Direct Amination of Nitrobenzenes by Vicarious Nucleophilic Substitution

Summary: 4-Amino-1,2,4-triazole reacts at 25 °C with nitrobenzene and some substituted nitrobenzenes in the presence of potassium *tert*-butoxide in Me_2SO to give 4-nitroanilines in good yields. The reaction represents an extension of Makosza's vicarious substitution to a convenient nitrogen nucleophile.

Sir: Few methods have been reported for the direct amination of nitrobenzene, and these are of limited applicability, proceed with poor yields, and/or involve inconvenient techniques. Thus, nitrobenzene can be aminated photochemically in liquid ammonia to give 30% of *p*-nitroaniline.[1] Treatment of nitrobenzene with hydroxylamine-*O*-sulfonic acid gave *m*-nitroaniline (1% yield).[2] Hydrazoic acid in the presence of $AlCl_3$ or sulfuric acid aminates some aromatic compounds,[3] but yields are poor for nitrobenzene.[2] A German patent claims that nitrobenzene is aminated in the presence of sulfuric and acetic acids and a $FeSO_4$ catalyst,[4] and a U.S. patent claims arenes are aminated by $NH_2OH{\cdot}HCl$ or $NO{\cdot}SnCl_2$ in liquid HF.[5] Under basic conditions, 1,3-dinitrobenzene is aminated by NH_2OH[6] as are 1-[7] and 2-nitronaphthalene.[6] With sodamide in liquid ammonia, nitrobenzene gives a complex mixture;[8] Levitt and Levitt formed ca. 5% of *m*-nitroaniline by refluxing nitrobenzene with lithium amide,[9] supposedly via a benzyne intermediate. Sodium salts of some organic amines form para-substituted products, e.g., nucleophilic amination of nitrobenzene with sodium or potassium diphenylamide in liquid ammonia gives *p*-nitrotriphenylamine (up to 45% based on the amide);[10] excess nitrobenzene is required to oxidize the hydride ion.

We now report the direct amination of nitrobenzene and some 3-substituted nitrobenzenes under mild conditions to give 4-nitroanilines in fair to excellent yields.

Vicarious nucleophilic substitution of hydrogen, described by Makosza et al., is applicable to a wide variety of substituted nitroarenes[11] and some nitro-substituted heterocycles.[12,13] The reaction involves the addition of a carbanion bearing a leaving group to an aromatic ring. An intermediate Meisenheimer complex is formed which undergoes base-catalyzed β-elimination to form the substituted product.[14]

We reasoned that a suitable nitrogen nucleophile with attached leaving group might enable a similar conversion of nitrobenzenes into nitroanilines (Scheme I). As nucleophile we selected readily available 4-amino-1,2,4-triazole: the low acidity suggested the use of highly basic conditions.

Scheme I

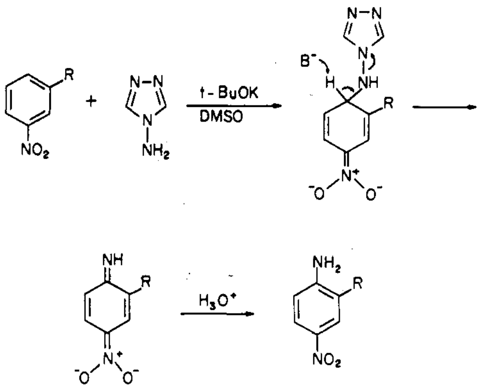

Table I. 4-Amination of 3-Substituted Nitrobenzenes

3-subst.	% yield	mp, °C	lit. mp, °C
H	58	146–148	148–149[15]
CH_3	74	130–130.5	134–135[15]
Cl	91	106.5–107	108[15]
CO_2H	60	279–280 dec	275–283 dec[16]
OCH_3	36	138.5–140	139–140[17]
F	47	133–133.5	135–136[18]
I	48	104.5–106	105[19]
CN	22	207–209	210[20]

A solution of nitrobenzene (5 mmol) and 4-amino-1,2,4-triazole (5 mmol) in Me_2SO (5 mL) was added to a solution of potassium *tert*-butoxide in Me_2SO (15 mL) over 30 min at 24–27 °C. Immediate formation of an intense yellow-brown color was observed. After 4 h at room temperature the reaction was quenched in saturated NH_4Cl (50 mL) and extracted with ether (3 × 50 mL). Evaporation of the solvent and purification of the residual yellow solid by flash chromatography (silica gel, 1:1 petroleum ether–ether) gave 4-nitroaniline in 58% yield, mp 146–148 °C (lit. mp 148–149 °C).[15] The product was recrystallized from water, giving yellow needles, mp 146–148 °C. The reaction proceeded exclusively in the 4-position with respect to the nitro group; no evidence of 2-nitroaniline was observed on examination of the crude product by TLC or NMR.

