JOC Article

Aromatic Allylation via Diazotization: Metal-Free C−C Bond Formation

Fredrik Ek,[†] Oskar Axelsson,[‡] Lars-Göran Wistrand,[‡] and Torbjörn Frejd*,[†]

Organic Chemistry 1, Department of Chemistry, Lund University, P.O. Box 124, S-221 00 Lund, Sweden, and Amersham Health R&D AB, Medeon-Malmö, S-205 12 Malmö, Sweden

torbjorn.frejd@orgk1.lu.se

Received April 11, 2002

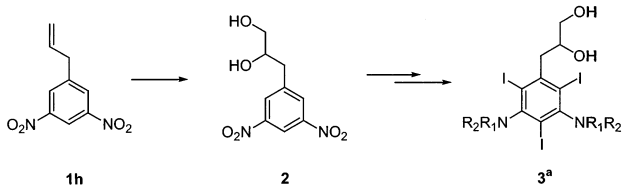
A new method for the synthesis of allyl aromatic compounds not involving any metal-containing reagent or catalyst has been developed. Arylamines substituted with a large number of different substituents were converted via diazotizative deamination with *tert*-butyl nitrite in allyl bromide and acetonitrile to the corresponding allyl aromatic compounds. The allylation reaction was found to be suitable for larger scale synthesis due to short reaction times, a nonextractive workup, and robustness toward moisture, air, and type of solvent.

Introduction

In our search for a new iodinated X-ray contrast agent, we found a group of compounds (**3**) with promising physiological and chemical properties (Scheme 1).[1] The substances were all synthesized from the same starting material, allyl-3,5-dinitrobenzene (**1h**, Scheme 1). Initial attempts to use the Stille cross-coupling reaction between 3,5-dinitroiodobenzene and allyltributyltin only gave 20% of **1h** after 7 days reaction time and workup involving preparative HPLC.[1] Furthermore, the sensitive nature of the electron-deficient aromatic moiety toward nucleophilic and reductive reagents prevented the synthesis of the diol **2** (Scheme 1) by other methods not involving **1h**.[2] To continue the project, we needed a new method suitable for synthesizing **1h** at a molar scale.

Several methods such as Claisen rearrangement of allyl phenyl ethers, cross-coupling catalyzed by transition metals,[3−9] allylation with reactive organometallic reagents,[5,10] and electrophilic aromatic substitution[11,12] have been developed and extensively used for the direct allylation of aromatic compounds. Despite their versatility their use in organic synthesis is somewhat limited, especially at a larger scale. Several of the methods use highly toxic catalysts or reagents, which makes the reactions environmentally problematic. In certain cases, poor regioselectivity or lack of functional group tolerance due to highly reactive reagents constitute major problems.

SCHEME 1. Synthetic Route toward Candidate Compounds Starting from Allyl-3,5-dinitrobenzene[a]



[a] See ref 1 for the structure of R_1 and R_2.

Free-radical allylations provide some of the mildest, most general methods to introduce allyl groups into functionalized molecules. Most research in this area has been focused on allylation of sp^3-hybridized carbons,[13−18] and only a few papers have demonstrated radical allylations of aromatic compounds.[19−23] Migita et al. were the

[†] Lund University.
[‡] Amersham Health R&D AB.

(1) Andersson, S.; Malmgren, H.; Golman, K.; Wistrand, L.-G.; Almen, T.; Hanno, P. Water-soluble contrast media for X-ray imaging. WO 0037115, **2000**, 35 pp.
(2) Dalla, V.; Cotelle, P.; Catteau, J. P. *Tetrahedron Lett.* **1997**, *38*, 1577−1580.
(3) Jolly, P. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, G., Eds.; Pergamon: Oxford, 1982; Vol. 8, pp 713−772.
(4) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, G., Eds.; Pergamon: Oxford, 1982; Vol. 8, pp 799−938.
(5) Larock, R. C. *Synthetic Organic Methodology: Comprehensive Organic Transformations. A Guide to Functional Group Preparations*; 1989.
(6) Lee, P. H.; Sung, S.-y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201−3204.
(7) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688.
(8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−83.
(9) Stille, J. K. *Angew. Chem.* **1986**, *98*, 504−19.
(10) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4415−4435.
(11) Kodomari, M.; Nawa, S.; Miyoshi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 1895−6.
(12) Lim, H. J.; Keum, G.; Kang, S. B.; Kim, Y.; Chung, B. Y. *Tetrahedron Lett.* **1999**, *40*, 1547−1550.
(13) Curran, D. P., Porter, N. A., Giese, B., Eds. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*, 1996.
(14) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*, 1986.
(15) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079−94.
(16) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209−10.
(17) Sibi, M. P.; Chandramouli, S. V. *Tetrahedron Lett.* **1997**, *38*, 8929−8932.
(18) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171.
(19) Al Adel, I.; Adeoti Salami, B.; Levisalles, J.; Rudler, H. *Bull. Soc. Chim. Fr.* **1976**, 934−8.

