Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201300880

A Versatile Metal-Free Intermolecular Aminochlorination of Alkenes

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Received: September 30, 2013; Published online: January 10, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300880.

Abstract: New reaction conditions for the rapid and productive intermolecular aminochlorination reaction of alkenes using a combination of chloramine-T and a Brønstedt acid are described. Upon simple protonation of chloramine-T, conditions for a mild and selective aminochlorination are obtained. In addition, the reaction can proceed to form either of the two possible regioisomers, depending on whether a stoichiometric amount of such an acid activator or acetic acid is used as solvent. The reaction is operative for all different classes of alkenes. A total of over 50 examples is presented to illustrate this concept.

Keywords: alkenes; aminochlorination; Brønstedt acids; chloramine-T; oxidation

Introduction

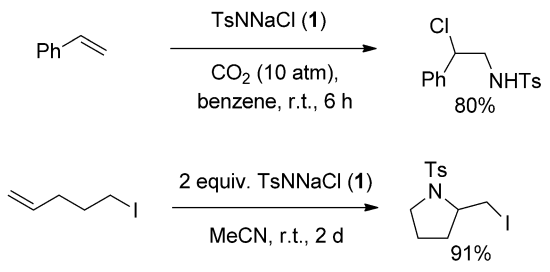
The vicinal difunctionalization of alkenes under intermolecular reaction control constitutes a veritable challenge in oxidation. At the same time, it represents an important synthetic approach in order to accomplish selective transformation of bulk materials into building blocks of higher complexity for subsequent diversification. Few truly general reactions have been developed so far.[1] Arguably, the most prominent example continues to be the osmium-catalyzed dihydroxylation reaction.[2] Additional metal-catalyzed difunctionalization reactions are available,[1,3] and recent progress has also centered on metal-free reactivity.[4–6]

Commercially available chloramine-T (**1**)[7] is a particularly useful oxidant that has found broader application in organic synthesis. For example, it serves as a suitable nitrene precursor and has found significant application in various alkene oxidation reactions such as the osmium-catalyzed aminohydroxylation[1,3a,8] and metal-catalyzed aziridination reactions.[9] Certain conditions were described for chloramine-T promoting the direct aziridination of alkenes without the requirement of a metal promoter.[10]

In addition, the N–Cl functionality in chloramine-T should be attractive for metal-free aminohalogenation reactions.[11] For the realization of such vicinal oxidation reactions, significant work was achieved by Minakata and Kumada. Different conditions were reported, which include the use of supercritical CO_2,[12] or hypervalent iodine reagents[13] as well as ω-iodoalkenes for oxidative pyrrolidine formation (Scheme 1).[14]

In general, aminohalogenation reactions have received wide attention due to the importance of the vicinal chloramine products as building blocks in organic synthesis.[11] These reactions have been widely developed using metal promoters to effect activation of the respective *N*-chloroamines prior to alkene oxidation. Among several other examples, the metal-catalyzed aminochlorination with chloramine-T has been explored.[15,16]

We here show that transition metal activation can be replaced by protonation of chloramine-T with



Scheme 1. Representative metal-free aminohalogenation reactions based on chloramine-T.

Brønstedt acids, which gives rise to an unexpected direct aminochlorination of alkenes under mild conditions. The reaction has an unprecedentedly broad substrate scope as it proceeds with all classes of alkenes. In addition, the regioselectivity of the reaction can be tuned according to the reaction conditions.

Results and Discussion

We started the screening for styrene as substrate (Table 1). As expected, no reaction takes place in the sole presence of 1.2 equivalents of chloramine-T even at elevated temperatures (entry 1). However, a clean aminochlorination is induced by the addition of an equimolar amount of pivalic acid (entry 2). Lowering the amount of acid activator decreases the yield in a proportional manner, while no reaction proceeds at lower temperature (entries 3 and 4). Among alternative proton sources, benzoic acid gives a comparable aminochlorination, while ammonium fluorides lead to reduced yields (entries 5–7). Interestingly, the regioisomeric product **4a** was formed when the reaction was carried out in acetic acid as solvent (entry 8).[17]

Under the conditions of activation with pivalic acid the reaction performs well for a series of monosubstituted alkenes (Table 2).

