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Efficient Route to Deuterated Aromatics by the Deamination of Anilines

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Supporting Information

ABSTRACT: One-step replacement of NH_2 groups in ring-substituted anilines by deuterium is reported. Approaches comprising both solid-phase and solution-phase syntheses can be used on a large variety of substrates. The method uses diazotization in a mixture of water and either dichloromethane or chloroform, which serve as a source of hydrogen. This protocol can be used as a general method for fast and easy incorporation of deuterium into an aromatic system using deuterated chloroform.

Deuterated compounds play significant roles in many areas of chemical research, such as the study of reaction mechanisms,[1] as important internal standards in mass spectrometry, or as additives in various NMR experiments. They are irreplaceable in elucidation of biosynthetic pathways and may enhance metabolic stability of drugs (so-called "heavy drugs")[2,3] when deuterium can be advantageously incorporated into active pharmaceutical ingredients. Although the application of deuterated compounds is very broad, current labeling methods[4−10] suffer from complexity, limited scope, and the use of expensive reagents. Another drawback of currently known methods is their incompatibility with the requirements of solid-phase chemistry, an important tool in many applications, including peptide synthesis. To the best of our knowledge, no rapid, mild, quantitative, metal-free, and inexpensive method for the labeling of aromatic compounds exists to date.

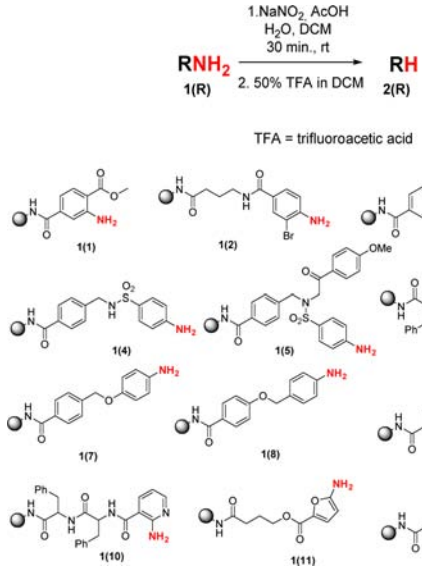
Herein, we report a fast, efficient one-step method for the reductive deamination of aromatic amines either in solution or on a solid support, which can serve as a tool for the removal of amino groups and for the easy introduction of deuterium into the system.

As a model system for one-step deamination, we suggest a biphasic water/dichloromethane mixture. This mixture is compatible with reactions in solution and was successfully applied in reduction on a solid support.[11] The water layer allows easy diazotization via a standard application of nitrite; dichloromethane serves as a hydrogen donor similarly to H_3PO_2,[12] $LiAlH_4$,[13] $NaHSO_3$,[14] DMF,[15] or THF,[16] application of which is more complicated and/or use for deuterium insertion is almost impossible. The biphasic system can also be advantageous for the easy separation of final products from inorganic and unreacted diazonium salts.

Reaction on Solid Support

Before the study of deuteration, which may possibly be complicated by isotopic effects, we attempted to verify the deamination principle with nondeuterated dichloromethane with selected amines according to Scheme 1.

Scheme 1. General Principle of Deamination on Solid Phase



Various aromatic amines, substituted by electron-withdrawing groups (anilines **1(1)**−**1(5)**), electron-donating groups (anilines **1(6)**−**1(9)**), and heterocyclic anilines (anilines **1(10)**−**1(12)**) were immobilized on Rink resin (Scheme 1). As shown in Table 1, deamination proceeds for all aromatic anilines that we chose. The yields of the reactions appear moderate; however, they comprise the entire reaction sequence, including the construction of starting compound **1**, deamination, and final HPLC

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Table 1. Crude Purities and Isolated Yields of Deaminated Products