10.1021/jo0258103 CCC: $22.00
Published on Web 08/15/2002

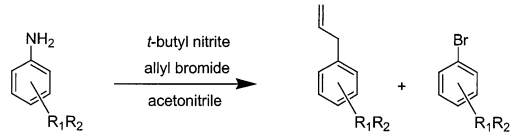
first to show that a phenyl radical, generated from phenylazotriphenylmethane or *N*-nitrosoacetanilide, reacted with allyl sulfides or allyl bromide to afford allylbenzene.[20] Later, they also showed that aromatic halides reacted with allyltributyltin, either via a thermal reaction in the presence of AIBN or via a photoinduced reaction, which gave allylbenzene.[22] Allyl radicals, generated in situ from allyl iodide, have also been used for direct allylation of aromatic compounds, although without any regioisomeric control.[24]

Since the radical reactions mentioned all involve hazardous reagents or lack of regioselectivity, they were unsuitable for our large-scale application. We therefore decided to develop an alternative method suitable for our purposes. Crucial information for the development of a new allylation reaction was presented in a paper describing a modified procedure for the Meerwein reaction.[25] In this paper, phenyl radicals were generated in situ from the corresponding arylamine, via deamination with an alkyl nitrite, which in turn reacted with acrylonitrile (and other conjugated olefins). Surprisingly, we could not find any applications of this convenient procedure of phenyl radical generation from an arylamine in combination with allyl bromide, although, as mentioned, phenyl radicals react with allyl bromide to give allyl aromatic compounds. In this paper, we report a new method for the synthesis of **1h** also allowing the synthesis of a large number of different allyl-substituted aromatics. We here focus on structural variation of the aryl moiety and have chosen arylamines preferably substituted with one or two nitro groups because of their usefulness in the synthesis of contrast agents and also because of the difficulties often encountered in the preparation of this type of allyl aromatic compounds utilizing existing methods.

Results and Discussion

The reactions presented in Table 1 were performed on a 3 mmol scale. The arylamine (solid) was added in portions to a dry and oxygen-free acetonitrile solution of *tert*-butyl nitrite and allyl bromide during approximately 20 min, while the temperature was maintained as shown in Table 1.[26] **Warning! A too rapid addition of the arylamine to the reaction mixture may result in an uncontrolled evolution of heat and nitrogen gas.** A reaction time of 60 min was employed, although in several cases complete conversion was achieved already ca. 5 min after the final addition of the arylamines. An extractive workup was not necessary, in contrast to the methods using metal-containing reagents and catalysts.

TABLE 1. Results of Allylation with Allyl Bromide



4 a-p 1 a-p 5 a-p

entry	R_1, R_2	T^a (°C)	yield^b (%)	selectivity **1a**−**p**/**5a**−**p**^{c}
1	2-Cl, 4-NO_2	11−13/23	79 (**1a**)	25:1
2	2-CF_3, 4-NO_2	18−19/26	85 (**1b**)	35:1
3	2-CN, 4-NO_2	23−27/25	65 (**1c**)	17:1
4	2-COPh, 4-NO_2	28−32/25	46 (**1d**)	7:1
5	2-Br, 5-NO_2	40−45/45	58 (**1e**)	14:1
6	3-NO_2, 4-OMe	35−40/40	40 (**1f**)	10:1
7	3-CF_3, 4-NO_2	13−15/25	62 (**1g**)	14:1
8	3,5-diNO_2	11.5−13/22	81, 89^d (**1h**)	25:1
9	3,5-diCl	30−35/30	48^e (**1i**)	5:1
10	3-COOEt, 5-NO_2	10−12/25	67 (**1j**)	12:1
11	4-NO_2, H	48−52/50	55 (**1k**)	6:1
12	4-Br, H	30−35/30	34 (**1l**)	3:1
13	4-*tert*-butyl, H	45−46/50	19 (**1m**)	2:1
14	4-OMe, H	60−61/61	18^f (**1n**)	2:1
15	2,6-diNO_2	>60	0 (**1o**)	
16	2,4-diNO_2	60−61/60	49^g (**1p**)	9:1

^{a} Temperature during the addition of the arylamines/temperature after the addition. ^{b} Isolated yields except for entry 14. ^{c} Determined by HPLC and ^{1}H NMR of the crude products. ^{d} Multigram scale synthesis. ^{e} 19% of 4-bromo-3,5-dichloroallylbenzene and 3% of 2,5-dibromo-1,4-dichlorobenzene were also formed in the reaction. ^{f} Determined by ^{1}H NMR using toluene as internal standard. ^{1}H NMR data were in agreement with literature data.[27] ^{g} Extended reaction time (18 h) and additional *tert*-butyl nitrite (8 equiv).

Subsequent removal of volatile compounds from the reaction mixture at reduced pressure gave the crude product, which was then purified by methods outlined in the Experimental Section. A slightly modified procedure was used for the synthesis of **1h** on a multigram scale (for details see the Experimental Section).