The reaction was successfully extended to several 3-substituted nitrobenzenes. In all cases they were aminated in the 4-position with respect to the nitro group, and no isomeric derivatives could be detected in the crude reaction mixtures. Results are shown in Table I; the identity of all the products were confirmed by ^1H and ^{13}C NMR spectroscopy and elemental analysis.

In summary, the feasibility of direct amination of nitrobenzenes under mild conditions and in synthetically useful yields has been demonstrated. Further studies are in progress.

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Registry No. $PhNO_2$, 98-95-3; *m*-$CH_3C_6H_4NO_2$, 99-08-1; *m*-$ClC_6H_4NO_2$, 121-73-3; *m*-$HO_2CC_6H_4NO_2$, 121-92-6; *m*-$CH_3OC_6H_4NO_2$, 555-03-3; *m*-$FC_6H_4NO_2$, 402-67-5; *m*-$IC_6H_4NO_2$, 645-00-1; *m*-$NCC_6H_4NO_2$, 619-24-9; *p*-$O_2NC_6H_4NH_2$, 100-01-6; 2-CH_3-4-$O_2NC_6H_3NH_2$, 99-52-5; 2-Cl-4-$O_2NC_6H_3NH_2$, 121-87-9; 2-H_2N-5-$O_2NC_6H_3CO_2H$, 616-79-5; 2-CH_3O-4-$O_2NC_6H_3NH_2$, 97-52-9; 2-F-4-$O_2NC_6H_3NH_2$, 369-35-7; 2-I-4-$O_2NC_6H_3NH_2$, 6293-83-0; 2-NC-4-$O_2NC_6H_3NH_2$, 17420-30-3; 4-amino-1,2,4-triazole, 584-13-4.

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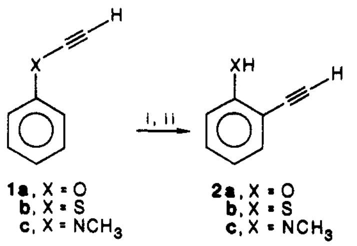
Halocarbon Chemistry. 3. Ortho Metallation-Induced Cyclization of Acetylenes: One-Flask Synthesis of 2,3-Disubstituted Benzofurans, Thianaphthenes, and Indoles

Summary: A new base-induced cyclization is described which involves the direct one-pot conversion of trifluoroethyl phenyl ethers, thioethers, and amines, in the presence of 4 equiv of alkyl- or aryllithium reagents, to 2,3-disubstituted benzofurans, thianaphthenes, and indoles, respectively.

Sir: Previously we have reported[1] an unprecedented anionic rearrangement of (aryloxy)acetylenes **1a** to the corresponding *o*-ethynylphenols **2** (Scheme I). More recently we have been able to effect the analogous reactions[2] with the corresponding sulfides **1b** and the *N*-alkylamines **1c**. However in the latter two cases the presence of a 2-bromo or a 3-methoxy group in the starting material is required to facilitate ortho deprotonation by the alkyllithium reagent. Preliminary mechanistic investigations in the case of **1a** led us to propose that the reaction proceeds by an anionic intramolecular attack of the *o*-lithio group on the lithioethynyl group. This leads to the rearranged product **2**, seemingly through an intermediate 2,3-dilithiobenzofuran. We believe that the rearrangements of the related sulfur and nitrogen compounds **1b** and **1c** proceed analogously through the 2,3-dilithiothianaphthenes and -indoles, respectively. These reactions suggested to us that a similar internal anionic attack on a disubstituted acetylene in a compound such as **4a**, might lead[3] via **4b** to anion **5**, and after quenching, to the corresponding 3-substituted and 2,3-disubstituted heterocycles (X = O, S, or NR) **6** and **7**, respectively, as shown in Scheme II. We now wish to report that investigations based on such speculation have led to the successful one-pot syntheses of benzofurans, thianaphthenes, and indoles.

