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Mild and efficient reduction of azides to amines: synthesis of fused [2,1-*b*]quinazolinones

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Abstract—$FeCl_3$/NaI has been employed for an efficient reduction of a variety of azides. This method is selective in the presence of a nitro functionality and has been extended for the synthesis of fused [2,1-*b*]quinazolinone ring systems such as deoxyvasicinone. © 2002 Elsevier Science Ltd. All rights reserved.

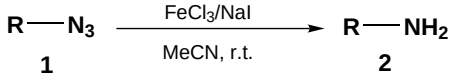
In recent years, azides[1] have attracted much attention, not only as excellent protecting groups, but as key intermediates for the synthesis of a large number of organic compounds such as nucleosides, carbohydrates,[2] *N*-containing heterocycles[3] like quinolines, quinazolines, benzodiazepines, lactams, cyclic imides etc. A variety of reagents have been reported in the literature[4] for the reduction of azides, and the most prominent employ borohydrides,[5] triphenylphosphine,[6] benzyltriethylammonium tetrathiomolybdate,[7] hexamethyldisilathiane,[8] SmI_2[9] etc. The majority of these methods have some shortcomings in relation to their general applicability, selectivity, commercial availability and reaction conditions. In view of these factors there has been considerable demand to further explore efficient, milder and selective methodologies.[10]

As a part of our continuing research work towards the synthesis of heterocyclic natural products, we have taken up the task of developing new versatile methods for azido group reduction. In this connection, we have recently reported the reduction of azides to amines by employing reagents such as TMSI and $FeSO_4$.[11–15]

As a result of these efforts, we can now report a new mild, efficient and selective method for the reduction of azides **1** to the corresponding amines **2** in quantitative yields employing $FeCl_3$/NaI (Scheme 1). Although $FeCl_3$ in combinations with different reagents has been reported for such reductions,[16] the present reagent system has not previously been investigated for the reduction of the azide functionality. The role of NaI is not clear in this process but a plausible explanation could be attributed to the in situ formation of FeI_3, which is not known to exist in a pure state. The use of an excess of NaI appears to be essential for this conversion as its use at less than 5 equiv. not only decreased the amount of conversion but also the rate of the reaction, thus supporting the above proposition. However, the formation of a NaI/Lewis acid complex cannot be ruled out.

As observed from the results in Table 1, this method offers excellent selectivity in the presence of other functionalities, particularly the nitro group, unlike some other reagents such as SmI_2. It is interesting to note that 2-carboxylic acid substituted aryl azides undergo intermolecular cyclization to produce dilactams. Additionally, this methodology can also be utilised for a wide range of substrates including benzyl and alkyl azides. However, demethylation of the methyl ether has been observed as seen in entry **c**.

In a typical procedure: to a solution of azide (1 mmol) in acetonitrile (10 ml) was added NaI (9 mmol), followed by $FeCl_3$ (1.5 mmol). The resulting mixture was stirred for 10–25 min and upon completion of the reaction was diluted with $CHCl_3$ (5 ml), then washed with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ solutions. The organic layer was further washed with brine,



Scheme 1.

Keywords: azides; amines; reductive cyclization; [2,1-*b*]quinazolines; deoxyvasicinone.

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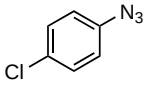
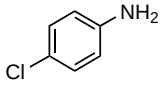
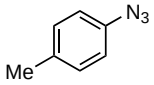
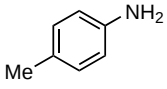
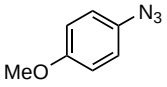
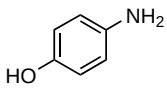
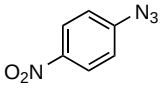
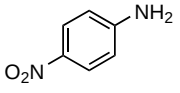
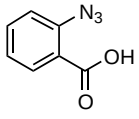
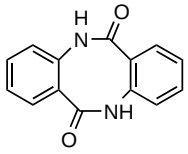
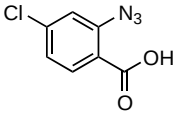
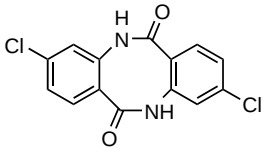
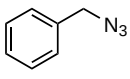
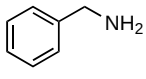
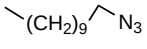
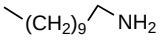
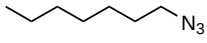
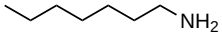
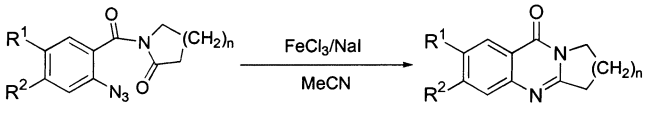
Table 1. Reduction of azides to amines employing the $FeCl_3$/NaI reagent system

Entry	Substrate **1**	Product **2**	Time (min)	% Yield
a			10	95
b			10	97
c			20	75
d			10	98
e			15	96
f			15	98
g			20	85
h			25	85
i			25	88

dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was filtered through a silica gel (60–120 mesh) pad with ethyl acetate/hexane (2:8) to afford the corresponding amine.

Further, taking advantage of the intermolecular azido-reductive cyclization, we have extended this procedure to the preparation of the pyrrolo[2,1-*b*]quinazolinone ring system, and related tetrahydropyrido and octahydroazepino fused quinazolinones. Deoxyvasicinone **6a** is a precursor for vasicinone, a bronchodilator.[17] This study is a continuation of our efforts towards the synthesis of various fused [2,1-*b*]quinazolinones and the exploration of their biological potential.[18] The development of this new reductive cyclization method affords an alternative route towards the preparation of these pharmacologically important fused quinazolinones in good yields ranging from 85 to 97% (Scheme 2).

In conclusion, we have demonstrated an efficient, mild and spontaneous method for the reduction of the azide functionality. Additionally, this method is selective for the azide functionality in the presence of a nitro group. Further, this protocol has been applied to the synthesis of deoxyvasicinone[19] **6a**, a precursor of vasicinone (a bronchodilator) and related analogues.



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Compd.	R^1	R^2	n	% yields
3a, 6a	H	H	1	97
3b, 6b	Me	H	1	97
3c, 6c	H	Cl	1	96
4a, 7a	H	H	2	88
4b, 7b	Me	H	2	87
4c, 7c	H	Cl	2	85
5a, 8a	H	H	3	95
5b, 8b	Me	H	3	94
5c, 8c	H	Cl	3	96

Scheme 2.

Acknowledgements

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19. Spectral characteristics of 2,3-dihydropyrrolo[2,1-*b*]quinazolin-9-one **6a**: mp 104–106°C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.3 (q, 2H, $J=7.5$ and 8.0 Hz), 3.2 (t, 2H, $J=8.0$ Hz), 4.2 (t, 2H, $J=7.5$ Hz), 7.5 (t, 1H, $J=7.4$ Hz), 7.6–7.8 (m, 2H), 8.3 (d, 1H, $J=8.0$ Hz); MS (EI) m/z 186 (M^+); HRMS calcd for $C_{11}H_{10}N_2O$ 186.0793, found 186.0789.