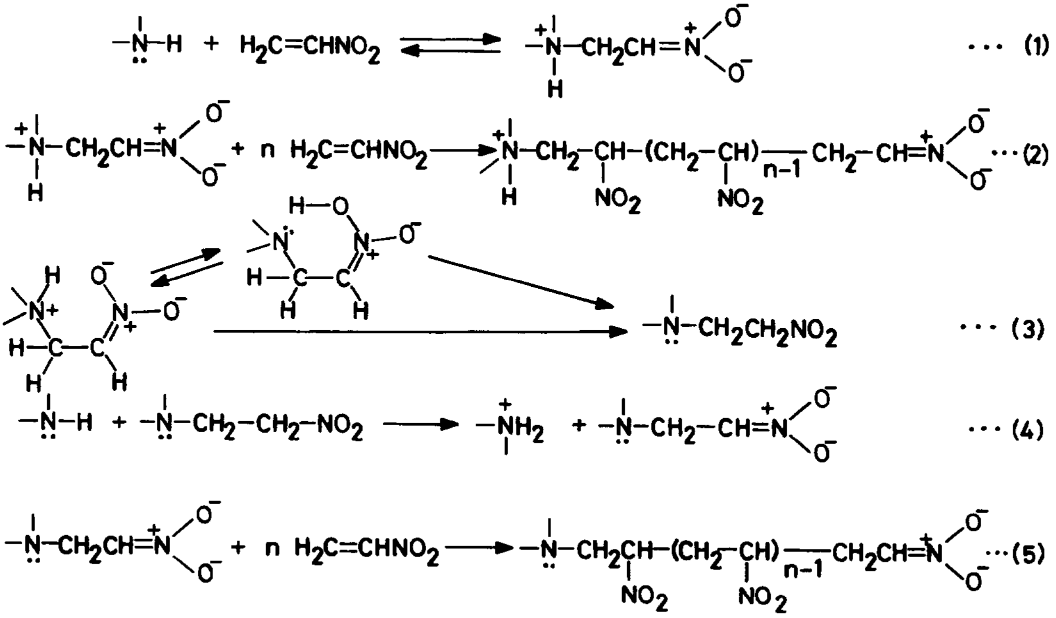
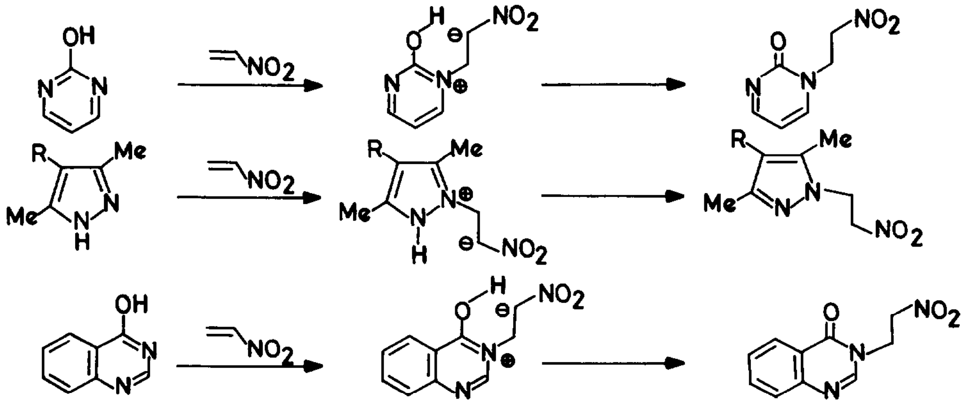
ABSTRACT: The nitroethylation of amines is demonstrated to be a general reaction for bases in the $pK_a$ range of 2 - 8 and that it proceeds through a key intra-molecular quenching step. The reaction, illustrated with aromatic amines, aliphatic amines and heterocyclic bases, offers inter alia attractive routes to diverse heterocyclic systems.