As seen in Table 1, allylated products were isolated in yields ranging from 0 to 85% on the basis of the corresponding arylamines.[28] In accordance with the typical behavior of radical reactions, a large number of functionalities were tolerated.[13,14] Electron-deficient arylamines generally had a higher reactivity and gave higher yield of the allylated products. A similar electronic effect on reactivity has been reported in radical addition reactions involving allyl, vinyl, and aryl substrates and also in radical abstraction of hydrogen or halogen atoms.[21,25,29,30] The common explanation for this behavior is that electron-withdrawing groups convert the phenyl radical (a probable intermediate in the mechanism of the allylation reaction, which will be discussed later) from a relatively nonpolar to an electrophilic radical.[21,30−32]

(20) Migita, T.; Kosugi, M.; Takayama, K.; Nakagawa, Y. *Tetrahedron* **1973**, *29*, 51−5.
(21) Migita, T.; Takayama, K.; Abe, Y.; Kosugi, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1137−42.
(22) Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2480−4.
(23) Yashkina, L. V.; Kopylova, B. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 957−9.
(24) Camaggi, C. M.; Leardini, R.; Zanirato, P. *J. Org. Chem.* **1977**, *42*, 1570−2.
(25) Doyle, M. P.; Siegfried, B.; Elliott, R. C.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2431−6.
(26) All experiments made in order to find the optimal reaction conditions for the allylation (including safety consideration) were performed at 0.5 mmol scale. The yields and selectivity were determined by HPLC using 2-nitrobenzyl alcohol as an internal standard (see the Experimental Section).
(27) Pouchert, C. J.; Behnke, J. In *The Aldrich Library of ^{13}C and ^{1}H FT NMR-spectra*, 1st ed.; Aldrich: Milwaukee, WI, 1993; Vol. 2, p 208.
(28) Additional examples can be found in ref 47.
(29) Tilset, M.; Parker, V. D. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 123−4.
(30) Takayama, K.; Kosugi, M.; Migita, T. *Chem. Lett.* **1973**, 193−5.
(31) Tichy, S. E.; Thoen, K. K.; Price, J. M.; Ferra, J. J., Jr.; Petucci, C. J.; Kenttaemaa, H. I. *J. Org. Chem.* **2001**, *66*, 2726−2733.
(32) Heidbrink, J. L.; Thoen, K. K.; Kenttaemaa, H. I. *J. Org. Chem.* **2000**, *65*, 645−651.

Similar to the behavior of other radical addition reactions, steric hindrance has an adverse effect on the outcome of the allylation reaction.[33−35] When **1o** was subjected to the standard conditions no evolution of nitrogen gas could be detected. Even when the temperature was increased to >60 °C, the corresponding allylated product could not be isolated. Also, **4p** was more unreactive than **4h**. According to HPLC analysis, only 20% of **4p** was consumed after 1 h when the allylation reaction was performed at 60 °C. However, extended reaction time (18 h) and addition of extra *tert*-butyl nitrite (8 equiv was added in portions during 4 h) gave almost complete conversion of **4p**, although the isolated yield of **1p** was only 49%. Similarly, the steric bulk of the benzoyl substituent in **4d** is probably the reason for the moderate yield of the allylated product **1d**.

Electron-withdrawing substituents not only facilitated the allylation reaction but also made the corresponding phenyl radical more selective for the addition to allyl bromide relative to abstraction of a bromine atom, the most important side reaction. As seen in Table 1, the more electron-deficient arylamines generally gave a higher ratio of allylation versus bromination. Additionally, steric hindrance appeared to increase the tendency of bromination as exemplified in entries 4 and 16 (Table 1).

Finally, a method for the large-scale (0.41 mol) synthesis of **1h** was developed. A smaller amount of acetonitrile was used in order to limit the total volume of the reaction mixture. The addition time of the arylamine had to be prolonged because of the exothermicity of the reaction. An increased yield compared to the same reaction at a 3 mmol scale was noticed. Filtration of the crude product dissolved in toluene through two pads of neutral alumina gave a product that was pure enough to be crystallized from isooctane. Thus, chromatography, which would not be acceptable in a larger scale procedure, was avoided.

Changes in the reaction conditions such as concentration, moisture levels, and temperature only moderately affected the yield (66−79%) and the selectivity (20−25:1).[26] The reaction proceeded even in allyl bromide as solvent with minor changes in the outcome (yield 70%, selectivity 15:1). Unexpectedly, the replacement of *tert*-butyl nitrite with isoamyl nitrite lowered the yield with 11%. A possible explanation could be the greater tendency of homolytic cleavage of the secondary carbon−hydrogen bonds in the isoamyl unit.[36] Further, to see if the phenyl radical was able to select between allylic substrates with and without a suitable terminal leaving group, equal amounts allyl bromide and allyl acetate were employed. (OAc is considered to be a poor leaving group in radical reactions due to the strong C−O bond).[20] The yield dropped from 74% to 45%. When only allyl acetate was used in the reaction the allyl product could not be detected. Instead, a multitude of nonidentified compounds was formed according to HPLC. These experiments indicated that the phenyl radical attacks both allylic components indiscriminately and that only attack on the bromide leads to allylation.

