Ultrasound-promoted aromatic nucleophilic substitution of dichlorobenzene iron(II) complexes

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ABSTRACT

The nucleophilic aromatic substitution under ultrasound irradiation of a dichlorobenzene iron η^6-complex with various secondary amines is reported. The reaction time at moderate temperatures is considerably shortened (15 min) compared to non sonicated reaction conditions at room temperature (several days) or at solvent refluxing temperature (12–48 h). Controlled mono- or di-substitution was achieved by the tuning of the amine nucleophilicity and the solvent polarity. The method was successfully applied to the synthesis of differently substituted phenylenediamines.

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N-substituted anilines and phenylenediamines are important compounds often used as metal coordinating ligands with particularly interesting electrochemical and spectroscopic properties.[1] Polyanilines, azoic dyes, methylene diphenyl-diisocyanat (MDI)—a precursor for the preparation of polyurethane and pesticides—are among the most widely used derivatives of aniline.[2] Würster's blue (tetramethyl-phenylenediamine, TMPD) for instance is a currently used redox reagent in analytical biochemistry for testing cytochrome c oxydase production in bacteria.[3] Moreover, its tetra-N-alkylated paraphenylenediamine (TAPD) analogs are reversibly oxidized to the corresponding radical cation or dication.[4] This property has been exploited for the development of cation sensors[5] and more recently for original cation release systems.[6] In this respect, the TAPD unit is a particularly efficient and well-adapted redox system, since one nitrogen is integrated into both the redox center as well as into the attached specific metal coordinating ligand. The sensing and release properties are based on the dependence of the respective association constant changing upon oxidation of the TAPD unit due to a partial localization of a positive charge onto the amine moiety, which significantly decreases its coordinating ability for cations.[6,7]

The synthetic challenge of targets such as compound **5**[6,8] consists in the preparation of dissymmetrically substituted TAPD, one nitrogen being integrated into the ligand, the other one remaining free to be attached to a solid support such as an electrode surface or to another molecule for labeling purpose. Hence, there is strong interest for developing a fast and operative synthetic platform for this class of compounds. Classic strategies involve the palladium or copper catalyzed aminations and the dialkylation of aniline derivatives, the latter sometimes encountering difficulties resulting from the weak nucleophilicity of aromatic amines.[2a] A more straightforward access to N-alkylated 4-halo-anilines and 1,4-diamino-benzenes (phenylene diamine: PDA) was described by Pearson,[9] based on the activation of halo-arenes by metal complexation.[10] The nucleophilic aromatic substitution of the dichlorobenzene iron η^6 complex **1** being the key step of the synthesis, a large variety of commercially available amines can be employed as nucleophiles leading directly to a wide series of desired target compounds.
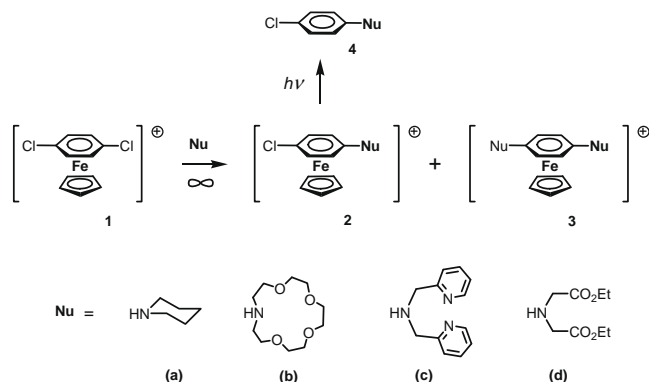
It is well known that ultrasonic irradiations may promote chemical and electrochemical reactions, by increasing reaction kinetics, giving higher yields, cleaner products and occasionally higher selectivities.[11] In this work we report the assistance of ultrasound waves in the substitution of compound **1**.