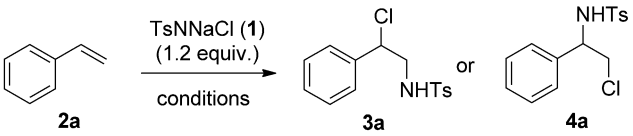
These include all kinds of styrenes bearing *para*-*meta*- and *ortho*-substituents as well as three allylbenzenes. The robustness of the reaction was further demonstrated by a reaction of **2a** on 95-mmol scale providing 27 g of the corresponding aminochlorinated product **3a** within a single reaction.[18] Aliphatic substituents are equally tolerated and products **3k–3n** were isolated as single regioisomers. For the latter example of **3n** from 5-hexenenitrile the structure was unambiguously secured by X-ray analysis.[19] Formation of **3n** underlines the selectivity of the aminochlorination reaction as no potentially competing Ritter-type reaction product was observed.[20]

Interestingly, for styrenes bearing electron-donating substituents, aminochlorination proceeds with inversion of regioselectivity as determined for products **4a–d**, **4g** and **4i–k** (Table 3). As observed during the screening process, such an inverted regioselectivity is observed as the general outcome from reactions in acetic acid as solvent, regardless of the nature of the substituent. This is illustrated for the cases of 4-bromo- and 4-chlorostyrene as well as 3-fluorostyrene and 1-octene. In these cases products **4e**, **4f** and **4h** are formed as regioisomers of **3b**, **3c** and **3g**, respectively. Only for 1-octene was the product formed in a 3:1-mixture in favor of the expected regioisomer **4l**.

The same trend is observed for geminally disubstituted alkenes (Table 4). In the presence of pivalic acid as activator, selective aminochlorination in favor of the terminal amination is obtained (products **5a–5e**), while the reaction in acetic acid furnishes the corresponding oxidation products **6a–6f** from terminal chlorination. The complete change in regioselectivity is best illustrated by comparison of the products **5a** and **6a** and **5e** and **6f**, respectively.

The general features are also maintained for the aminochlorination of 1,2-disubstituted alkenes (Table 5). Here, with pivalic acid both isomers **7a** and

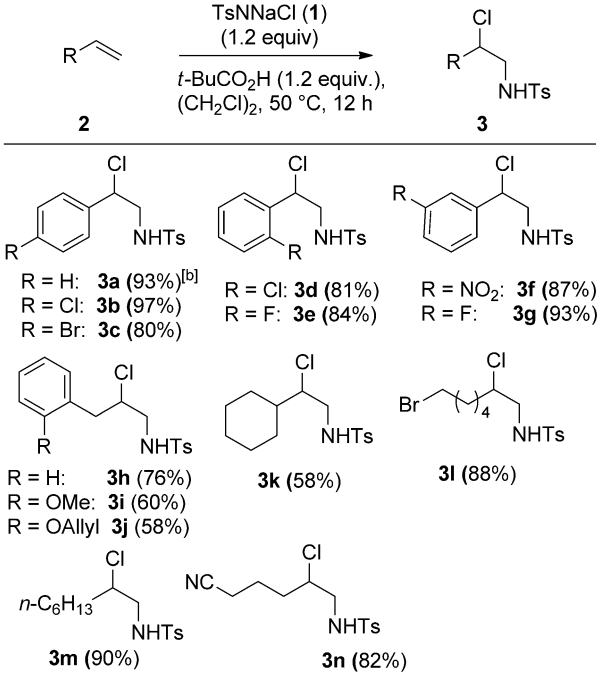
Table 1. Aminochlorination of styrene: optimization of conditions.



2a 3a 4a

Entry	Conditions	Product	Yield [%]
1	$(CH_2Cl)_2$, 50 °C, 12 h	-	-
2	*t*-$BuCO_2H$ (1.2 equiv.), $(CH_2Cl)_2$, 50 °C, 12 h	**3a**	96
3	*t*-$BuCO_2H$ (0.6 equiv.), $(CH_2Cl)_2$, 50 °C, 12 h	**3a**	45
4	*t*-$BuCO_2H$ (1.2 equiv.), $(CH_2Cl)_2$, 25 °C, 12 h	-	-
5	$C_6H_5CO_2H$ (1.2 equiv.), $(CH_2Cl)_2$, 50 °C, 12 h	**3a**	92
6	Et_3NHF (1.2 equiv.), $(CH_2Cl)_2$, 50 °C, 12 h	**3a**	66
7	HF-py (1.2 equiv.), $(CH_2Cl)_2$, 50 °C, 12 h	**3a**	77
8	CH_3CO_2H, 50 °C, 12 h	**4a**	64