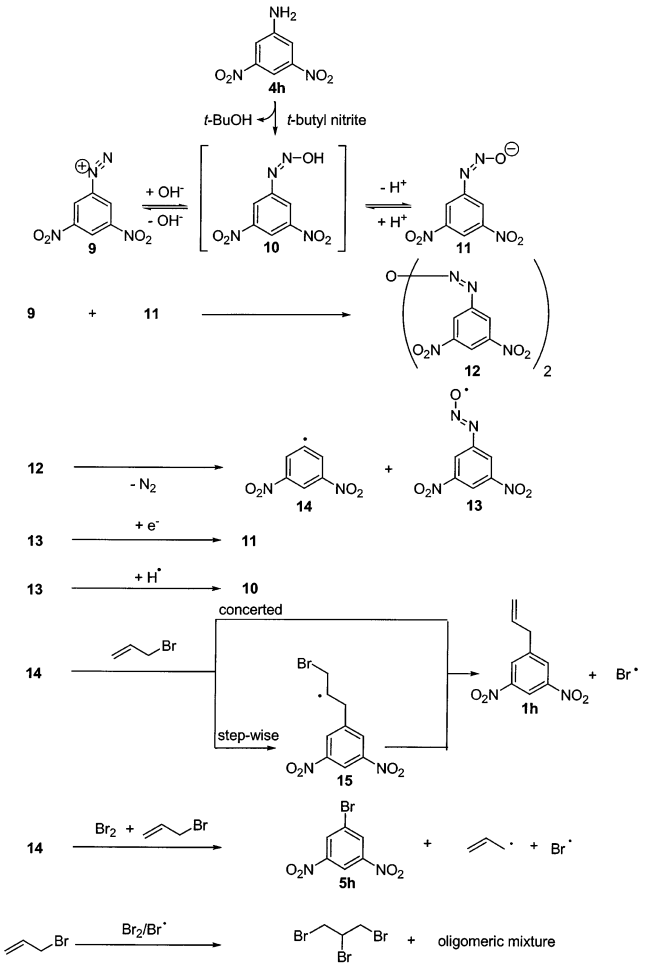
In our standard method, a large amount (15 equiv) of allyl bromide was used. The yield of the desired allylation product decreased considerably at lower than 7.5 equiv of allyl bromide. However, most of the excess of allyl bromide could be recovered by distillation directly from the reaction mixture; the distilled allyl bromide contained acetonitrile and traces of *tert*-butyl nitrite. Thus, approximately 10−11 equiv of allyl bromide could be isolated and reused after the reaction, indicating that 4−5 equiv was consumed. We also noted that while the yield of the allylation product was quite dependent on the amount of allyl bromide the yield of the side product **5h** was only marginally effected (±1%).

In agreement with the general behavior of radical reactions, we found only small variations in the product distribution when changing the solvent. Acetonitrile (74%, 25:1) and nitromethane (75%, 20:1) were found to be the best solvents, although both acetone and dimethoxyethane could be applied with minor alteration of the yield and selectivity (69%, 20:1). DMSO and tetrachloromethane gave somewhat lower yield (55−60%) and showed a poorer selectivity (10:1). THF gave the same yield of the allylated product as acetone but resulted in the lowest ratio of allylation versus bromination (8:1).

The mechanism of the aprotic diazotization of arylamines is not yet fully understood. However, we believe that the mechanism for the Gomberg−Bachmann (GB) reaction, proposed by Rüchhardt et al.,[37] is probably also applicable to aprotic diazotization of arylamines, including the allylation reaction (Scheme 2). We have been able to isolate a reactive precipitate from the reaction mixture formed during the addition of **4h**. It slowly dissolved when the addition of **4h** was completed.[38] Analysis of the isolated polar precipitate (**Warning! The precipitate violently decomposed upon heating**), with TOF HRMS (APCI-) (acetonitrile) and ^{1}H NMR (DMSO-d_6) suggested that the material was similar to **10**, thus supporting the GB mechanism. This material is likely to be in a pH-dependent equilibrium with the corresponding diazonium salt **9** and the diazotate **11**.[39,40] Furthermore, addition of the precipitate to allyl bromide in acetonitrile resulted in the evolution of nitrogen gas and formation of **1h** and the byproducts normally found in the allylation reaction. Similar to the mechanism postulated for the GB reaction, **9** and **11** then form the diazotic anhydride (**12**) which, in turn, decomposes and gives nitrogen gas, phenyl radical (**14**), and the long-lived diazotyl radical (**13**).[41,42] The diazotyl radical probably abstracts a hydrogen atom or an electron from the reaction mixture, thus regenerating the diazotic acid/diazotate system (**9**−**11**). There is also a possibility that

(33) Colombani, D. *Prog. Polym. Sci.* **1999**, *24*, 425−480.
(34) Mella, M.; Fagnoni, M.; Albini, A. *J. Org. Chem.* **1994**, *59*, 5614−22.
(35) Zarkadis, A. K.; Neumann, W. P.; Duennebacke, D.; Penenory, A.; Stapel, R.; Stewen, U. *Chem. Ber.* **1993**, *126*, 1179−85.
(36) Kopinke, F. D.; Zimmermann, G.; Anders, K. *J. Org. Chem.* **1989**, *54*, 3571−6.
(37) Ruechardt, C.; Merz, E. *Tetrahedron Lett.* **1964**, 2431−6.
(38) A precipitate was also formed with other arylamines but were not analyzed as thoroughly as the one from **4h**.
(39) Machackova, O.; Sterba, V. *Collect. Czech. Chem. Commun.* **1972**, *37*, 3313−27.
(40) Kuokkanen, T. *Finn. Chem. Lett.* **1987**, *14*, 184−92.
(41) Binsch, G.; Ruechardt, C. *J. Am. Chem. Soc.* **1966**, *88*, 173−4.
(42) Binsch, G.; Merz, E.; Ruechardt, C. *Chem. Ber.* **1967**, *100*, 247−58.

