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HPLC monitored synthesis of R_2NCH_2 substituted benzene derivatives used as (C,N)-ligands for organometallic compounds

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Abstract: 2-(Diethylaminomethyl)phenyl bromide and 1,3-bis(dimethylaminomethyl)-benzene, useful ligands for the synthesis of hypervalent organometallic compounds, were prepared and characterized by NMR (^{1}H, ^{13}C, 2D experiments) spectroscopy. Their synthesis was monitored by the HPLC method. The compounds were eluted on a Nucleosil 120 Si column (5 μm, 25 × 0.4 cm) with *n*-hexane at room temperature using a 1.0 ml/min flow-rate. The maximum values of absorbance for the studied compounds, excepting the diethylamine, were located in a narrow range around 212 nm, the wavelength used for their UV detection. The diethylamine was detected at 190 nm. The calibration curves are straight lines with correlation factors $r > 0.995$. The HPLC data are in good agreement with those provided by NMR spectroscopy.

Keywords: Benzene derivatives with pendant arms, HPLC monitoring

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1 Introduction

Substituted benzene derivatives with one or two pendant arms containing donor atoms [e.g. (**1**) and (**2**)] are largely used as organic ligands for transition and main group metals due to their potential ability to establish intramolecular coordination to the metal center [e.g. (**3**) and (**4**)] [1-7] (Scheme 1).

These organic compounds are not commercially available. They have to be obtained

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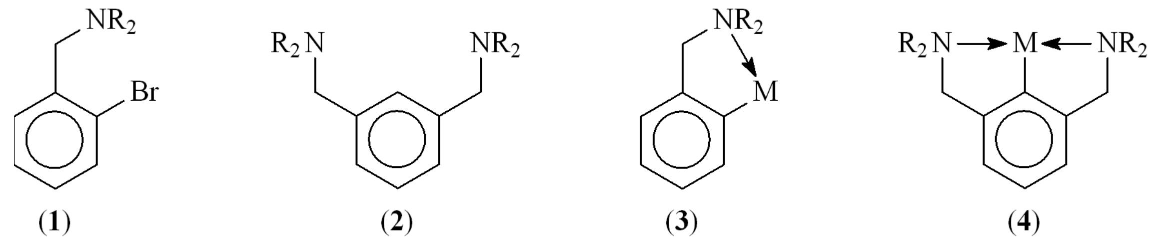


Scheme 1

in the laboratory and their purity is an essential condition for the preparation of the lithiated derivatives further used in the synthesis of organometallic compounds.

High performance liquid chromatography (HPLC) is one of the most important separation methods and analytical techniques [8]. The chromatographic methods coupled with different detectors can be used for the quantitative determination of different substances. The HPLC method is not commonly used to monitor the synthesis of organometallic compounds. This method was applied to monitor the synthesis of (tributylstannyl)methanol through unstable lithiated intermediates without success. It was found to be inadequately sensitive and specific. In addition, the process impurities were not being readily derivatized and therefore remained undetectable by UV [9].

In the present study, the synthesis of compounds **1a** (R = C_2H_5) and **2a** (R = CH_3) was monitored by the HPLC method.

2 Experimental

2.1 Synthesis and spectroscopic details

Starting materials, which were also used as standards, i.e. 2-bromotoluene (**5**) (Merck), 2-bromobenzyl bromide (**6**) (Merck), *m*-xylylenediamine (**7**) (Aldrich) and diethylamine (**8**) (Merck) were commercial products. The ^1H and ^{13}C NMR spectra were recorded on a BRUKER AV 400 instrument operating at 400.16 and 100.62 MHz respectively, at room temperature in $CDCl_3$ (ref. $CHCl_3$ = 7.26 ppm). The chemical shifts are reported in ppm relative to tetramethylsilane (TMS). The ^1H and ^{13}C chemical shifts were assigned based on H,H-COSY, H,C-HSQC and H,C-HMBC experiments.

