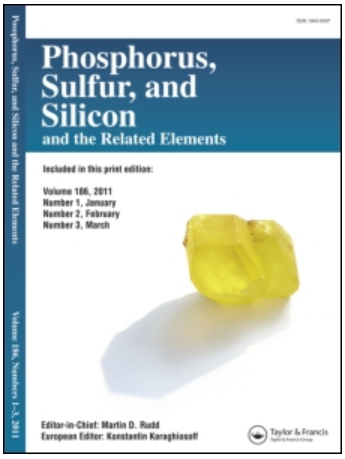

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

CHEMOSELECTIVE REDUCTION OF AZIDES WITH SODIUM SULFIDE HYDRATE UNDER SOLVENT FREE CONDITIONS

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Online publication date: 16 August 2010

To cite this Article Kazemi, Foad , Kiasat, Ali Reza and Sayyahi, Sohyl(2004) 'CHEMOSELECTIVE REDUCTION OF AZIDES WITH SODIUM SULFIDE HYDRATE UNDER SOLVENT FREE CONDITIONS', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 9, 1813 — 1817
To link to this Article: DOI: 10.1080/10426500490466544
URL: http://dx.doi.org/10.1080/10426500490466544

Phosphorus, Sulfur, and Silicon, 179:1813–1817, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490466544

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CHEMOSELECTIVE REDUCTION OF AZIDES WITH SODIUM SULFIDE HYDRATE UNDER SOLVENT FREE CONDITIONS

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(Received January 22, 2004)

Sodium sulfide hydrate has been employed for an efficient reduction of a variety of azides to the primary amines in good-to-excellent yields under solvent-free system and without perturbing many active functionalities such as ether, carbonyl, sulfonyl, and nitro.

Keywords: Azides; reduction; sodium sulfide; solvent free

Primary amines have widely been recognized as an important class of compounds due in part to their role as intermediates in organic synthesis, such as in the preparation of nitrogen containing heterocycles, carbohydrates, and in nucleoside chemistry.[1] In addition, it is known that many of the primary amines are biologically active compounds or are the important building blocks for the syntheses of biologically active compounds.[2] Of the several methods to prepare amines, reduction of azides is of immense importance. Since numerous methods are available for the preparation of azides with excellent regio-, stereo-, and enantioselectivity, the reduction of azides permits a controlled introduction of amine functionality.[3] A number of reagents have been described in the literature[4] for this reductive process which includes lithium aluminum hydride,[5] borohydrides,[6] diborane,[7] triphenylphosphine,[8] benzyltriethylammonium tetrathiomolymbdate,[9] hexamethyl-disilathiane,[10] samarium iodide,[11] etc. In terms of practical applicability, selectivity, toxicity, reaction conditions, or commercial availability, most of these methods have some disadvantages. For

Authors acknowledge the partial support of this work by Shahid Chamran Ahvaz University Research Council.

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instance, $LiAlH_4$ is not tolerable to many functionalities, such as CO_2R, NO_2, and catalytic hydrogenation and diborane reduction have limitations when being applied to unsaturated compounds containing a double or a triple bond. Borohydrides and modified borohydride reagents are generally milder reagents, but they also face certain disadvantages with regard to the rate and selectivity. In view of these factors, there has been considerable demand to explore efficient, milder, and selective methodologies further.

Although a reduction system consisting of $Na_2S.9H_2O$ and a catalytic amount of NEt_3 in methanol has been reported previously[12] for the conversion of vinyl azides to the corresponding carbonyl compounds, a literature survey reveals that no attention has been focused on the application of this mild reagent, Na_2S, for the reduction of azides to amine, especially under solvent-free conditions.

In view of developing a mild and chemoselective reagent system, an attempt has been made to exploit the utility of the relatively less explored and inexpensive reagent Na_2S for the reduction of azides to amines. A number of observations (entries 1–15 in Table I) reveal that when an azide was ground with a pestle in a mortar with sodium sulfide hydrate and in the presence of a few drops of methanol, it undergoes excellent conversion to amine. To the best of my knowledge, no such reagent has so far been reported for the reduction of azide.

To extend the scope of this reducing reagent for the reduction of other azides, a variety of azides, prepared according to the literature,[13] was tested for this transformation. All azides were reduced completely with sodium sulfide hydrate to readily give the corresponding amines in good-to-excellent isolated yields.