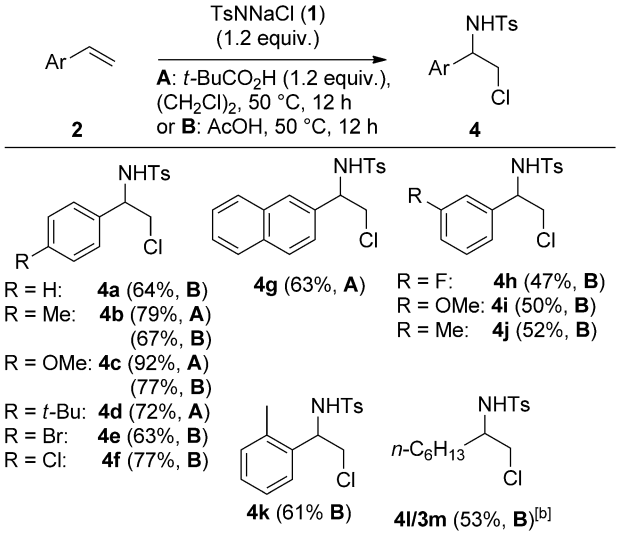
Table 2. Aminochlorination of terminal alkenes.[a]



2 3

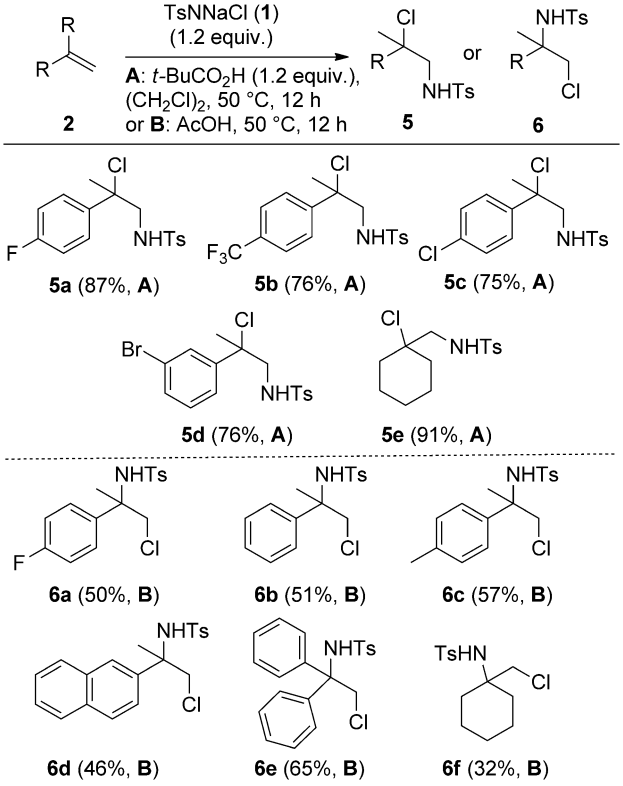
[a] Yields refer to isolated product after purification.
[b] 95-mmol scale.

Table 3. Aminochlorination of monosubstituted alkenes: inversion of regioselectivity.[a]



[a] Yields refer to isolated product after purification.
[b] 3:1 regioisomeric mixture.

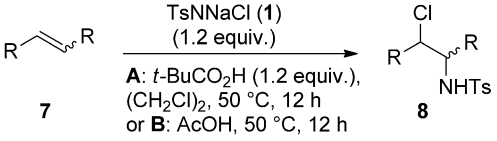
Table 4. Aminochlorination of 1,1-disubstituted alkenes.[a]



[a] Yields refer to isolated product after purification.

7b of β-methylstyrene undergo regioselective aminochlorination to a comparable product formation of **8a**/**8a′** in a 4–5:1 diastereomeric ratio (entries 1 and 2).