The starting material **1** was prepared as described before.[6] The nucleophilic substitution of compound **1** needed at least 5 days at

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room temperature and 12–48 h under reflux conditions depending on the nature of the solvents and the substrate. However, selective monosubstitution is generally favored by stronger kinetic control at low temperature or in less polar solvents. By increasing either the temperature or the solvent polarity, disubstitution is favored and symmetric or dissymmetric PDAs can be obtained. With the aim of decreasing the reaction time at low temperatures and thus maintaining high selectivity, we employed ultrasonic irradiation using a standard commercial cleaning bath operating at a frequency of 42 kHz.[12] In a systematic study, compound **1** was reacted with piperidine in the presence of pyridine, leading to a mixture of the monosubstituted (**2a**) and the disubstituted (**3a**) product shown in Scheme 1. Since ultrasonic irradiation slightly raises the bath temperature, all reactions in this work were performed at 45 °C, thus avoiding a thermostated cooling system. Table 1 displays the relative yields of **2a**, **3a**, and the remaining starting material determined by ^{1}H NMR spectroscopy. The reactions were carried out in four different solvents with significantly different outcomes.

Using almost equimolar amounts of piperidine and complex **1**, after 1 h, less than 50% conversion was observed in THF (see Table 1). Increasing the solvent polarity by switching to acetonitrile, the reaction time could be considerably shortened (entry 3). When using a fourfold excess of amine under the same conditions, compound **1** was completely converted into **2a** and **3a** with a ratio of 95:5 in less than 15 min (entry 4). Maintaining the ultrasound bath

at room temperature (entry 6) does not change the yield of the ultrasound-induced reaction.

In more polar solvents, such as DMF, the selectivity for the monosubstituted product decreased considerably. After 30 min, almost 20% of disubstituted **3a** was obtained (entry 8). When using a 10-fold excess of piperidine, the yield increased to 34% (entry 10). In DMSO the reaction (4 equiv of piperidine) afforded after 1 h over 40% of **3a**. In all cases, longer irradiation (several hours) did not significantly change the product ratios but was leading to partial degradation of the products and thus to lower yields.

Considering the weaker nucleophilicity of the secondary amines **b**, **c**, and **d** (see Scheme 1) compared to piperidine, DMF seemed to be the ideal solvent for mono substitution. As shown in Table 2, this assumption could be confirmed by the results obtained for the 1-aza-15-crown-5 (**b**) and the dipicolylamine (**c**). Only in the case of imino-diethylacetate (**d**) no reaction took place and the unreacted starting compound **1** was recovered.

Photochemical decomplexation[13] of the compounds **2a–c** occurred in high yields (up to 90% for **1**→**4**), giving the para substituted chloro-benzenes **4a–c**,[14] confirming the structures of the corresponding iron complexes **2** (Scheme 1).

This reaction procedure was applied to the synthesis of TAPD aza-crown ether **5** (Scheme 2). The subsequent reactions of compound **1** with the 1-aza-15-crown-5 ether and then with piperazine in DMF afforded without any further purification the corresponding dissymmetrically disubstituted iron complex. The crude reaction product was dissolved in acetonitrile and irradiated with UV light, affording the free phenylene diamine derivative **5**[14] following the general reaction procedure.[12,13] The three-step synthesis demands a single chromatographic purification as the only separation method in an overall yield of 78%.

In conclusion, using a simple ultrasonic bath, the ultrasound promotion of the nucleophilic aromatic substitution of a dichlorobenzene iron (II) complex by various secondary amines proved to be a particularly elegant, simple, and useful method. The reaction time at moderate temperatures was considerably shortened compared to non sonicated reaction conditions. Selective mono- or di-substitution was achieved by the tuning of the amine nucleophilicity and the solvent polarity. The method was successfully applied to the synthesis of N,N′-tetra-alkylated phenylenediamines, an important class of compounds.

Scheme 1.

Table 1
Relative yields of the reaction between piperidine and **1** under ultrasonic irradiation at 45 °C

Entry	Solvent	Piperidine (equiv)	Time (min)	**1**[a] (%)	**2a**[a] (%)	**3a**[a] (%)
1	THF	1.2	30	64	36	—
2		1.2	60	55	42	3
3	CH$_3$CN	1.2	30	45	52	3
4		4	15	—	95	5
5		4	30	—	94	6
6		4	15[b]	—	94	6
7	DMF	4	15	—	90	10
8		4	30	—	83	17
9		4	60	—	73	27
10		10	30	—	66	34
11	DMSO	4	15	—	91	9
13		4	30	—	85	15
14		4	60	—	57	43

[a] The yields were determined by ^{1}H NMR spectroscopy. The reaction conditions are described in the general procedure.
[b] Bath at room temperature.