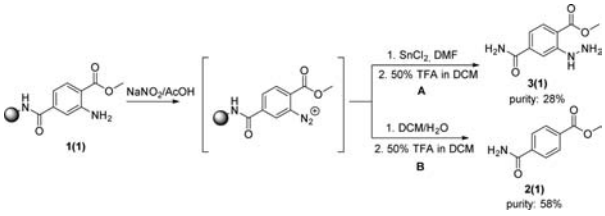
substitution (R)	purity of 1(R) (%)[a]	purity of 2(R) (%)[a]	yield of 2(R) (%)[b]
(1)	91	62	45
(2)	100	80	38
(3)	78	85	39
(4)	80	68	41
(5)	85	80	26
(6)	90	90	43
(7)	84	65	30
(8)	80	62	32
(9)	82	27	19
(10)	90	*c*	
(11)	82	*c*	
(12)	65	*c*	

[a]Determined by LC/MS directly after cleavage. [b]Overall yield calculated to the initial loading of the resin after cleavage and HPLC purification. [c]No conversion (**1(10)**) or decomposition (**1(11)** and **1(12)**).

purification with individual efficiency; therefore, the success of the deamination step is evaluated as the change in purity between starting compound **1** and product **2** (Table 1). This method failed for the heterocyclic substrate **1(10)**, which did not undergo diazotization, and derivatives **1(11)** and **1(12)**, which decomposed. The problematic diazotization of heterocyclic amines previously described in the literature[17] and the low stability of some diazonium salts limit this reaction.

To support our theory that the diazonium salt is the real intermediate, we treated aniline **1(1)** with $NaNO_2$ in AcOH. One part of the resin was reacted with $SnCl_2 \cdot 2H_2O$ in DMF (Scheme 2, path A), and the second part was reacted with DCM

Scheme 2. Direction of the Reaction toward Deamination (Path A) or Reduction (Path B)



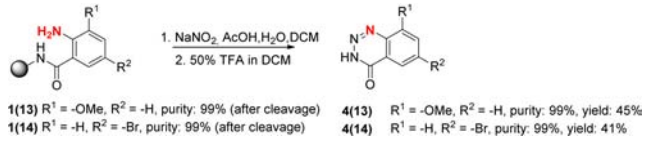
and water (Scheme 2, path B). Treatment with $SnCl_2 \cdot 2H_2O$ afforded expected hydrazine **3(1)**, which is evidence of diazonium salt formation. Treating the diazonium salt with DCM/water afforded a clearly deaminated product **2(1)**.

Additionally, compounds bearing two amino groups **1(13)** and **1(14)** that are able to form a triazine ring via a competitive intramolecular coupling reaction were chosen. These compounds yielded only benzotriazinones **4(13)** and **4(14)**, respectively, verifying that the intramolecular cyclization proceeds faster than diazo group substitution under this experimental conditions (Scheme 3).

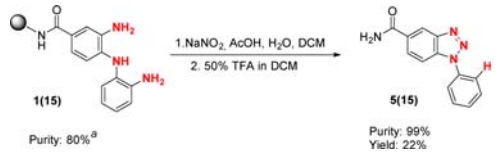
When three amine groups are introduced in one system, a combination of competitive reactions occurred, and deaminated triazole **5(15)** formed (Scheme 4).

Consequently, two experiments with cheaper chloroform, which works with the same efficiency as DCM, were carried out to prove the source of the hydrogen formally replacing the amino group (Table 2).

Scheme 3. Formation of Benzotriazinone Rings from Diamines



Scheme 4. Combination of Deamination and Triazole Formation



[a]Purity was determined after cleavage and is decreased due to formation of trifluoroacetyl derivatives.

Table 2. Influence of the Deuterated Solvents on the Structure of the Final Compound

entry	chloroform	water	acetic acid	D/H (%)
1	$CHCl_3$	D_2O	CD_3CO_2D	0
2	$CDCl_3$	H_2O	CH_3CO_2H	75
3	$CDCl_3$	D_2O	CD_3CO_2D	75

These results indicate that the amino group was replaced by the deuterium from chloroform. The reaction with $CDCl_3$ was then used for transfer of deuterium to the aromatic ring. Although the reaction proceeded with the same purity, the deuteration was incomplete (Scheme 5 and Table 3).