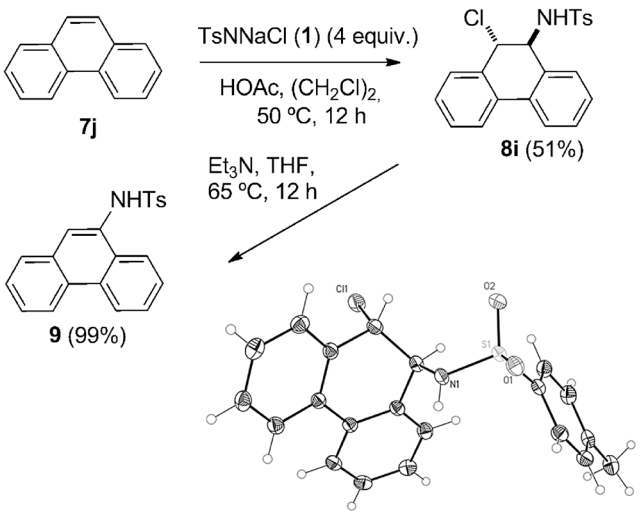
Table 5. Aminochlorination of 1,1-disubstituted alkenes.



Entry	Substrate	Conditions	Product(s)	Ratio	Yield [a]
1	**7a**	A	**8a** + **8a′**	5:1	88%
2	**7b**	A	**8a** + **8a′**	4:1	89%
3	**7a**	B	**8b** + **8b′**	4:1	50%
4	**7b**	B	**8b** + **8b′**	7:1	57%
5	**7c**	A	**8c** + **8c′**	5:1	51%
6	**7d**	A	**8c′**	5:1	61%
7	**7e**	A	**8d** + **8d′**	1.7:1	71%
8	**7f** (Ar = 4-Cl-C_6H_4)	A	**8e** + **8e′**	2.5:1	67%
9	**7g**	A	**8f** + **8f′**	2:1	75%
10	**7h**	A	**8g**		50%
11	**7i**	A	**8h**		54%

[a] Isolated yield after purification.

For acetic acid, the corresponding regioisomers of **8b**/**8b′** in a 4–7:1 diastereomeric ratio are formed (entries 3 and 4). For the cinnamic esters **7c** and **7d** the regioselective aminochlorination provides the two 1,2,3-trisubstituted products **8c**/**8c′** in 5:1 *dr* (entries 5 and 6). Stilbenes **7e** and **7f** provide the corresponding products in high yields, although with diminished *dr* (entries 7 and 8), while aminochlorination of indene again proceeds with the expected full regioselectivity (entry 9). Finally, two aliphatic substrates, cyclopentene **7h** and 1,5-cyclooctadiene **7i** provide aminochlorination products **8g** and **8h** as single diastereoisomers.



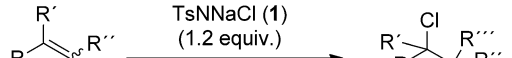
Scheme 2. Aminochlorination reaction of phenanthrene.

In addition to isolated alkenes, the aminochlorination of phenanthrene gave the expected oxidation at C-9 and C-10 (Scheme 2). The corresponding product **8i** is formed as a single diastereomer in 51% yield. Treatment of the aminochlorination product with base provides the expected re-aromatization to give 9-tosylamidophenanthrene **9** in quantitative yield. The reaction can also be conducted as a one-pot sequence, thereby formally resembling an aromatic C–H amination reacion.

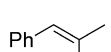
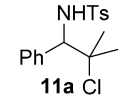
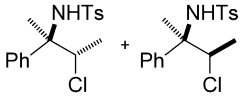
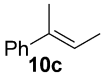
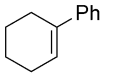
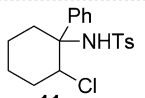
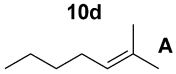
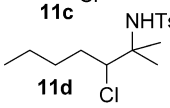
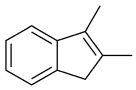
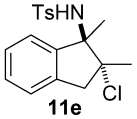
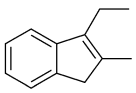
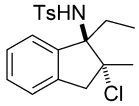
While higher substituted alkenes usually constitute a challenge for vicinal oxidation of alkenes, the present protocols tolerates both tri- and tetrasubstituted alkenes (Table 6). Here, a single regioisomer **11a** was formed under both reaction conditions **A** and **B** in the oxidation of β,β-dimethylstyrene (entries 1 and 2). Again independent of the conditions, a single regioisomer is obtained as a 1:1-diastereomeric mixture in the case of the aminochlorination of α,β-dimethylstyrene (entries 3–5), and consequently, 1-phenylcyclohexene gives a single product **11c** (entry 6). Alkene **10e** bearing three alkyl substituents again provides a single isomer, albeit with low overall yield (entry 7). Finally, the two tetrasubstituted alkenes **10f** and **10g** form single regio- and diastereomeric products **11e** and **11f** in 60 and 80% isolated yields, respectively (entries 8 and 9), and the expected relative configuration was confirmed from an X-ray analysis of **11f**.[19]