2.1.1 Synthesis of 2-bromobenzyl bromide (**6**)

The title compound **6** was prepared using an adapted method reported for the photobromination of toluene with bromine in water [10]. A reaction mixture of 10 ml (14.22 g, 83.14 mmol) 2-bromotoluene (**5**) (d = 1.422 g/cm^3), 300 ml distilled water and 2.14 ml (6.64 g, 41.6 mmol) bromine (d = 3.102 g/cm^3) was irradiated under stirring, using a light bulb (200 W) placed in the proximity (ca. 5 cm) of the reaction flask. The disappearance of the red colour indicated that all the bromine was consumed during the photobromination reaction. The reaction mixture was cooled to room temperature, the organic layer was separated and the water phase was washed twice with 50 ml CH_2Cl_2.

The methylene chloride was removed under vacuum and the crude product was distilled twice at reduced pressure. The title compound **6** was obtained as a colourless liquid (b. p. 60–65 ^oC at 10^{-1} atm) that solidified on cooling. Yield 10.2 g (98 %); m.p. 31 ^oC; ^1H NMR ($CDCl_3$, rt): 4.61s (2H, H_7), 7.17ddd (1H, H_4, $^3J_{HH}$ 7.6, 7.6, $^4J_{HH}$ 1.8 Hz), 7.30dd (1H, H_5, $^3J_{HH}$ 7.6, 7.6 Hz), 7.46dd (1H, H_3, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.8 Hz), 7.58d (1H, H_6, $^3J_{HH}$ 7.6 Hz); ^{13}C NMR ($CDCl_3$, rt): 33.33s (C_7), 124.43s (C_2), 127.90s (C_5), 130.07s (C_4), 131.22s (C_3), 133.29s (C_6), 136.97s (C_1).

2.1.2 Synthesis of 2-(diethylaminomethyl)phenyl bromide (**1a**) [11]

The title compound **1a** was prepared by reacting diethylamine (**8**) (50.41 g, 0.69 mol) and compound **6** (46.8 g, 0.18 mol) in benzene, according to a method [11]. Yield 130.1 g (66 %); b.p. 53 ^oC at 10^{-3} atm; ^1H NMR ($CDCl_3$, rt): 1.06t (6H, N-CH_2-CH_3, $^3J_{HH}$ 7.1 Hz), 2.58q (4H, N-CH_2-CH_3, $^3J_{HH}$ 7.1 Hz), 3.65s (2H, H_7), 7.08ddd (1H, H_4, $^3J_{HH}$ 7.8, 7.8, $^4J_{HH}$ 1.8 Hz), 7.28ddd (1H, H_5, $^3J_{HH}$ 7.6, 7.6 $^4J_{HH}$ 1.2 Hz), 7.52dd (1H, H_6, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.2 Hz), 7.57dd (1H, H_3, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.6 Hz); ^{13}C NMR ($CDCl_3$, rt): 11.92s (N-CH_2-CH_3), 47.15s (N-CH_2-CH_3), 57.12s (C_7), 124.08s (C_2), 127.11s (C_5), 127.90s (C_4), 130.48s (C_3), 132.42s (C_6), 139.56s (C_1).

2.1.3 Synthesis of 1,3-bis(dimethylaminomethyl)benzene (**2a**) [12]

The title compound **2a** was prepared by reacting *m*-xylylenediamine (**7**) (20.64 g, 0.152 mmol) with formic acid (28 mL) and paraformaldehyde (18.2 g, 0.607 mol) in water, according to a literature method [12]. Yield: 19.1 g (66 %); ^1H NMR ($CDCl_3$, rt): 2.19s (12H, -CH_3), 3.37s (4H, -CH_2-N), 7.15d (2H, $H_{4,6}$, $^3J_{HH}$ 7.8 Hz), 7.21s (1H, H_2), 7.23t (1H, H_5, $^3J_{HH}$ 7.6 Hz); ^{13}C NMR ($CDCl_3$, rt): 45.23s (N-CH_3), 64.17s (-CH_2-N-), 127.70s ($C_{4,6}$), 127.97s, 129.65s ($C_{2/5}$), 138.68s ($C_{1,3}$).

