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# Direct reductive alkylation of amine hydrochlorides with aldehyde bisulfite adducts

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#### ABSTRACT

A mild procedure for the direct reaction of aromatic and aliphatic aldehyde bisulfite adducts with primary and secondary amine hydrochlorides in the presence of sodium cyanoborohydride in methanol is reported.

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The reaction of aldehydes with ammonia, primary amines or secondary amines under reductive conditions (reductive alkylation of the amines or *reductive amination* of the aldehydes) is a very useful and versatile method for the synthesis of amines.<sup>1</sup> The reaction involves first the formation of a carbinolamine, which dehydrates to form an imine/iminium salt that is subsequently reduced to the product. Although it is possible to perform the reaction in a stepwise process, with isolation of the imine/iminium salt, usually the reaction is carried out directly in one step, with the imine/ iminium salt being reduced during formation. In this second, more common approach, an obvious difficulty is avoiding the reduction of the aldehyde before its reaction with the amine. The two most commonly used selective reductor agents are hydrogen, particularly interesting in large scale reactions,<sup>2</sup> and several borohydrides such as sodium cyanoborohydride<sup>3</sup> (Borch reaction),<sup>4</sup> or sodium triacetoxyborohydride.<sup>5</sup> Numerous alternative reagents have also been used.<sup>6</sup>

A widespread problem while working with aldehydes is their instability (e.g., tendency to epimerize, undergo air oxidation to the carboxylic acid). Moreover, several liquid aldehydes are difficult to purify. Bisulfite adducts, are usually crystalline, easy to handle solids, synthesized simply by mixing the aldehyde with aqueous sodium bisulfite. They show desirable physical properties such as facile isolation and purification and can be stored for prolonged

http://dx.doi.org/10.1016/j.tetlet.2014.03.046 0040-4039/© 2014 Elsevier Ltd. All rights reserved. periods of time.<sup>7</sup> Although the most common used counterion in the preparation of aldehyde bisulfite adducts is sodium, very recently Kissane et al. have reported that, for several aldehydes, the potassium bisulfite adduct shows more advantageous solid state properties.<sup>8</sup>

Surprisingly, the direct use of the bisulfite adducts of aldehydes in reductive amination reactions has scarcely been reported in the scientific literature. In a pioneering work, Pandit and Mani reported in 2009 that secondary amines may be reductively alkylated with aldehyde bisulfite adducts using NaBH(OAc)<sub>3</sub> in anhydrous 1,2dichloroethane at room temperature.9 The expected tertiary amines were isolated in high yields (>80%). Two drawbacks of this method are that it was limited to secondary aliphatic amines and that 2 equiv of the amine was needed. It was postulated that the first equivalent of the amine liberated the aldehyde from the bisulfite adduct, while the second one participated in the amination reaction. In order to avoid the use of an excess of a valuable amine the authors also reported a method involving prior treatment of the aldehyde bisulfite adduct with 1 equiv of triethylamine in order to liberate the aldehyde in situ, followed by the addition of 1 equiv of the required secondary amine.

In 2013, Vounatsos and co-workers reported a direct reductive amination reaction of aldehyde bisulfite adducts with primary amines in methanol at 30 °C using 2-picoline borane as the hydride source. The expected secondary amines were obtained in medium yields, although in one particularly interesting example the reaction was further optimized giving yields >80%. The main drawback

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## **ARTICLE IN PRESS**

M. Barniol-Xicota et al. / Tetrahedron Letters xxx (2014) xxx-xxx



Scheme 1. Processes for the direct reductive amination of aldehyde bisulfite adducts.

of this approach was that again, 2 equiv of the starting primary amine was required.<sup>10</sup> This recent Letter prompted us to disclose our own progress in this field.

We reasoned that the salt break may be brought about by using only 1 equiv of the amine if it was added to the reaction as its corresponding hydrochloride. In this way, the use of a second equivalent of the amine may be avoided (Scheme 1).

In order to investigate the use of bisulfite adducts in the direct reductive alkylation of amine hydrochlorides, a series of aromatic and aliphatic aldehyde bisulfite adducts were first prepared. Thus, an ethanolic solution of the aldehyde at 30–35 °C was treated with an aqueous solution of sodium bisulfite.<sup>11</sup> The resulting solid was filtered, dried under vacuum and used directly in the reductive amination experiments (Scheme 2).<sup>12</sup>

With the structurally different aldehyde bisulfite adducts in hand, the direct reductive alkylation reaction with amine hydrochlorides was attempted (Scheme 3).

After some preliminary experiments, we carried out the reaction of dimethylamine hydrochloride with 1.12 equiv of the



**Scheme 2.** Synthesis of bisulfite adducts. Reagents and conditions: (a) NaHSO<sub>3</sub> (1 equiv), EtOH, H<sub>2</sub>O, 30–35 °C, 16 h. Yields: **1a**, 98%; **1b**, 94%; **1c**, 90%; **1d**, 76%; **2**, 97%; **3**, 94%; **4**, 88%; **5**, 91%.

$$\begin{array}{c} R'(H) \\ H'^{N} R'' \\ R'$$

**Scheme 3.** Direct reductive alkylation of amine hydrochlorides with aldehyde bisulfite adducts.

*p*-methoxybenzaldehyde bisulfite adduct, **1b**, in the presence of NaCNBH<sub>3</sub> in methanol at room temperature. After an extractive work-up, the expected tertiary amine, **12**, was isolated in 90% yield (Table 1, entry 1). An excellent yield, 91%, was also obtained when the reaction was conducted with dimethylamine hydrochloride and *p*-chlorobenzaldehyde bisulfite adduct, **1d** (Table 1, entry 2).