Scheme 5. General Principle of Deuteration on Solid Phase

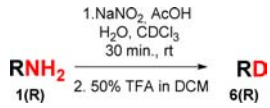


Table 3. Deuteration on a Solid Phase

entry	1(R)	D/H (%) in 6(R)
1	1(1)	38
2	1(2)	75
3	1(4)	68
4	1(8)	38
5	1(15)	46

According to these results, we hypothesized that the competitive source of hydrogen is the linker or polymeric matrix. Significant difference between the same polymer equipped with a different linker of similar loading (Table 4, entries 2 and 4) confirms that the linker is a competitive donor of hydrogen. Remarkable difference between two different polymer supports with the same linker (Table 4, entries 2 and 5) confirms that the polymeric support can be the competitive source of hydrogen. Higher D/H ratio in the reaction of the same substrate with a lower loading resin, in which the reactive sites are located mainly on the surface and top part of the pores (Table 4, couples of entries 1, 2 and 3, 4), can be explained by a diminishing interaction of the substrate with the polymeric matrix in deeper and tighter pore parts.

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Table 4. Deuteration of 1-Methyl-2-aminoterephthalate on Different Solid Supports

entry	resin (loading in mmol/g)	D/H (%) in **6(R)**
1	Rink[a] (0.60)	38
2	Rink[a] (0.35)	45
3	Wang[a] (0.85)	84
4	Wang[a] (0.44)	>99
5	TentaGel Rink (0.37)	8

[a]Linker is bound to standard Merrifield resin.

After evaluation of the contribution and efficiency of each of the variables in the system, we chose the system that gave the best results—low-loading Wang linker—and investigated deuteration of more substrates (Figure 1 and Table 5).

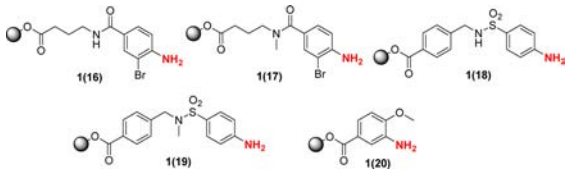

Figure 1. Deamination of substrates on a Wang linker according to Scheme 1.

Table 5. Deamination of Substrates on a Wang Linker

entry	**1(R)**	D/H (%) in **6(R)**
1	**1(16)**	64
2	**1(17)**	60
3	**1(18)**	36
4	**1(19)**	60
5	**1(20)**	18

It is obvious that there is no guarantee of quantitative deuteration, and the structure−reactivity relationship is difficult to determine. Isotopic purity is dependent on resin and the structure of the substrate; therefore, high or complete isotopic purity is only obtained when a specific combination of all factors occurs. Although the deuteration is not quantitative for the majority of substrates, the isotopic mixture could be further purified by HPLC or GC depending on the substrate's nature.[18,19]

Reaction in Solution

The reaction in solution was performed comparatively with $CHCl_3$ and $CDCl_3$ (Scheme 6).

For this experiment, we chose simple and easily accessible amines with various electronic properties (Scheme 6). First, we performed deamination in solution in which all solvents were nondeuterated. Subsequently, the substrates were subjected to the same reaction with deuterated chloroform. Purities and yields of both products (protonated/deuterated) are summarized in Table 6.

Scheme 6. Deamination in Solution of Selected Amines

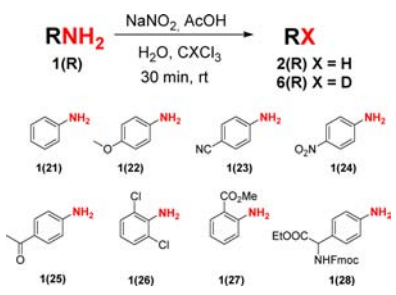

Table 6. Deamination/Deuteration in Solution

entry	amine	yield of **2(R)**[a] (%)[c]	yield of **6(R)**[b] (%)[c]	D/H in **6(R)**[b] (%)[d]
1	**1(21)**	*e*		
2	**1(22)**	*e*		
3	**1(23)**	66	51	>99
4	**1(24)**	87	43	>99
5	**1(25)**	70	50	>99
6	**1(26)**	58	*e*	
7	**1(27)**	60	49	>99
8	**1(28)**		60	>99

[a]Reaction with $CHCl_3$. [b]Reaction with $CDCl_3$. [c]Yield determined via LC/MS analysis of the crude reaction mixture according to the calibration curve of an appropriate standard. [d]Determined by ^1H NMR. [e]Complicated mixture of products formed.