These entries demonstrate that with the successful examples of aminochlorination on monosubstituted, (*E*)- and (*Z*)-disubstituted, 1,1′-disubstituted, (*E*)- and (*Z*)-trisubstituted and tetrasubstituted alkenes, all the seven different alkene classes are within the substrate scope. This is a particularly broad scope, which is only common to the dihydroxylation of alkenes[1,2] and which should promote reliable applications in organic synthesis.

Table 6. Aminochlorination of tri- and tetrasubstituted alkenes.



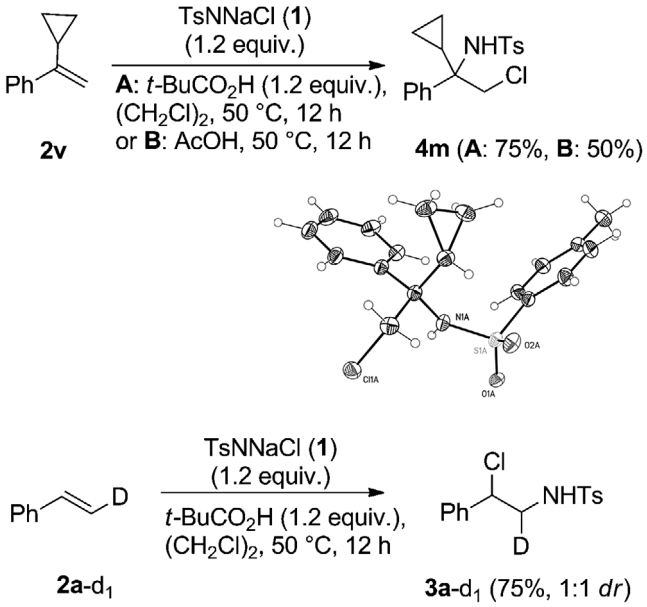
10 11

Entry	Substrate	Conditions	Product(s)	Yield [%][a,b]
1	 10a	A	 11a	43 (91)
2		B		30 (95)
3	 10b	A	 11b + 11b′	47 (92)
4	 10c	A	11b + 11b′	43 (95)
5		B	(11b:11b′= 1:1)	30 (98)
6	 10d	A	 11c	51
7	 10e	A	 11d	15 (90)
8	 10f	B	 11e	60 (95)
9	 10g	B	 11f	80

[a] Isolated yield after purification.
[b] Yields in brackets based on re-isolated starting material.

Based on control experiments (Scheme 3), the Brønstedt acid-mediated aminochlorination is suggested to be an ionic process. The involvement of radical intermediates is ruled out on the basis of the α-cyclopropylstyrene **2v**, which forms a single product **4l** without degradation of the cyclopropyl substituent. Aminochlorination of the monodeuterated styrene **2a**-d_1 reveals the formation of an equimolar mixture of diastereomers. This loss of diastereoselectivity is the consequence of the involvement of a cationic intermediate, which leads to diastereomeric equilibration at the benzylic position. For the observed cases of internal alkenes, the independence of the product configuration from the alkene geometry and the formation of diastereomers are the consequences of such intermediates.

Such stereochemical infidelity was also observed when an attempt toward enantioselective aminochlorination[21] was carried out in the presence of 10 mol% of $(DHQD)_2PHAL$. Although a four-fold



Scheme 3. Control experiments.

rate enhancement was observed for the transformation of **2a** into **3a**, the latter one was isolated only in racemic form.