SCHEME 2. Suggested Mechanism of the Allylation Reaction



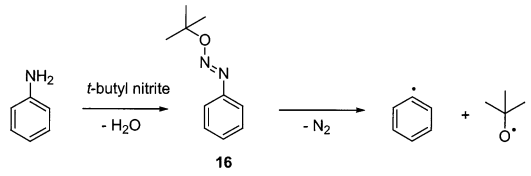
the diazotyl radical (**13**) may form a dimer, which then could decompose into nitrogen, oxygen, and two phenyl radicals.

The phenyl radical **(14)** reacts with the allyl bromide, either in a concerted or a stepwise mechanism (via **15),** resulting in the formation of an allyl aromatic compound and a bromine atom. The bromine atom then continues to react with the excess of the allyl bromide resulting in partial polymerization. In fact, purification of the crude product left a fraction that contained the oligomerized allyl bromide. Analysis of the ^{1}H NMR spectrum and mass spectrum of this fraction revealed a complex mixture of compounds, substituted with up to three bromine atoms.

The phenyl radical **14** may also abstract a bromine atom from allyl bromide forming the corresponding bromobenzene derivative (**5h**). As mentioned, the bromine abstraction often constitutes the major side reaction in this process. The halogen abstraction, which is a unique behavior of radicals, strongly indicates that phenyl radicals are indeed formed in the allylation reaction.[43] An alternative bromine atom source would be Br_2, which could be formed by dimerization of bromine atoms. This would result in, e.g., 1,2,3-tribromopropane,

(43) Wassmundt, F. W.; Kiesman, W. F. *J. Org. Chem.* **1997**, *62*, 8304−8308.

SCHEME 3. Alternative Mechanism for the Formation of Phenyl Radicals



which was indeed found in the reaction mixture in substantial amounts (a control using authentic material was made).[44]

In an alternative mechanism suggested for aprotic diazotization of arylamines with alkyl nitrite, a diazotic ester (**16**) has been suggested as the precursor of phenyl radicals (Scheme 3).[25,45] However, the assumed less polar character of **16** (in our case substituted with two nitro groups) compared to the polar nature of the precipitate together with the fact that the diazotic ester was not detected by MS nor was the ^{1}H NMR analysis consistent with the diazotic ester as the precipitate makes this alternative mechanism less probable.

In conclusion, a new method for the synthesis of allyl aromatic compounds has been developed. Arylamines substituted with a large number of different substituents gave the corresponding allyl aromatic compounds with complete regioselectivity. Electron-withdrawing substituents were necessary to obtain good yields. The allylation reaction was relatively insensitive toward moisture, air, and type of solvent. The robustness of the reaction combined with nonextractive workup, reaction temperature above 0 °C and short reaction times makes it suitable for larger scale synthesis. This allylation procedure constitutes a carbon−carbon bond forming reaction without the need for metal-containing reagents and catalysts, thus avoiding the problem of residual toxic metals in compounds for biological testing. Furthermore, the large number of commercially available aniline derivatives makes it possible to synthesize a broad range of allyl aromatic compounds.

Experimental Section

General Methods. HPLC analyses were performed on a HiChrom column (Kromasil 100−5C18, 150 × 4.6 mm); eluent: CH_3CN (HPLC grade)/H_2O (0.1% TFA); flow rate 1 mL/min. Preparative HPLC was performed with a HiChrom column (Kromasil 100−10C18, 250 × 20 mm); eluent: CH_3CN (HPLC grade)/H_2O; flow rate 20 mL/min. NMR spectra were recorded at 400 MHz using $CDCl_3$ or acetone-d_6 as internal standard. Mass spectra were recorded in the following modes: EI(+) (70 eV) using both direct inlet and inlet via a gas chromatograph equipped with a CP−SIL 8CB column, FAB(+) and APCI(−) (−25 V, source temperature 120 °C and probe temperature of 500 °C). Chromatographic separations were performed on Matrex Amicon normal phase silica gel 60 (0.035−0.070 mm). TLC was performed on Merck precoated TLC plates with silica gel 60 F-254, 0.25 mm. After eluation, the TLC plates were visualized with UV light and sprayed with a solution of $KMnO_4$ (10 g), K_2CO_3 (50 g), NaOH (20 mL, 5%), and H_2O (900 mL) followed by heating. Chemicals were reagent grade. Ethyl 3-amino-5-nitrobenzoate was synthesized according to a literature procedure, mp 159−161 °C (lit. mp

(44) We appreciate the suggestion by the reviewer.

(45) Doyle, M. P.; Dellaria, J. F., Jr.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494−8.