In contrast to the solid phase, deamination in solution works only for electron-poor substrates. On the other hand, those substrates that undergo deamination are excellent starting compounds for H/D exchange and give labeled compounds with >99% isotopic purity. Figure 2 displays the ^1H NMR

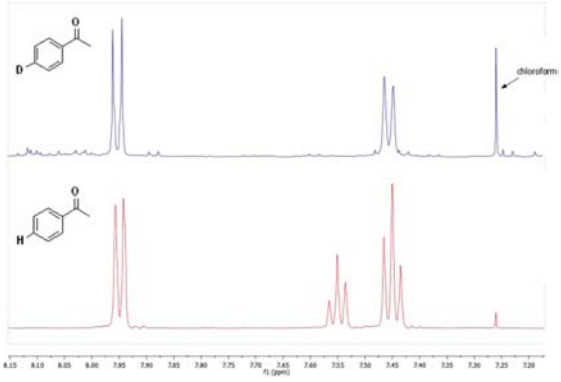

Figure 2. ^1H NMR spectrum of crude 4-deuterated acetophenone **6(25)** in comparison with the nondeuterated analogue **2(25)**.

spectrum of the crude product **6(25)** as an example of the reaction using $CDCl_3$ in comparison to $CHCl_3$. Reaction also proceeds smoothly with a pharmaceutically relevant Fmoc-phenylalanine derivative **1(28)**, affording deuterated Fmoc-phenylalanine, which is directly applicable in the solid-phase synthesis of peptide drugs.

The mechanism of the reaction can be explained by radical decomposition of diazonium salt and halogenated hydrocarbon. We tried to confirm it by addition of TEMPO as a radical scavenger. Unfortunately, the application of TEMPO in the solution-phase approach was unsuccessful because of its low solubility in water, which contains the diazonium salt. Therefore, we turned our attention to solid-phase reaction. Amine **1(1)** was treated with the usual deamination mixture in the presence of TEMPO (Scheme 7, route A). Instead of the TEMPO-bound adduct **30**, phenol derivative **31** was isolated after cleavage from the resin. The hypothesis for decomposition of TEMPO during the cleavage of the substrate from the resin was successfully confirmed by bonding of TEMPO adduct **29** to resin prepared in

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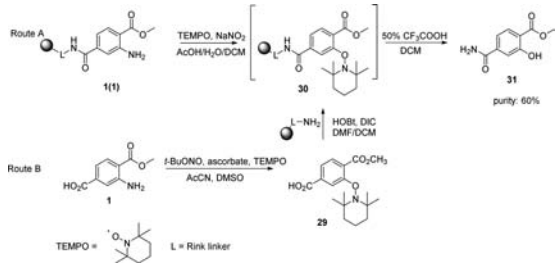
Scheme 7. Deamination in the Presence of a TEMPO Scavenger



solution and its cleaving from the resin (Scheme 7, route B). These results confirm the facile radical decomposition of diazonium salts. Presumably, these radicals react with DCM or chloroform in a subsequent step.

In conclusion, we developed a fast and efficient method for the reductive deamination of anilines that is applicable in the synthesis of deuterated compounds. This protocol is compatible with solid-phase and solution-phase chemistry. Contrary to solution chemistry, where only systems deactivated to electrophilic substitution are applicable, solid-phase approaches enable the deamination of a much wider scope of substrates. Solution deamination offers great progress in the preparation of deuterated compounds because the isotopic purity of its products is >99%. Deuteration reaction proceeds under very mild conditions (rt, catalytic amount of acid, no metal catalyst) using cheap deuterated chloroform in a short reaction time. Additionally, incorporation of deuterium into the aromatic system is very selective; its position is given by the position of the amine functionality and can be changed as demanded.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01438.

Experimental procedures, characterization, ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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