Pergamon

Tetrahedron Letters 42 (2001) 5367–5369

TETRAHEDRON LETTERS

Chemoselective one-pot reductive deamination of aryl amines

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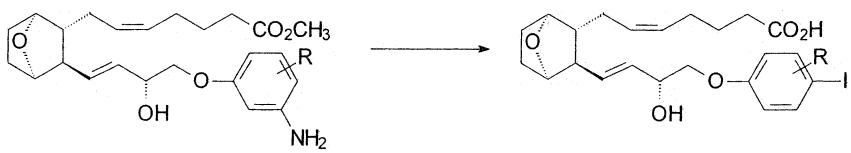
Received 15 May 2001; accepted 4 June 2001

Abstract—A one-pot deamination of a wide variety of substituted anilines is described. The process involves a diazotization-dediazotization utilizing acetic acid, sodium nitrite, and sodium bisulfite- inexpensive, 'green' reagents. The process occurs quickly under mild conditions, tolerates sensitive functionality, and gives products in modest-to-good yields (16–88%).

Deamination of aryl amines is an important reaction that has been the focus of synthetic investigations for over 100 years.[1] It is used primarily as a method for removal of amines after they have been utilized for directing electrophilic aromatic substitution reactions. The transformation is typically achieved by a two-step process involving diazotization followed by reduction with various inorganic or organic reductants including hypophosphorous acid,[2] various alcohols such as ethanol,[3] nitric oxide,[4] triphenylphosphine,[5] a variety of structurally related amides including *N*,*N*-dimethylformamide,[6] a variety of amines including triethylamine,[7] alkyl nitrites,[8] trichlorosilane[9] and ferrocene.[10] Many of these reductants have also been developed for use in catalysed as well as uncatalyzed procedures.[11] Finally, there are two methods that have been developed as 'one-pot' reactions: the direct diazotization–dediazotization with sodium nitrite in hypophosphorous acid[12] and the reaction with alkyl nitrites in dimethyl formamide.[8a] One problem with many of these methodologies is that they require the initial preparation of unstable aryldiazonium salts. A second problem is that frequently the reduction processes do not proceed well with electron donating groups in the *para* position or with any substituent in the *meta* position.[1,4b] Finally, many of these reactions proceed via radicals and thus suffer from problems common to these intermediates such as dimerization,[4a] halogen scrambling,[6] and extraction of iodine from aryl iodides.[13]

Recently we needed to utilize an amine-directed nuclear iodination followed by a deamination for the synthesis of a series of thromboxane A_2 mimetics as exemplified in Scheme 1.

Since both the starting material and final products contain sensitive functionalities, we explored several mild processes for removing the amine. The approach that we initially found best for our compounds utilized a mild diazotization method (AcOH, $NaNO_2$, ethanol, water), followed by an in situ reduction by ethanol (24°C), as described in Kornblum's review.[1a] These reductions proceeded in modest to good yield, required long reaction times at room temperature (12–32 h), and gave variable amounts of ethyl ethers derived both from displacement of the diazonium salt and some of the substituents. The rates of the reactions were faster in refluxing ethanol, but resulted in lower yields of the desired product.



Scheme 1.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)01027-9

Table 1.

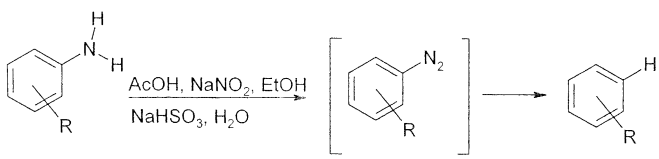
$ArNH_2$		Bisulfite reduction[15]		Ethanol reduction[14,15]	
		Yield (%)	Time (h)	Yield (%)	Time (h)
2-I, 4-CO_2CH_3	**1**	83±1	1	62	18
				72	32
2-I, 5-OCH_3	**2**	72	2	64	24
2-I	**3**	34	6	53	24
		80	20	67	38
2-I, 4-OH	**4**	16[a]	4	0[b]	24
2-CN, 3-Cl	**5**	82	4	69	24
4-CO_2CH_3	**6**	88	4	69	24
2-F, 4-Cl	**7**	83	2	75	24
3-OCH_3	**8**	73	4	0	24
2-I, 4-I, 5-SO_3H	**9**	67	4	60	24
RPPG(4-NH_2, 3-I)F[c]	**10**	26	4	5	0.5[d]

[a] 18% of the corresponding ethyl ether was isolated.
[b] A red tarry material was the only product obtained.
[c] Single letter code for amino acids.
[d] Monitoring the reaction showed the reaction gave a maximum yield at 0.5 hr which decreased with time, 3.2% at 18 h and 2.2% at 24 h.