2.2 Chromatographic studies

The chromatograms of the standards [2-bromotoluene (**5**) (Merck), 2-bromobenzyl bromide (**6**) (Merck), diethylamine (**8**) (Merck) and *m*-xylylenediamine (**7**) (Aldrich)] as well as of the synthesized products [2-bromobenzyl bromide (**6**), 2-(diethylaminomethyl)phenyl bromide (**1a**), 1,3-bis(dimethylaminomethyl)benzene (**2a**)] were obtained using a high performance liquid chromatograph (Jasco 980, Japan). This HPLC system is equipped with a pump (Model PU-980), a low-pressure gradient unit (Model LG-980-02), an in-line degasser (Model DG-980-50) and a UV-VIS detector (Model UV-970/975).

The solutions of the studied compounds were prepared in *n*-hexane and were worked-up through special syringe filters (PTFE 0.45 μm, TRASER) to avoid eventual particle solidification. These solutions were then manually injected into the liquid chromatograph with a 100 μL Hamilton Rheodyne syringe through a Rheodyne valve of 20 μL loop volume.

The separations were performed in isocratic conditions, on a Nucleosil 120 Si column

(5 μm, 25×0.4 cm) at room temperature, using a 1.0 ml/min flow-rate. All compounds were eluted with *n*-hexane. The maximum values of absorbance for the studied compounds, excepting the diethylamine, were located in a narrow range around 212 nm, the wavelength used for their UV detection. The diethylamine was detected at 190 nm. The maximum absorption was determined on the basis of UV-VIS spectra recorded in the range 190–900 nm with a UV-VIS spectrometer (type UNICAM UV 4) equipped with photomultiplicator detection. The UV-VIS spectra were processed using the SOFT VISION program.

The chromatograms were registered and processed with the SOFT BORWIN program. The calibration curves of standard solutions were obtained by plotting peak area *versus* a known, injected amount of compound, using 7 points in the 5–60 μg/mL range, except for *m*-xylylenediamine, for which points in the 1–10 mg/mL range were used. The calibration curves are straight lines with correlation factors $r > 0.995$ (Table 1).

Compound	Number from synthesis	Source of compound	RT [min]	DL [mg/mL]	r
2-Bromotoluene	(**5**)	Merck	2.82	$1 \cdot 10^{-4}$	0.99525
2-Bromobenzyl bromide	(**6**)	Merck	3.14	$5 \cdot 10^{-3}$	0.99450
		Synthesis (1)	3.08	–	–
Diethylamine	(**8**)	Merck	2.81	–	–
2-(Diethylaminomethyl)phenyl bromide	(**1a**)	Synthesis (1)	2.73	–	–
m-Xylylenediamine	(**7**)	Aldrich	2.84	1	0.99542
1,3-bis(Dimethylaminomethyl)-benzene	(**2a**)	Synthesis (2)	3.01	–	–

Table 1 Retention times, detection limits and regression factors for studied compounds.

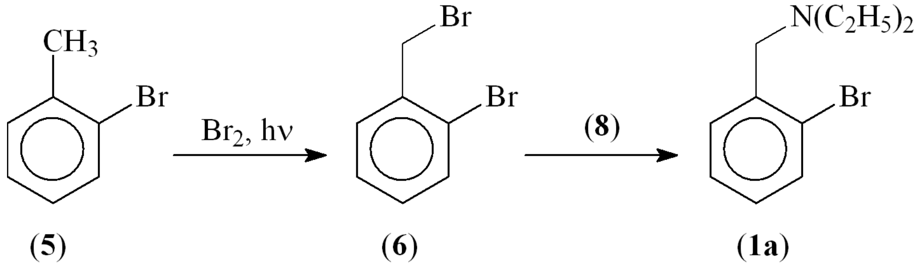
3 Results and discussion

The 2-bromobenzyl bromide (**6**) used as the starting material for the synthesis of compound **1a**, was prepared from commercial 2-bromotoluene (**5**) by photobromination in water, as described for toluene [10]. Treating compound **6** with an excess of diethylamine (**8**), we obtained the compound **1a** (Scheme 2) which was isolated as a colourless liquid and was sensitive to light [11].