Although the exact mechanistic context must await further studies, we suggest the following two reaction pathways to be involved (Figure 1). First, for simple acid activation the neutral species TsNHCl will be generated that provides an electrophilic nitrogen for subsequent attack from a neutral, sterically non-hindered alkene. This attack generates an aziridinium intermediate[11] with certain stereochemical lability in the case of the benzylic position. Recombination with

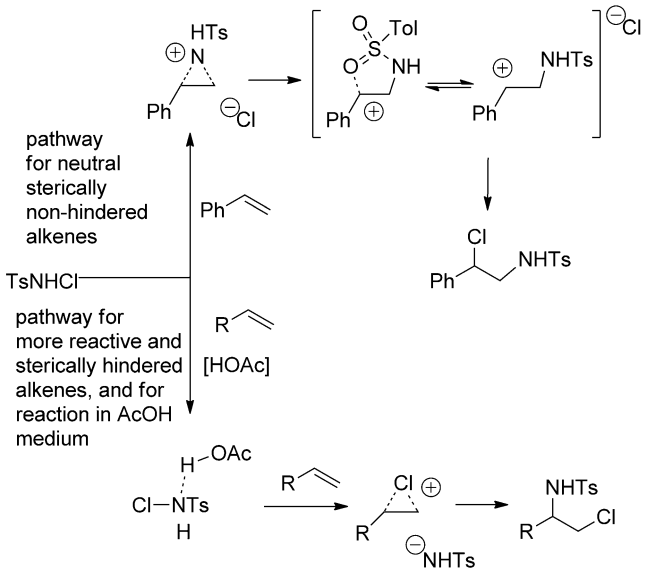
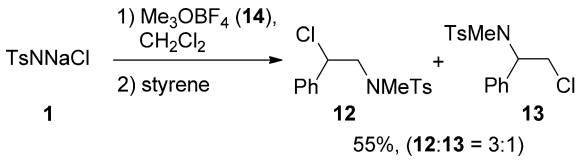


Figure 1. Mechanistic proposal.



Scheme 4. Aminochlorination reaction of styrene using an activation through *N*-alkylation.

the chlorine anion results in regioselective aminochlorination product.

For more reactive and sterically more demanding alkenes, the more accessible chlorine of TsNHCl will serve as the electrophilie in the initial alkene attack. The same should happen in acetic acid; with acetic acid as reaction medium, partial protonation of the nitrogen in *N*-chlorotosylamide through the acid network should enhance the electrophilicity of the attached chlorine atom. These reactions involve a chloronium intermediate[11] and will ultimately undergo Markovnikov-type C–N bond formation.

Alternative to protonation, the electrophilic activation of chloramines-T also proceeds through alkylation. For example, treatment of chloramine-T with Meerwein salt **14** followed by reaction with styrene leads to a clean process of aminochlorination in 55% yield (Scheme 4). The formation of *N*-chloro-*N*-methyltosylamide as the reactive reagent was confirmed by its independent isolation after step 1.[22]

Conclusions

In summary, we have described conditions for an unprecedented metal-free aminochlorination reaction of alkenes, which is of experimental ease and can be conveniently upscaled. The reaction is based on Brønstedt acid activation of chloramine-T and provides an unparalleled substrate scope, and its regioselectivity can be switched according to the reaction conditions.[23] It is a rare example of an alkene oxidation reaction that is operative for all seven classes of alkenes as substrates.

Experimental Section

Typical Procedures

Conditions A: A Pyrex tube equipped with a stirrer bar was charged with 142 mg chloramine-T (0.50 mmol, 1.2 equiv.), 51 mg pivalic acid (0.50 mmol, 1.2 equiv.) and the alkene (0.42 mmol, 1 equiv.) in 0.6 mL of absolute dichloroethane. The solution was stirred at 50 °C for 20 h. After cooling down to room temperature, CH_2Cl_2 was added and the residue was washed with a saturated aqueous solution of $NaHCO_3$. The solvent was evaporated under reduced pres-

sure and the crude product was purified by chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) to give the pure aminochlorinated product.

Conditions B: A Pyrex tube equipped with a stirrer bar was charged with 240 mg chloramine-T (0.84 mmol, 2.0 equiv.) and the alkene (0.42 mmol, 1 equiv.) in 0.6 mL of AcOH. The solution was stirred at 50 °C for 20 h. After cooling down to room temperature, CH_2Cl_2 was added and the residue was washed with a saturated aqueous solution of $NaHCO_3$. The combined organic layers were extracted with CH_2Cl_2 (3×) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was purified by chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) to obtain the pure aminochlorinated product.

Acknowledgements

The authors thank Fundación ICIQ and the Spanish Ministerio de Economía (CTQ2011-25027) for financial support, and Dr. Eduardo Escudero, Dr. Marta Bahamonte and Dr. Eddy Martin from ICIQ's X-Ray Department for the solid state structures.

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