158−160 °C).[46] *tert*-Butyl nitrite and allyl bromide were distilled prior to use. Reagents and solvents used in the large-scale synthesis of allyl-3,5-dinitrobenzene were used as received. Solvents were of p.a. quality except for the acetonitrile used in analytical and preparative HPLC, which was of HPLC grade. The acetonitrile used in the reactions presented in Table 1 was distilled under argon atmosphere from CaH_2 and then degassed for 30 min with argon prior to use. In retrospect, this was probably unnecessary. Spectral data for the allyl aromatic compounds were in agreement with spectral data published if not otherwise stated.[47]

General Procedure for the Allylation. The arylamine (3.0 mmol) was added during 20 min to a solution of *tert*-butyl nitrite (535 μL, 4.5 mmol) and allyl bromide (3.9 mL, 45.0 mmol) in dry and degassed CH_3CN (3 mL) under argon atmosphere while maintaining the specified temperature (Table 1). At the end of the addition of arylamine, extra *tert*-butyl nitrite (180 μL, 1.5 mmol) was added. The reaction mixture was then stirred at a temperature specified in Table 1 for 1 h. The volatile material in the reaction mixture was then removed at reduced pressure.

With Internal Standard. 3,5-Dinitroaniline (92 mg, 0.5 mmol) was added to a solution of *tert*-butyl nitrite (119 μL, 1.0 mmol) and allyl bromide in 0.5 mL of the appropriate solvent during 10 min while maintaining the temperature of the reaction mixture between 11.5 and 14 °C. The reaction mixture was then stirred at 22 °C for 1 h followed by addition of 2-nitrobenzyl alcohol (50 mg) as an internal standard. The yield and product distribution were determined by HPLC.

Allyl-2-chloro-4-nitrobenzene (1a). Column chromatography (heptane−ethyl acetate 97:3) followed by preparative HPLC (gradient solution: 50:50 to 70:30 for 30 min and then 95:5 (CH_3CN/H_2O)) gave 467 mg (79%) of **1a** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, 1H, J = 2.4 Hz), 8.07 (dd, 1H, J = 8.5, 2.3 Hz), 7.42 (d, 1H, J = 8.5 Hz), 6.01−5.89 (m, 1H), 5.23−5.10 (m, 2H), 3.59 (d, 2H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.0, 145.4, 134.9, 133.6, 130.8, 124.6, 121.8, 118.1, 37.6; IR (neat) 1522, 1350 cm^{-1}; HRMS (EI$^+$) calcd for $C_9H_8ClNO_2$ (M) 197.0244, found 197.0247.

Allyl-4-nitro-2-trifluoromethylbenzene (1b). Column chromatography (heptane−ethyl acetate 49:1) gave 587 mg (85%) of **1b** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, 1H, J = 2.4 Hz), 8.34 (dd, 1H, J = 8.5, 2.4 Hz), 7.58 (d, 1H, J = 8.5 Hz), 6.00−5.88 (m, 1H), 5.24−5.12 (m, 2H), 3.67 (d, 2H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.4, 146.1, 134.4, 132.6, 130.0 (q, J = 32.2 Hz), 127.2, 126.4, 124.5, 121.8, 121.7 (q, J = 6.0 Hz), 118.3, 36.4 (m); IR (neat) 1533, 1356, 1312, 1132 cm^{-1}; HRMS (EI$^+$) calcd for $C_{10}H_8F_3NO_2$ (M) 231.0507, found 231.0515.

Allyl-2-cyano-4-nitrobenzene (1c). Column chromatography (heptane−ethyl acetate 23:2) gave 367 mg (65%) of **1c** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, 1H, J = 2.4 Hz), 8.39 (dd, 1H, J = 8.6, 2.4 Hz), 7.58 (dd, 1H, J = 8.6, 0.5 Hz), 6.00−5.90 (m, 1H), 5.29−5.17 (m, 2H), 3.74 (d, 2H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.9, 146.4, 133.1, 131.0, 128.0, 127.5, 119.2, 115.8, 114.0, 38.5; IR (neat) 2232, 1530, 1354 cm^{-1}; HRMS (EI$^+$) calcd for $C_{10}H_8N_2O_2$ (M) 188.0585, found 188.0585.

2-Allyl-5-nitrobenzophenone (1d). Column chromatography (heptane−ethyl acetate 23:2) gave 370 mg (46%) of **1d** as a pale yellow oil, which crystallized upon standing overnight in the refrigerator: mp 50−52 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.35 (dd, 1H, J = 8.5, 2.5 Hz), 8.19 (d, 1H, J = 2.4 Hz), 7.85−7.81 (m, 2H), 7.74−7.68 (m, 2H), 7.59−7.53 (m, 2H), 5.95−5.84 (m, 1H), 5.04−4.97 (m, 2H), 3.55 (m, 2H, J = 6.6 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 196.2, 147.1, 147.0, 140.7, 137.7, 136.5, 134.8, 132.7, 130.9, 129.7, 125.7, 124.0, 117.8, 37.9; IR (neat) 1670, 1526, 1348 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{16}H_{14}NO_3$ (M + H) 268.0974, found 268.0964.