We have recently shown that nitroethylene can be readily prepared, stored and handled and that it is a reagent of promise[1]. This communication demonstrates that the nitroethylation of amines, namely, $-\overset{|}{N}-H + H_2C{=}CHNO_2 \longrightarrow -\overset{|}{\underset{..}{N}}-CH_2CH_2NO_2$ change, is a reaction of great utility in the synthesis of a variety of synthons. A novel and surprising feature of this reaction is that it is effective with nitrogen bases only in the 2-8 $pK_a$ range (CHART I, II & III) with best yields around $pK_a$ 5-6. Whilst the failure of amines of lower $pK_a$ can be understood on the basis of low basicity, the absence of adducts with amines of higher $pK_a$ is now rationalized, on the basis of events outlined below:



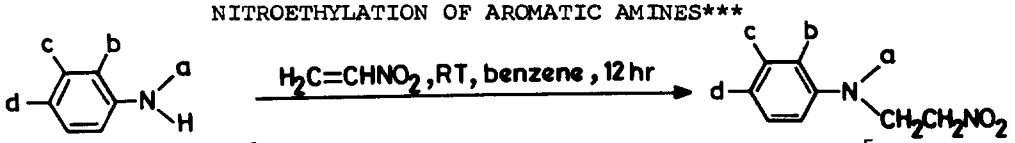
In the case of amines of $pK_a$ lower than 2, the reaction is not observed because of equation 1. We propose that nitroethylation results in cases where the initially formed zwitter ionic compound (equation 1) undergoes effective intramolecular self-quenching (equation 3). The absence of nitroethylation of amines of $pK_a$ higher than 8, could be due to factors that promote the polymerization of the initially formed zwitter ion (equations 2,4+5)[2], since in these cases the nitroethylation (equation 3) is not important because of the weakly acidic nature of the adduct. That the polymerization is initiated by the nitrogen base in evident from the fact that the polymers invariably incorporated the base (IR). Good support for the intra-molecular quenching step (equation 3) has been obtained from nitroethylation studies with heterocyclic nitrogen bases. Pyridine, inspite of favourable $pK_a$, gave, with nitroethylene, in protic and aprotic media, only polymers. In this case, the initially formed intermediate (equation 1) lacking opportunity for intramolecular neutralization, undergoes polymerization, in preference to proton abstraction from solvent. Further, pyrazoles having opportunity for intramolecular proton transfer (equation 3) underwent smooth nitroethylation, in sharp contrast to imidazole, which, although having favourable $pK_a$, as is the case with pyrazole, but not the opportunity for intra-molecular quenching, gave, under various conditions, only polymers[7]. The synthetic utility of this novel facet of nitroethylation has been illustrated with the smooth nitroethylation of the unusual substrates, 2-hydroxypyrimidine and 4-hydroxyquinazoline, leading to products of exceptional synthetic potential(CHART III).



CHARTS I, II & III summarize data from a number of experiments.[3] The results, <u>inter alia</u>, repeatedly demonstrate the correlation between $pK_a$ and nitroethylation and therefore this reaction could be tried with confidence in other substrates as well. The wide spectrum of products presented in CHART I, II & III each of which could be further structured in a variety of ways, with or without retaining the nitro function, coupled with the criterion in terms of $pK_a$, should make nitroethylation of amines an important reaction.[4,5]