Bisulfite is a little known[1b] reducing agent for diazonium ions that has not been extensively explored.[1a,14] Since bisulfite is such a mild reducing agent and the corresponding acid is a weak acid, we explored the ability of a mixture of bisulfite and nitrite to effect the simultaneous diazotization and reductive dediazotization of aryl amines (Scheme 2).

The anilines were dissolved in a solution of ethanol, water, and acetic acid at 24°C and a solution of sodium nitrite in water was added followed immediately by addition of aqueous solution of sodium bisulfite. The reaction was faster (1–20 h), cleaner, and consistently gave higher yields of the desired deaminated products than our previous method (Table 1).

Several features of the process are significant. Starting materials with functionality *ortho* to the intermediate diazonium group (**1**, **2**, **3**, **5**, **7**, **9**, and **10**), which have been shown to undergo displacement in other reduction schemes[1], gave good yields of the desired product and minor amounts of the corresponding ethers. Compound **4** is the exception to this observation, with 16% of the desired product and 18% of the ether being isolated. However the corresponding reduction process with ethanol gave only tarry material. Additionally, no halogen-scrambling was detected (replacement of the diazonium ion with iodine from the deaminated product), suggesting that if the reaction proceeds via a radical intermediate, trapping by the hydrogen of the bisulfite is faster than the reaction with the aryl iodides. The source of the hydrogen was briefly studied with a view to the ability of this process to provide selective deuteration and to explore the mechanism of the reaction: reaction with CD_3CO_2D, $NaDSO_3$, and C_2H_5OD gave product with exclusive (>95%) substitution of deuterium for the amine and indicates that the hydrogen is not provided by the alkyl portion of the alcohol. *meta*-Substitution, which typically decreases the yields in alcohol or hypophosphorous acid reductions,[1,4b] does not appear to significantly influence this reaction as indicated by the good yields from the reactions of compounds **2**, **5**, **8**, and **9**. Even compounds that can form diazo-quinones (**4**), and usually give lower yields of the deaminated products,[1] gave a modest yield of the deaminated product. The application of this process to highly functionalized compounds, such as the synthesis of peptides containing iodinated phenylalanines, is also successful as seen in the diazotization–dediazotization of compound **10**.



Scheme 2.

In summary, this report describes a one-pot, simultaneous diazotization–dediazotization of a wide variety of substituted anilines to give the deaminated product. The process utilizes inexpensive and relatively environmentally benign reagents—acetic acid, sodium nitrite, and sodium bisulfite. The process occurs quickly, gives products in modest-to-good yields (16–88%), and is successful even in sensitive compounds such as peptides or those with leaving groups *ortho* to the diazonium ion.

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15. Reaction conditions. *Bisulfite reduction:* the aniline (0.24 mmol) was dissolved in ethanol (10 mL) and acetic acid (1.5 mL) at room temperature. Solutions of sodium nitrite (2.4 mmol in 3 mL of water) and sodium bisulfite (2.4 mmol in 4 mL of water) were added sequentially to the stirred aniline solution. The reaction was monitored by TLC. Upon completion (1–20 h) the reaction mixture was extracted with chloroform and the organic phase washed with water. The solvent was removed under vacuum and the product isolated by chromatography over silica gel. *Ethanol reduction:* the aniline (0.24 mmol) was dissolved in ethanol (10 mL) and acetic acid (1.5 mL) at room temperature. A solution of sodium nitrite (2.4 mmol in 3 mL of water) was added to the stirred aniline solution and the reaction was monitored by TLC (0.5–36 h). The work-up and isolation was the same as described for the bisulfite reduction.