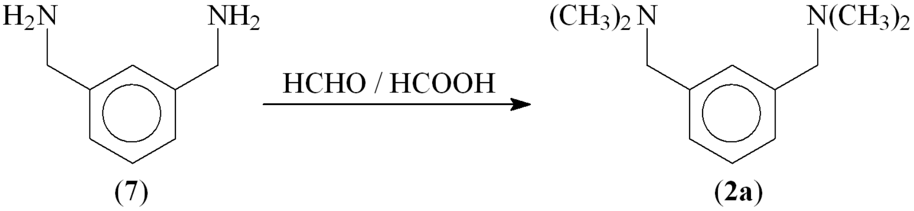
Compound **2a**, containing two pendant arms, was prepared according to a literature method [12], by the permethylation of *m*-xylylenediamine (**7**) using a mixture of paraformaldehyde/formic acid (Scheme 3):

3.1 NMR characterization

Compounds **1a**, **2a** and **6** were characterized by NMR spectroscopy, which confirmed the identity of the isolated compounds. Some NMR data for compounds **1a** (^{1}H [13-15],

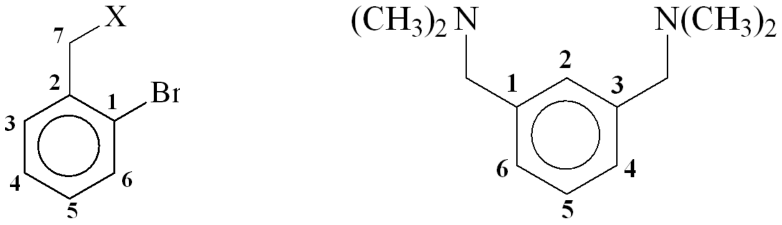


Scheme 2



Scheme 3

^{13}C [15]), **2a** (^1H [11,16]) and **6** (^1H [12]) were previously reported, but no assignments were made for the aromatic protons and carbon resonances. Therefore ^1H and ^{13}C NMR spectra were recorded for these compounds and the assignments of the resonances were made using 2D experiments, according to the numbering sequences given in Scheme 4:



Scheme 4

The NMR spectra of the liquid obtained by distillation of the crude product isolated from the photobromination reaction indicated the presence of a mixture containing the desired compound **6** (δ 4.62 ppm) as well as the starting material **5** (δ 2.41 ppm) and traces of the dibrominated derivative, 2-(dibromomethyl)phenyl bromide (δ 4.77 ppm). Subsequent distillation at reduced pressure allowed the isolation of pure compound **6**.

For both compounds **1a** and **6,** the aromatic region of the ^1H NMR spectra contains four multiplet signals corresponding to the aromatic protons. The ^{13}C NMR spectra of compounds **1a** and **6** show the resonances of the nine and seven different carbons, respectively.

The ^1H NMR spectrum of compound **2a** contains a complex multiplet signal for the aromatic protons and two singlets for the methylene and methyl protons. The ^{13}C NMR spectrum exhibits the expected resonances in the alkyl (two singlets) and aromatic (four singlets) regions, respectively.

3.2 HPLC characterization

In order to monitor the synthesis of R_2NCH_2-substituted benzene derivatives, HPLC analyses were carried out on the starting materials and the synthesized products.

The HPLC chromatograms (Fig. 1) of 2-bromotoluene (**5**) and 2-bromobenzyl bromide (**6**) standards were recorded to monitor the synthesis of 2-bromobenzyl bromide (**6**) [first step of synthesis (1)]. Compound **6** was further used in the synthesis of 2-(diethylaminomethyl)phenyl bromide (**1a**) [second step of synthesis (1)].