In our preliminary work we selected the phenyl 2,2,2-trifluoroethyl ethers **3** (X = O) (easily prepared[4] from the sodium phenoxide and 2,2,2-trifluoroethyl tosylate) as the starting materials because of their known[4] concomitant dehalogenation and alkylation by 3 equiv of an alkyllithium (RLi) to acetylenes **4a** (X = O). We have now found that addition of a fourth equivalent of the alkyllithium reagent apparently generates anion **4b** (X = O), which cyclizes[5] to **5** (X = O), because, when the reaction mixture is proton-quenched, the corresponding 3-substituted benzofuran **6** (X = O) is obtained. Alternatively, quenching with a nonprotic electrophile (E) gives the 2,3-disubstituted benzofuran **7** (X = O).[5]

Scheme I[a]



[a] Reagents: (i) 2BuLi/THF/−78 °C to 25 °C; (ii) H_2O.

Scheme II

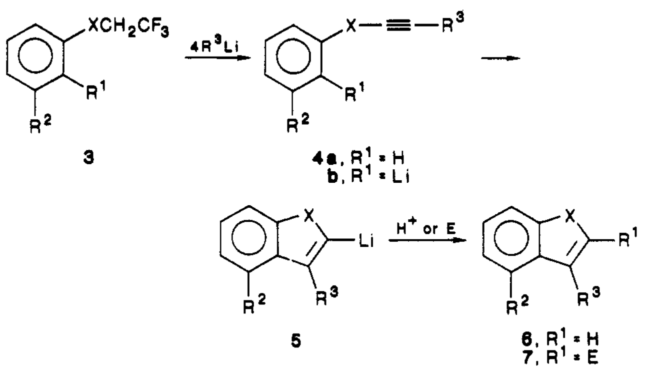


Table I[9-11]

item	substrate 3	product 6 or 7	yield, %
1	X = O, R^1 = R^2 = H	**6a**, R^2 = H, R^3 = *n*-Bu	40
2	X = O, R^1 = R^2 = H	**6b**, R^2 = H, R^3 = *sec*-Bu	40
3	X = O, R^1 = R^2 = H	**6c**, R^2 = H, R^3 = Pr	40
4	X = O, R^1 = R^2 = H	**7a**, R^2 = H, R^3 = *n*-Bu, E = I	30
5	X = S, R^1 = Br, R^2 = H	**6d**, R^2 = H, R^3 = *n*-Bu	40
6	X = S, R^1 = Br, R^2 = H	**6e**, R^2 = H, R^3 = *sec*-Bu	40
7	X = S, R^1 = Br, R^2 = H	**6f**, R^2 = H, R^3 = C_6H_5	60
8	X = S, R^1 = Br, R^2 = H	**7b**, R^2 = H, R^3 = *n*-Bu, E = I	40
9	X = NCH_3, R^1 = H, R^2 = OCH_3	**6g**, R^2 = OCH_3, R^3 = *n*-Bu	60
10	X = NCH_3, R^1 = H, R^2 = OCH_3	**6h**, R^2 = OCH_3, R^3 = *sec*-Bu	50
11	X = NCH_3, R^1 = H, R^2 = OCH_3	**7c**, R^2 = OCH_3, R^3 = *n*-Bu, E = CH_2OCH_3	50
12	X = NCH_3, R^1 = H, R^2 = OCH_3	**7d**, R^2 = OCH_3, R^3 = *n*-Bu, E = $CH_2CHOHCH_2CH_3$	60

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(2) These results will be the subject of a separate publication.

(3) To our knowledge only one example of the anionic cyclization of acetylenes is known. This involves the conversion of 1-bromo-8-(2-phenylacetylene)acenaphthene to 1-phenylacenaphthane by butyllithium. Kandil, S. A.; Dessy, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 3027.

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(5) The driving force for the formation of the carbon–carbon σ bond at the expense of the acetylenic bond may be derived from (a) the energy of rehybridization (acetylene to ethylene), (b) the additional delocalization of the newly formed heterocyclic system, and (c) the stabilization of the final anion at the 2-position by the adjacent heteroatom, although the differeces in energy between anion **4b** and anion **5** may only be marginal. Dessy and co-workers have discussed the cyclization mentioned in ref 3 above in a similar context.

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