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A NITROGEN-NITROGEN INTRAMOLECULAR AROMATIC SUBSTITUTION REACTION

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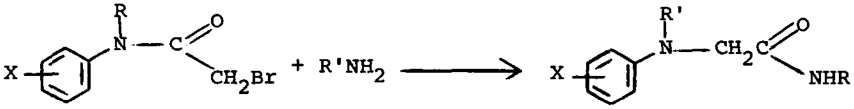
We wish to report on a new reaction of 2-bromoacetanilides with amines which leads to an intramolecular nucleophilic aromatic rearrangement.



X = *o*- or *p*-electron withdrawing group

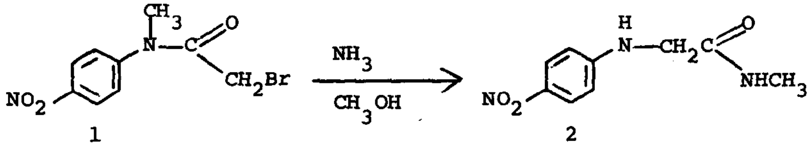
In a formal sense, this reaction represents a nucleophilic displacement of an amide group from an aromatic ring by an amine. The reaction shown above was found to be very general for various substrates and a large number of primary amines. The main requirement for inducement of the rearrangement was that the aromatic ring had to be activated by an electron-withdrawing group in the ortho or para position, preferably a nitro function.

Aromatic rearrangements which result in the migration of an aromatic system from one hetero atom to another belong to a class of reactions known as the Smiles rearrangement.[1]

X,Y = heteroatoms

Although most of the early work on the Smiles rearrangement dealt with cases in which X was a sulfone group and Y was an oxygen or nitrogen atom, and two carbon bridge was an aromatic ring, further investigations have shown that other heteroatom combinations are possible for X and Y.[1a,2,3,4,5] However, few examples have been reported for the case in which the bridge is acyclic.[6] In addition, to date, no examples of a nitrogen-nitrogen displacement have been reported. The reaction of 2-bromoacetanilides with amines represents a novel extension of the Smiles rearrangement.

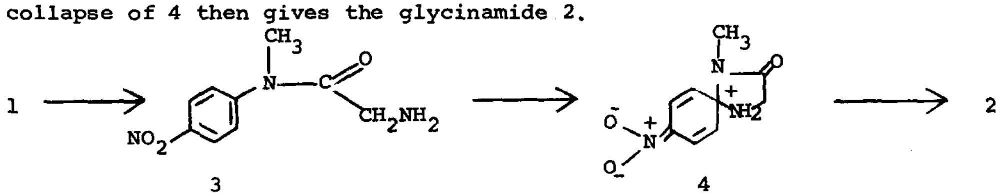
The reaction of 2-bromo-4'-nitro-N-methylacetanilide (1)[7] with methanolic ammonia, at room temperature for 18 hours, led to a 68% yield of the rearranged glycinamide (2).[8]



1 2

The assignment of the rearranged structure 2 was based on the nmr data[9] (N-methyl, 160 cps, doublet, J = 5Hz; methylene 229 cps, doublet, J = 6Hz; N-H, 443 cps, broad triplet, J = 6Hz), and on the acid hydrolysis of 2 which led to N-(4-nitrophenyl)glycine, a known compound.[10] The utilization of primary amines instead of ammonia also led to rearranged products.[11]

In analogy with the widely accepted addition-elimination mechanism for the Smiles rearrangement,[12,13] the formation of 2 must involve the S_N2 displacement of bromide by ammonia to give 3 followed by a nucleophilic attack on the aromatic ring leading to the intermediate 4. The collapse of 4 then gives the glycinamide 2.



3 4

In order to show that 3 could be an intermediate in the rearrangement, the corresponding phthalimido compound[14] was prepared and treated with hydrazine. By this procedure, the only product isolated (75% yield) was the rearranged compound 2, indicating that the intermediate 3 rearranges rapidly, presumably through 4.[15]

Further work to determine the synthetic utility and mechanistic details of this novel rearrangement are in progress.

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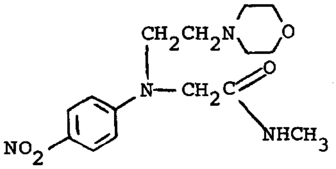
8. All new compounds gave satisfactory elemental analysis and spectral data (ir, nmr, mass spec). Yields reported are for purified products.
9. Nmr spectra were obtained in $DMSO_{d-6}$ at 60 Mhz.
10. L. Lantz and P. M. J. Obellianee, Bull. Soc. Chim. Fr., 311 (1956).
11. For example, the reaction of methylamine, allylamine, cyclohexylamine and N^1, N^1-dimethylethylene diamine with 1 all lead to clean rearrangements in high yields.
12. J. F. Bunnett, Quart. Rev., **12**, 1 (1958).
13. F. Pietra, ibid., **23**, 504 (1969).
14. Prepared by reacting 1 with potassium phthalimide in dimethylformamide.

15. In addition, the reaction of 1 with β-morpholinoethylamine in a non-polar solvent led to the isolation of the S_N2 displacement product, which, in a separate reaction, could be rearranged to



in 90% yield in methanol. The reaction was catalyzed by the presence of triethylamine.