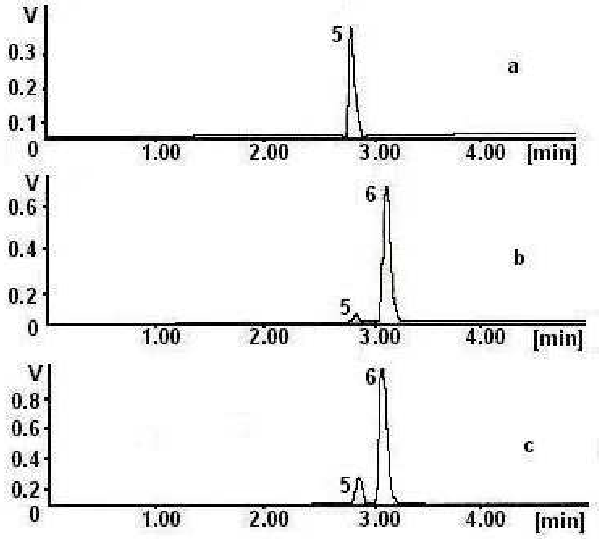
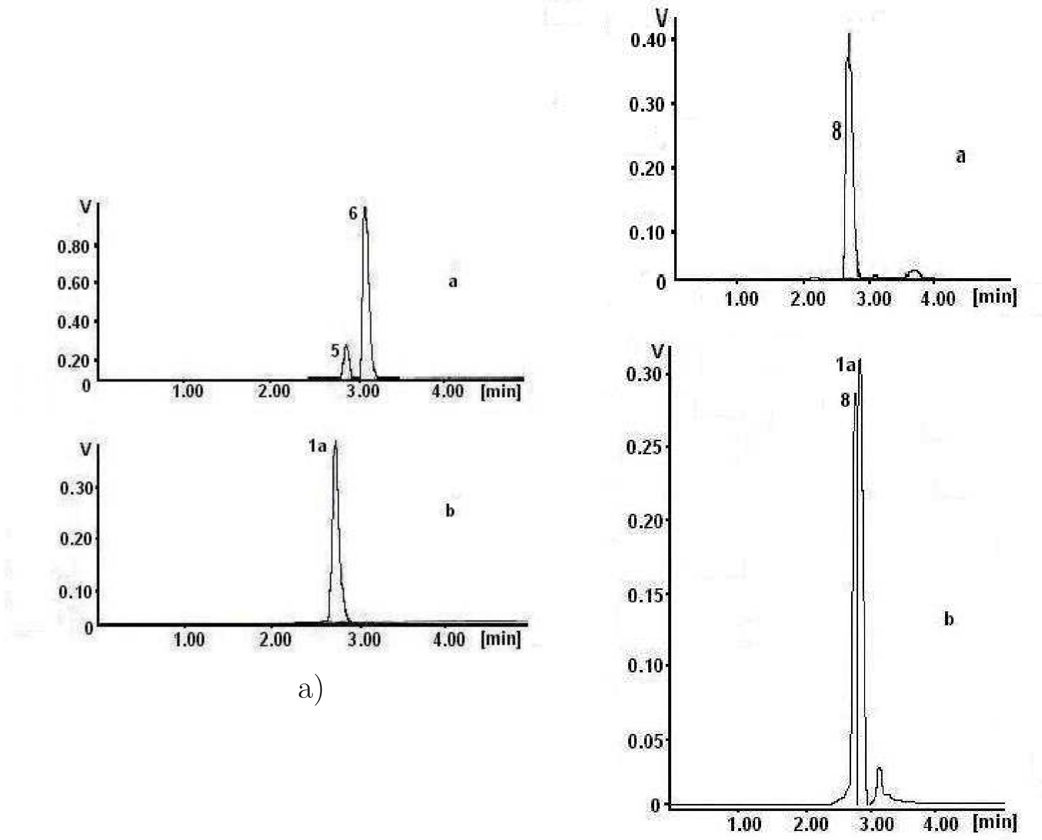


Fig. 1 HPLC monitoring (212 nm) of crude 2-bromobenzyl bromide (**6**): a) chromatogram of 2-bromotoluene (**5**) (Merck); b) chromatogram of 2-bromobenzyl bromide (**6**) (Merck); c) chromatogram of crude 2-bromobenzyl bromide (**6**) [impurified by (**5**)].

The HPLC chromatograms for the reactants used in the second step of synthesis (1), i.e. 2-bromobenzyl bromide (**6**) at 212 nm (Fig. 2Aa) and diethylamine (**8**) at 190 nm (Fig. 2Ba) were recorded to monitor the synthesis of 2-(diethylaminomethyl)phenyl bromide (**1a**). The chromatogram of diethylamine (**8**) was registered at 190 nm where it has a maximum absorbance. The presence of diethylamine (**8**) along with compound **1a** in the chromatogram recorded at 190 nm should be noted (Fig. 2Bb), as this was not observed when the chromatogram was recorded at 212 nm (Fig. 2Ab).