## CHART I

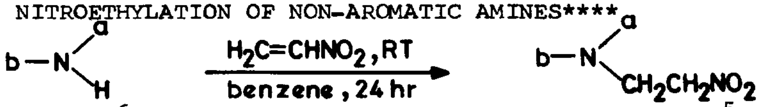
## NITROETHYLATION OF AROMATIC AMINES***



| No. | a | b | c | d | $pK_a^6$ | Yld (%) | mp/bp (°C) | No. | a | b | c | d | $pK_a^6$ | Yld | mp/bp (°C) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | 4.60 | 90 | 37 | 13 | H | H | H | Br | 3.86 | 83 | 51 |
| 2 | Me | H | H | H | 4.85 | 96 | 155/3mm | 14 | H | $NO_2$ | H | H | -0.26 | 0 | - |
| 3 | Ph | H | H | H | 0.85 | 0 | - | 15 | H | H | $NO_2$ | H | 2.47 | 45 | 75 |
| 4 | H | Me | H | H | 4.45 | 94 | syrup | 16 | H | H | H | $NO_2$ | 1.11 | 0 | - |
| 5 | H | H | Me | H | 4.72 | 93 | 37 | 17 | H | COOMe | H | H | 2.23 | 72 | 85 |
| 6 | H | H | H | Me | 5.10 | 90 | 83 | 18 | H | $NH_2$ | H | H | 4.47 | 60 | 97 |
| 7 | H | OMe | H | H | 4.52 | 85 | 35 | 19 | H | H | $NH_2$ | H | 4.98 | 50 | 60 |
| 8 | H | OEt | H | H | 4.47 | 86 | 38 | 20 | H | H | H | $NH_2$ | 6.16 | 74 | 131 |
| 9 | H | Cl | H | H | 2.64 | 30 | syrup | 21 | H | H | H | $ArNH_2$ | 4.89 | 60 | 177 |
| 10 | H | H | Cl | H | 3.50 | 70 | 150/3mm | 22 | H | $-C_4H_4$ | - | H | 3.92 | 74 | 71 |
| 11 | H | H | H | Cl | 3.98 | 85 | 70 | 23 | H | H | $-C_4H_4-$ | | 4.16 | 66 | 87 |
| 12 | H | H | H | F | 4.60 | 97 | 140/2mm | 24 | H | $-COC_6H_4CO-$ | | H | 2.0 | 20 | 193 |

## CHART II

## NITROETHYLATION OF NON-AROMATIC AMINES****



| No. | a | b | $pK_a^6$ | Yld (%) | mp/bp (°C) | No. | a | b | $pK_a^6$ | Yld (%) | mp/bp (°C) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | H | $H_2NCS$ | -1.0 | 0 | - | 32 | H | $Me_2CHCH_2CHE$ | 7.57 | 96 | 120/.1mm |
| 26 | H | $H_2NCO$ | 0.18 | 0 | - | 33 | H | Indolyl-$CH_2CHE$ | 7.35 | 55 | syrup |
| 27 | $CO-(CH_2)_5$ | | 0.3 | 0 | - | 34 | $CH_2-(CH_2)_2-CHE$ | | 8.5 | 49 | syrup |
| 28 | $CH_2-(CH_2)_4$ | | 10.98 | P | - | 35 | H | $Ph-CH_2$ | 9.35 | P | - |
| 29 | H | $E-CH_2$ | 7.59 | 59 | 70 | 36 | H | $H_2N-(CH_2)_6$ | 10.93 | P | - |
| 30 | H | $CN-CH_2$ | 5.34 | 90 | 90/.3mm | 37 | H | $C_6H_{11}$ | 11.1 | P | - |
| 31 | H | $MeSCH_2CH_2CHE$ | 7.33 | 46 | 110/.1mm | 38 | $C_5H_9$ | $C_5H_9$ | 11.0 | P | - |

## CHART III

## NITROETHYLATION OF HETEROCYCLIC BASES****

| No. | Base | $pK_a^6$ | Yld (%) | mp/bp (°C) | No. | Base | $pK_a^6$ | Yld (%) | mp/bp (°C) |
|---|---|---|---|---|---|---|---|---|---|
| 39 | 2-OH-pyrimidine | 2.15,9.2 | 66 | 185 | 42 | 4-OH-quinazoline | 2,9.8 | 95 | 118 |
| 40 | 3,5-$(Me)_2$pyrazole | 4.38,12 | 96 | 110/.4 mm | 43 | Imidazole | 7.14.5 | P | - |
| 41 | 3,4,5$(Me)_3$pyrazole | 5.1,13 | 98 | 35 | 44 | 8-OH-quinoline | 5,9.8 | P | - |