Allyl-2-bromo-5-nitrobenzene (1e). Column chromatography (heptane−ethyl acetate 49:1) gave 510 mg of a pale yellow oil. The oil was dissolved in pentane, and the solution was cooled to −20 °C upon which **1e** precipitated as white crystals. Recrystallization (pentane, room temperature to −20 °C) gave 420 mg (58%) of the title compound as white crystals: mp 43−44 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, J = 2.7 Hz), 7.95 (dd, 1H, J = 8.7, 2.7 Hz), 7.74 (d, 1H, J = 8.7 Hz), 6.03−5.92 (m, 1H), 5.26−5.13 (m, 2H), 3.60 (m, 2H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.3, 141.6, 133.7, 133.7, 131.9, 124.9, 122.5, 118.4, 40.1; IR (neat) 1526, 1346 cm^{-1}; HRMS (EI$^+$) calcd for $C_9H_8BrNO_2$ (M) 240.9738, found 240.9739.

Allyl-4-methoxy-3-nitrobenzene (1f). The crude product was dissolved in 20 mL of ethyl acetate−heptane (1:2), and the solution was filtered through a pad of silica. The solvent was removed at reduced pressure. Column chromatography (heptane−ethyl acetate 97:3) of the residue gave 230 mg (40%) of **1f** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, 1H, J = 2.7 Hz), 7.26 (d, 1H, J = 8.6 Hz), 7.09 (dd, 1H, J = 8.6, 2.7 Hz), 6.01−5.89 (m, 1H), 5.11−5.01 (m, 2H), 3.85 (s, 3H), 3.61 (m, 2H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.4, 149.6, 135.5, 132.8, 126.8, 119.8, 116.7, 109.2, 55.8, 36.4; IR (neat) 1533, 1352, 1252 cm^{-1}; HRMS (EI$^+$) calcd for $C_{10}H_{11}NO_3$ (M) 193.0739, found 193.0743.

Allyl-4-nitro-3-trifluoromethylbenzene (1g). Column chromatography (heptane−ethyl acetate 97:3) gave 430 mg (62%) of **1g** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, 1H, J = 8.3 Hz), 7.65 (d, 1H, J = 1.2 Hz), 7.55 (dd, 1H, J = 8.3, 1.4 Hz), 6.00−5.89 (m, 1H), 5.26−5.14 (m, 2H), 3.54 (d, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.1, 134.6, 132.9, 128.1 (q, J = 5.0 Hz), 125.4, 124.0, 123.7, 123.4, 120.7, 118.4, 39.6; IR (neat) 1541, 1360, 1315, 1144 cm^{-1}; HRMS (EI$^+$) calcd for $C_{10}H_8F_3NO_2$ (M) 231.0507, found 231.0499.

Allyl-3,5-dinitrobenzene (1h). Column chromatography (heptane−ethyl acetate 23:2) gave 505 mg (81%) of **1h** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (t, 1H, J = 2.1 Hz), 8.40 (d, 2H, J = 2.1 Hz), 6.04−5.94 (m, 1H), 5.30−5.20 (m, 2H), 3.65 (d, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 144.6, 134.0, 128.9, 119.2, 116.9, 39.5; IR (neat) 1541, 1344 cm^{-1}; HRMS (EI$^+$) calcd for $C_9H_8N_2O_4$ (M) 208.0484, found 208.0486.

Allyl-3,5-dichlorobenzene (1i). Column chromatography (pentane) followed by preparative HPLC (gradient solution: 50:50 to 80:20 for 30 min and then 95:5 (CH_3CN/H_2O) gave 267 mg (48%) of **1i** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (t, 1H, J = 1.9 Hz), 7.08 (t, 2H, J = 1.9 Hz), 5.95−5.84 (m, 1H), 5.16−5.08 (m, 2H), 3.34 (d, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4, 135.6, 134.8, 127.1, 126.4, 117.3, 39.5; IR (neat) 1587, 1568, 1431, 922, 849, 797 cm^{-1}; HRMS (EI$^+$) calcd for $C_9H_8Cl_2$ (M) 186.0003, found 186.0003.

Ethyl 3-Allyl-5-nitrobenzoate (1j). Column chromatography (heptane−ethyl acetate 47:3) gave 470 mg (67%) of **1j** as a pale yellow oil, which crystallized upon standing overnight in the refrigerator; melting below +20 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70 (m, 1H), 8.24 (m, 1H), 8.20 (m, 1H), 6.03−5.91 (m, 1H), 5.24−5.13 (m, 2H), 4.44 (q, 2H, J = 7.1 Hz), 3.56 (d, 2H, J = 6.5 Hz), 1.44 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 148.4, 142.7, 135.5, 135.1, 132.2, 127.3, 122.5, 118.0, 61.9, 39.5, 14.3; IR (neat) 1728, 1537, 1352, 1283, 1200 cm^{-1}; HRMS (EI$^+$) calcd for $C_{12}H_{13}NO_4$ (M) 235.0845, found 235.0846.

4-Allylnitrobenzene (1k). Column chromatography (heptane−ethyl acetate 23:2) followed by preparative HPLC (gradient solution: 50:50 for 10 min then 60:40 for 20 min (CH_3CN/H_2O) gave 267 mg (55%) of **1k** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H, J = 8.8 Hz), 7.34 (m, 2H, J = 8.8 Hz), 5.99−5.89 (m, 1H), 5.18−5.09 (m, 2H), 3.49 (d, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.8, 146.6, 135.5,

(46) Curtis, R. *J. Prakt. Chem.* **1907**, *76*, 255.