Table 2
Reaction between **1** and various nucleophiles in DMF under ultrasonic irradiation at 45 °C

Cmpd.	Nucleophile (4 equiv)	Time (min)	**1**[a] (%)	**2**[a] (%)	**3**[a] (%)
a	Piperidine	15	—	90	10
		30	—	83	17
b	1-Aza-15-crown-5	15	—	93	7
		30	—	90	10
c	Dipicolylamine	15	—	92	8
		30	—	89	11
d	Imino-diethylacetate	15	100	—	—
		60	100	—	—

[a] The relative yields were determined by ^{1}H NMR spectroscopy. The reaction conditions are described in the general procedure.
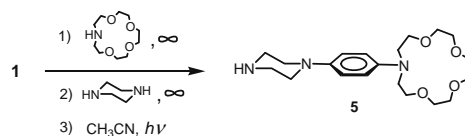
Scheme 2.

Acknowledgments

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12. *General procedure of the ultrasound-assisted reactions*: A mixture of compound **1** (50 mg, 0.12 mmol), pyridine (0.5 mL), anhydrous solvent (1.5 mL) and the desired nucleophile was introduced in a glass vial ($V = 5$ mL) and closed with a septum. After homogenization, the sample was irradiated by ultrasound using a Branson 1510 MTH apparatus operating at 42 kHz (70 W). The temperature of the bath was maintained to 45 °C if not indicated otherwise. The solvent was removed by evaporation (high vacuum distillation) and the resulting solid residue was washed twice with petrol ether (10 mL). The NMR spectrum was recorded in acetone-d_6 on a 250 MHz AC Bruker apparatus.
13. *General procedure of the photochemical decomplexation*: The solid substitution product was dissolved in acetonitrile (20 mL) and irradiated with UV light ($\lambda = 412$ nm) for 3–4 h. Filtration of the brownish precipitate and subsequent evaporation of the solvent yielded the resulting amines. Column chromatography on silica gel afforded the pure product in high yields (up to 90% over two steps **1→4**).
14. *Characteristic spectroscopic data*: Compound **4a**: MS (CI⁺, CH₄), *m/z* 196 (100%, M+H with ³⁵Cl), 198 (32%, M+H with ³⁷Cl). Compound **4b**: MS (CI⁺, NH₃) *m/z* 310 (M+H, 100%, ³⁵Cl), 312 (M+H, 42%, ³⁷Cl). Compound **5**: MS (CI⁺, NH₃): *m/z* 380 (100%, M+H). ¹H NMR (CD₃CN) δ 6.99 (2H, d, *J* = 9 Hz, aromatic), 6.74 (2H, d, *J* = 9 Hz, aromatic), 3.79–3.66 (16H, m, CH₂), 3.37 (4H, t, *J* = 4.7 Hz, CH₂–N), 3.06 (4H, t, *J* = 4.7 Hz, piperazinyl-CH₂), 2.74 ppm (t, *J* = 4.7 Hz, 4H, piperazinyl-CH₂).

^{1}H NMR (250 MHz, acetone-d_6): phenylene protons (–C₆H₄–)

Cmpd.	Chemical shifts (ppm)	Coupling
1	7.00	s
2a	6.07, 6.53	dd, *J* = 7 Hz
2b	6.11, 6.51	dd, *J* = 7 Hz
2b	6.10, 6.49	dd, *J* = 7 Hz
3b	5.76	s
3b	5.48	s
3b	5.44	s
4b	6.94, 7.18	dd, *J* = 9 Hz
4b	6.68, 7.15	dd, *J* = 9 Hz
4b	6.71, 7.09	dd, *J* = 9 Hz