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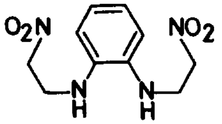
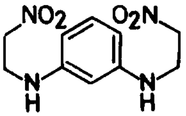
*** All compounds gave analytical results in excellent agreement with that anticipated; the nitroethylated products exhibited typical IR: $\nu_{max}$(3300(NH), 1530, 1360($NO_2$)cm$^{-1}$) and NMR $\delta$(4.5(t,$-CH_2-NO_2$),3.8(m,$-NH-CH_2$)). All adducts are brightly coloured because of charge transfer interactions involving the aromatic system (Nos. 8-orange, 13-red, 20-green, all others yellow).

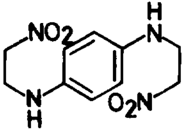
Nos. 18 to 21 gave the bis-adducts, namely,



18



19



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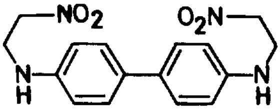

21

Nos. 21:benzidine, 22:α naphthylamine, 23: β naphthylamine, 24· 1-amino-anthraquinone

**** P=Polymer; 27: caprolactam; 28: piperidine; Nos. 29,31,32,33 and 34 (E=COOMe) from D. Ranganathan, S. Ranganathan, C.B. Rao and K. Kesavan, Synthesis, 885(1980); Yields based on hydrochloride. For 29. bis-adduct: 46%, mono-adduct: 13%. For 33: bis-adduct: 13%, mono-adduct: 42%. No.30: $H_2NCH_2CN$, preparation: A.H. Cook, I. Heilbron and A.L. Levy, J. Chem. Soc., 201(1948); analysis, IR and NMR as in ***.

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2. The rapid hydroxide (trace) mediated polymerization of nitroethylene is initiated by nitronate.

3. In a typical nitroethylation experiment, 10 mmoles of nitroethylene as a 10% solution in dry benzene is added, in drops, to a stirred and cooled (~10°) solution of 10 mmoles of the amine in ~ 50 ml of dry benzene. The reaction mixture is left stirred for 12 hr, solvents evaporated and the residue chromatographed over a short column of silica gel. Elution with benzene followed by evaporation of solvents gave the nitroethylated product, which was crystallized or distilled.

4. The importance of nitroethylation of amines was recognized as early as 1919 by Wieland and Sakellarios (Ber., 52, 898 (1919). However theirs and subsequent commendable endeavours by Heath and Rose (J. Chem. Soc., 1486 (1947), Bachman and Welton (J. Org. Chem., 12, 208 (1947) and Hopff and Copaul (Helv. Chim. Acta, 43, 1898 (1960), failed to attract notice, most probably because either nitroethylene was presumed as an intermediate or the conditions for its generation unacceptably harsh.

5. We are grateful to Dr. Popli, CDRI, Lucknow, Professor T.R. Govindachari, Amrutanjan Research Institute, Madras and Dr. S. Rajappa, CIBA-Geigy, Bombay for spectral facilities. We thank UGC for financial support.

6. a. D.D. Perrin, "Dissociation constants of organic bases in aqueous solution", Butterworths, 1965; b. E.M. Arnett, "Progress in Physical Organic Chemistry", Vol. I, p. 223, 1963, c. J.W. Smith, "The Chemistry of the Amino Group", Ed. S. Patai, Interscience, 1968, p.182, d. P.A.S. Smith, "Open Chain Nitrogen Compounds", Benjamin, 1965, p.89, 123; The $pK_a$ for Nos. 24, 31, 34, 38 and 41 are estimated values.

7. We are most grateful to the referee for these suggestions.

(Received in UK 23 April 1982)