The generality of the method was further evaluated by performing the reaction with various aldehyde bisulfite adducts and the hydrochlorides of several primary and secondary amines. Specifically, five different aromatic benzaldehydes, cinnamaldehyde and two aliphatic aldehydes were used (Scheme 2). Regarding the amines, three secondary amine hydrochlorides, including

Table 1	
Amines 12-24 produced via Scheme 3	

Entry	Amine <sup>a</sup>	Aldehyde	Product <sup>b</sup>	% <sup>c</sup>
1	6	1b	CH <sub>3</sub> O 12	90
2	6	1d		91
3	7	1b	CH30 14	61
4	8	1b	CH <sub>3</sub> O 15 OCH <sub>3</sub>	74
5	8	2		65
6	8	4	17 NOCH3 OCH3	80
7	9	1b	CH <sub>3</sub> O 18 CO <sub>2</sub> CH <sub>3</sub>	95
8	10	1b	CH30 - 19	58
9	11	1a		67
10	11	1b	CH <sub>3</sub> O 21	60
11	11	1c		92
12	11	4		67
13	11	5	F <sub>3</sub> C 24	90 <sup>d</sup>

<sup>a</sup> All the starting amines were used as hydrochlorides.

 $^{\rm b}$  All final products were isolated as hydrochlorides, except compounds 12, 18 and 19.

<sup>c</sup> The yields are unoptimized.

<sup>d</sup> 91% yield using Et<sub>3</sub>N BH<sub>3</sub>.

2



Figure 1. Primary and secondary amine hydrochloride tested.

dimethylamine hydrochloride, **6**, a pyrrolidine derivative, **7** and the tetrahydroisoquinoline derivative **8**, and three primary amine hydrochlorides, the methyl ester of phenylalanine, **9**, the sterically hindered 2-adamantanamine, **10** and the enantiopure (R)-1-(1-naphthyl)ethylamine, **11**, were investigated (Fig. 1).

All the reactions worked well with the sole exception of the reaction of **11** with the bisulfite adduct of cinnamaldehyde, **3**, that furnished a mixture of products, probably arising from the competitive reduction of the carbon–carbon double bond. Table 1 summarizes the different examples including the starting amine hydrochloride, the bisulfite adduct, the final products and the yields. Typically, the yields (unoptimized) ranged from 58% to 92%. Notably, this novel methodology has permitted the synthesis of the calcimimetic drug *cinacalcet hydrochloride*, **24**·HCl, in 90% yield (entry 13).<sup>6</sup>

The data from the NMR spectra of all the known compounds matched with the reported values, while all new compounds have been fully characterized.

Although NaCNBH<sub>3</sub> is a widely used reagent for laboratory purposes, its use on a large scale may raise concerns. For this reason, we have also briefly evaluated the alternative use of other reductor agents. While the use of triethylamine borane complex worked well, unfortunately, the lower priced NaBH<sub>4</sub> gave the expected products in much lower yield and an unpleasant odour was observed. Of note, while acetic acid is usually added in the sodium cyanoborohydride-mediated reductive aminations, in the present procedure no acetic acid is required.

In summary, we have developed a mild, efficient and general reaction procedure for the direct reductive amination of bisulfite aldehyde adducts with amine hydrochlorides using sodium cyanoborohydride in methanol. The described methodology avoids the use of rather unstable amines that are usually stabilized by formation of a salt (e.g., hydrochlorides). Moreover, amines of low molecular weight, such as dimethylamine, are usually commercially available as salts. Thus, our approach is particularly interesting for this kind of amine. The reductive amination conditions described fulfil the principle of atom economy because equimolecular amounts of bisulfite adduct and amine hydrochloride are used.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03. 046.

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- 11. General procedure for the synthesis of the aldehyde bisulfite adducts. To a stirred solution of the aldehyde (50 mmol) in ethanol (100 mL) at room temperature was added dropwise (15 min) a solution of NaHSO<sub>3</sub> (5.3 g, 50 mmol) in water (10 mL). The resulting suspension was stirred at 30–35 °C for 16 h and subsequently at 4–5 °C for 4 h. Then, the product was filtered, washed with hexane (3 × 50 mL) and dried in vacuo to afford the bisulfite adduct as a white powder.
- 12. General procedure for the reductive amination of bisulfite adducts with amine hydrochlorides. To a solution of amine hydrochloride (1 mmol) in methanol (10 mL) was added the aldehyde bisulfite adduct (1.12 mmol). To the resulting suspension NaCNBH<sub>3</sub> (2.5 mmol) was slowly added, and the mixture was stirred for 20 h at rt. Then, the evaporation of the mixture furnished a residue which was partitioned between a 5 N NaOH solution and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic phases were dried and evaporated to give a residue which was to give a residue which was cooled down for 13 h at 0 °C and the precipitated white solid was filtered and dried in vacuo to afford the amine **12–24**.