(47) Ek, F.; Wistrand, L. G. Preparation of allylic aromatic compounds by reaction of aromatic amines with a nitrite and an allylic olefin. EP 1013636, **2000**, 11 pp.

129.4, 123.7, 117.4, 39.9; IR (neat) 1518, 1348 cm^{-1}; HRMS (EI^+) calcd for $C_9H_9NO_2$ (M) 163.0633, found 163.0641.

4-Allylbromobenzene (1l). Column chromatography (pentane) gave 200 mg (34%) of **1l** as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42 (m, 2H, J = 8.3 Hz), 7.07 (m, 2H, J = 8.3 Hz), 6.00−5.88 (m, 1H), 5.11−5.04 (m, 2H), 3.34 (d, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 136.8, 131.5, 130.4, 119.7, 116.3, 39.6; HRMS (EI^+) calcd for C_9H_9Br (M) 195.9888, found 195.9887. ^1H NMR data were in agreement with literature data.[48]

4-Allyl-*tert*-butylbenzene (1m). Column chromatography (heptane) gave 100 mg (19%) of **1m** as a colorless oil. ^1H NMR data were in agreement with literature data.[49]

Allyl-2,4-dinitrobenzene (1p). In addition to the general procedure for the allylation, the reaction time was extended 18 h (60 °C reaction temperature). During the first 4 h of this additional reaction time, extra *tert*-butyl nitrite (2.86 mL, 24 mmol) was added in portions to the reaction mixture. Column chromatography (heptane−ethyl acetate 23:2) followed by preparative HPLC (gradient solution: 60:40 to 70:30 for 20 min and then 95:5 (CH_3CN/H_2O) of the remaining residue gave 305 mg (49%) of **1p** as a yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.77 (d, 1H, J = 2.4 Hz), 8.38 (dd, 1H, J = 8.5, 2.4 Hz), 7.62 (d, 1H, J = 8.5 Hz), 6.00−5.90 (m, 1H), 5.24−5.12 (m, 2H), 3.80 (d, 2H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.1, 146.6, 142.0, 133.3, 133.2, 127.1, 120.3, 118.9, 36.9; IR (neat) 1526, 1347 cm^{-1}; HRMS (EI^+) calcd for $C_9H_7N_2O_4$ (M − 1) 207.0406, found 207.0407.

Large-Scale Synthesis of Allyl-3,5-dinitrobenzene (1h). Neat **4h** (75 g, 0.41 mol) was added in portions to a solution of *tert*-butyl nitrite (84.6 mL, 0.71 mol) and allyl bromide (530 mL, 6.15 mol) in CH_3CN (25 mL), keeping the temperature between 11 and 15 °C. Before the addition of the final 25% of **4h**, more *tert*-butyl nitrite (21 mL, 0.18 mol) was added. The reaction mixture was then stirred at room temperature (23−25 °C) for 1 h. Excess *tert*-butyl nitrite, allyl bromide, and CH_3CN were distilled off from the reaction mixture at reduced pressure, and toluene (500 mL) was added to the orange-brown residue. The resulting mixture was filtered twice through alumina pads (10 × 10 cm), and the pads were washed with a total of 1.5 L of toluene. The toluene was distilled off at reduced pressure, and isooctane (200 mL) was added to the remaining pale yellow residue. The mixture was stirred at 60 °C for 0.5 h (to extract the partly polymerized allyl bromide and 1,2,3-tribromopropane from the product) and then cooled to approximately −50 °C. As soon as a white precipitate (partly polymerized allyl bromide and 1,2,3-tribromopropane) started to form, the solvent was decanted (including the precipitate) and to the remaining yellow oil another portion of isooctane (200 mL, 20 °C) was added. The oily residue in isooctane was then stirred at −50 °C with a spatula until crystals formed. In some cases, it was necessary to decant the isooctane phase and add fresh isooctane before the oil started to crystallize. The crystals (remaining in the flask) were then washed twice with isooctane (precooled to −50 °C) at −50 °C. Residual isooctane was removed at reduced pressure to give 78.9 g of **1h** as a yellow oil containing less than 4% of **5h** according to ^1H NMR analysis. This corresponds to 89% yield of allyl-3,5-dinitrobenzene. In an alternative procedure, the crystals (after washing with isooctane at −50 °C) were collected by filtration at −50 °C and then washed once with isooctane (precooled to −50 °C). The latter method gave the same yield of slightly purer **1h**. Spectral data were identical to those of the reference sample from the small scale synthesis.

Acknowledgment. We thank Amersham Health R&D AB for financial support, Dr. Peter Michelsen and Einar Nilsson for obtaining mass spectral data, and Jan Glans for help with the preparative HPLC.

Supporting Information Available: ^{13}C NMR spectra for all compounds analyzed by HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0258103

(48) Jones, L. B.; Foster, J. P. *J. Org. Chem.* **1970**, *35*, 1777−81.
(49) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242−5243.