Table I summarizes our results on the reduction of a number of alkyl, aryl, and arylsulfonyl azides. In all the reactions, the cleavage takes place between the N–N bond rather than the C–N or S–N bond. As observed from the results in Table I, this method offers excellent selectivity in the presence of other functionalities such as nitro, sulfonyl, and aromatic methoxy groups, unlike some other reagents. It is interesting to note that carbonyl-substituted aryl azides undergo facile reduction to the corresponding amines without any further reduction, and the sensitive carbonyl group remains intact. Moreover, the reduction of

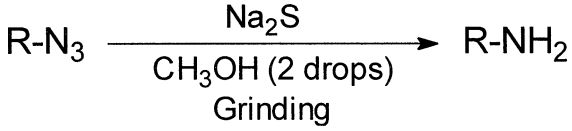
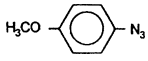
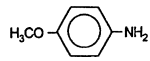
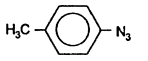
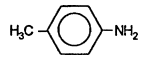
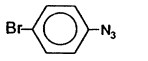
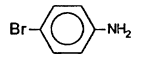
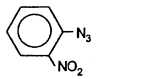
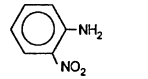
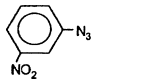
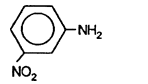
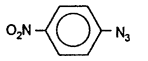
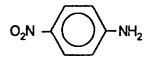
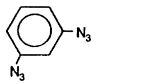
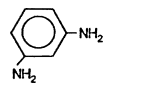
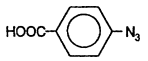
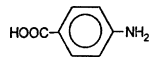
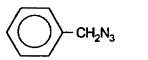
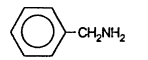
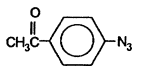
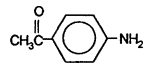
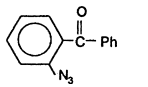
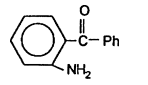
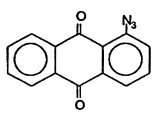
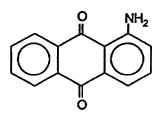
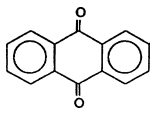
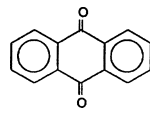
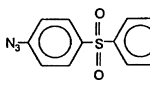
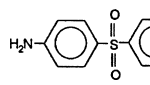
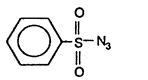
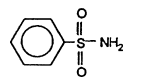


FIGURE 1

TABLE I Reduction of Azides to Amines with Sodium Sulfide Hydrate

Entry	Substrate	Product	Ratio Na_2S: Azide (mol:mol)	Time (min)	Yield %[a,b]
1			2	10	75
2			1	1	65
3			2	10	75
4			1	1	95
5			1	10	93
6			1	1	98
7			2	1	94
8			3	10	85
9			1	1	85
10			1	1	85
11			2	10	70
12			1	1	85
13			1	1	85
14			1	5	95
15			1	1	90

[a]Yields refer to pure isolated products.

[b]Products were characterized by comparison of their physical data, and IR and NMR spectra, with known samples.

benzenesulphonyl azide was performed under similar reaction conditions to afford the corresponding sulfonamide.

The rapid and selective formation of reductive products demonstrates the efficiency of this new method. The structure of all the products were established from their analytical and spectral (infrared (IR), ^{1}H NMR) data and by direct comparison with authentic samples.

In summary, reduction of azido groups with sodium sulfide hydrate in solvent-free system has advantages over previously reported methods and provides a facile, useful, and inexpensive addition to the existing methodologies. The advantages of this environmentally friendly protocol are mild and neutral reaction condition, unique selectivity, manipulatively simple, and short reaction time.

EXPERIMENTAL

General

All azides were prepared from amines according to the literature.[13] All products are known compounds and were characterized by comparison of their physical data with literature values. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

General Procedure for the Reduction of Azides to Amines with Sodium Sulfide Hydrate

A mortar was charged with sodium sulfide hydrate, neat azide (l mmol), and two drops of methanol; the mixture was ground with a pestle for the time specified in Table I. The progress of reaction was monitored by TLC using ether-CCl_4. Then the reaction mixture was poured into a mixture of ether (20 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to afford the TLC and ^{1}H NMR pure products in 65–98% isolated yields.

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