The chromatogram of the *m*-xylylenediamine (**7**) standard (Fig. 3) was recorded for HPLC monitoring of the synthesis (2) of 1,3-bis(dimethylaminomethyl)benzene (**2a**), a ligand with two pendant arms. The chromatogram of compound **2a** indicates small quantities of *m*-xylylenediamine (**7**), consistent with the NMR spectra.

The calibration curves were performed for the standard starting compounds, namely 2-bromotoluene, 2-bromobenzyl bromide, diethylamine and *m*-xylylenediamine. The retention times (RT), detection limits (DT) and regression factors (r) for these compounds are given in Table 1. The HPLC chromatograms of the standard compounds and of



a)

b)

Fig. 2 HPLC monitoring of the 2-(diethylaminomethyl)phenyl bromide (**1a**) synthesis:
A. Chromatograms recorded at 212 nm:
a) 2-bromobenzyl bromide (**6**) [impurified by (**5**)];
b) 2-(diethylaminomethyl)phenyl bromide (**1a**);
B. Chromatograms recorded at 190 nm:
a) diethylamine (**8**);
b) 2-(diethylaminomethyl)phenyl bromide (**1a**) [impurified by (**8**)].

the synthesis products [2-bromobenzyl bromide, 2-diethylaminomethyl)phenyl bromide, 1,3-bis(dimethylaminomethyl)benzene] have been registered.

On the basis of the chromatograms obtained, we identified the reactants and the products of synthesis. Using the calibration curves we determined the quantities of unreacted starting compounds after synthesis. Also, the purity of the prepared 2-bromobenzyl bromide (**6**) [synthesis (1)] was established.

Thus we can conclude that:

- after first distillation of the 2-bromobenzyl bromide (**6**) synthesized by the photobromination of 2-bromotoluene (**5**), the purity of the product is 54%; it still contains 6% unreacted **5**; and up to 100% there are secondary products according to the NMR spectra too.
- in the purified 2-(diethylaminomethyl)phenyl bromide (**1a**) (synthesis (1)), the unreacted starting material **6** was not identified according to the NMR spectra. By means of the HPLC method we found traces of diethylamine (**8**) in addition to

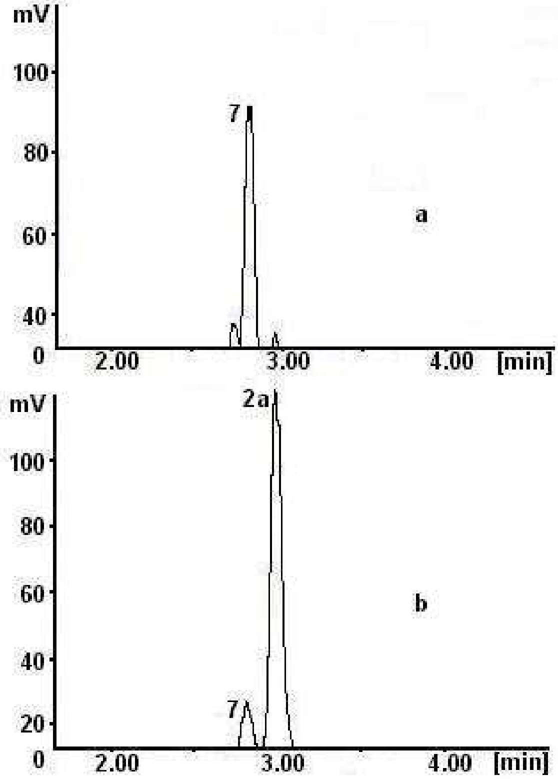


Fig. 3 HPLC monitoring (212 nm) of the 1,3-bis(dimethylaminomethyl)benzene (**2a**) synthesis: a) chromatogram of $m-$xylylendiamine (**7**); b) chromatogram of 1,3-bis(dimethylaminomethyl)-benzene (**2a**).

compound **1a**.

- 1,3-bis(dimethylaminomethyl)benzene (**2a**) obtained according to the synthesis (2) contains 2.6% unreacted m-xylylenediamine (**7**), thus we can note its purity of 97.4%.

The results obtained by the HPLC method are in good agreement with those obtained by NMR spectroscopy. We can conclude that the HPLC data gave useful information, which allows the monitoring of the synthesis of R_2NCH_2-substituted benzene derivatives.

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