Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c6ob00737f

New (green) methodology for efficient hydrazine cleavage†

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Received 7th April 2016,
Accepted 26th April 2016

DOI: 10.1039/c6ob00737f

www.rsc.org/obc

An efficient method for removal of the hydrazine group from (hetero)aromatic substrates has been developed. It can be realized both on a solid support and in solution by synthesis employing a low concentration solution of trimethylsilanolate in tetrahydrofuran or *N,N*-dimethylformamide. For water-soluble substrates, the reaction can be performed in water, highlighting the eco-friendly attributes of this methodology.

Hydrazine chemistry is a part of important areas in organic synthesis.[1] Monosubstituted hydrazines are frequently used intermediates in many synthetic applications, including reactions with carbonyl compounds to produce hydrazones,[2] preparation of indoles by Fisher Indol synthesis,[3] synthesis of aminopyrroles[4] and many others.[2,5] Although hydrazine synthesis is well described,[6] including the chiral species,[7–9] only few methodologies have been reported for dehydrazination reactions, which can be advantageously used for indirect removal of halogens,[10] removal of hydrazine as a protective group in synthetic pathways[10] or labelling of compounds with deuterium.[11]

To the best of our knowledge, the published dehydrazination protocols are mostly based on facile oxidation of hydrazines. The oxidizing agents are typically metallic oxides, very often silver oxide[12] or HgO,[13] which cause complications due to the toxicity of the traces of mercury ions remaining in the synthesized product or the precipitation of metallic silver as well as its salts derived from the treated compounds. Dehydrazination by aqueous copper sulphate was also described.[14,15] In this reaction, the principles of green chemistry are respected, employing a catalytic amount of copper sulphate in water[11] or employing microwave irradiation on supported copper sulphate.[16] The disadvantage of this method is the possible complexation of a substrate by copper ions.

A reaction with nitric oxide in the presence of oxygen in tetrahydrofuran (THF) belongs to the methods that avoid the use of metal ions for removal of hydrazine, but this reaction results in the subsequent formation of azides as co-products.[17]

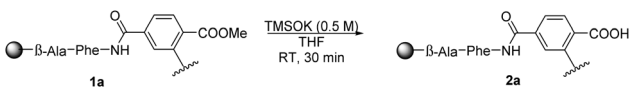
The other oxidative dehydrazination reaction free of metal ions described by Wobus *et al.*[10] is based on dehydrogenation of the hydrazino group to form diazene, followed by spontaneous loss of nitrogen. This reaction is limited to π-deficient (hetero)aromatic systems such as derivatives of pyridazine. Finally hydrazines able to undergo tautomery can be cleaved *via* Wolff–Kishner reduction in strong alkaline solutions. The reaction is limited to heteroaromatic systems able to form hydrazones.[18]

All of these above-mentioned reactions either require oxidizing agents causing potential side reactions or implementing toxicity or they are limited to electron-poor substrates.

Herein, we report a very fast and efficient methodology for dehydrazination of (hetero)aromatic substrates occurring under mild conditions. This protocol can be applied in solution as well as in solid phase organic synthesis (SPOS), which is not limited only to a laboratory scale but can also be applied in commercial drug production.[19]

During our study on the saponification reaction of immobilized ester **1a** using potassium trimethylsilanolate (TMSOK) in THF, we observed not only hydrolysis of the methyl ester group but also removal of the hydrazine moiety as well (Scheme 1).

Realizing the potential application of this result, we decided to study this unusual hydrazine cleavage in detail. For this purpose, we prepared a series of immobilized aromatic and heteroaromatic hydrazines. Their synthesis employed either immobilization of commercially available hydrazines or their direct preparation on a solid support by nucleophilic substitution from the corresponding fluoro derivatives (for details



1a 2a

Scheme 1 Dehydrazination reaction under saponification conditions.

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†Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra. See DOI: 10.1039/c6ob00737f

see the ESI†). Widely used aminomethylene polystyrene with a Rink linker was used as the solid support. For better monitoring of the products by LC/MS, a dipeptide linker (β-Ala-Phe) was introduced before the arylhydrazine moiety.

The hydrazine derivatives selected to be studied in the reaction were monosubstituted arylhydrazines and arylhydrazines protected by using Fmoc, mesyl (Ms) and acetyl groups.

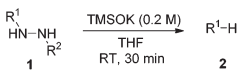
The reaction was carried out in THF, where TMSOK was dissolved at a concentration of 0.2 mol l^{-1}. The reaction time was optimized to 30 min at room temperature (RT).

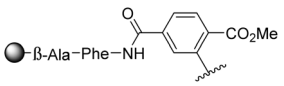
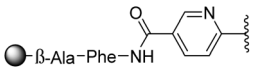
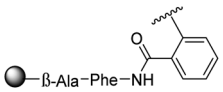
The results of the complete four step synthesis of derivative **2** are summarized in Table 1. The products were isolated by HPLC purification directly after the reaction, and yields were calculated compared to the initial loading of the resin. The methylester group of compounds **1a**, **1c** and **1d** were hydrolysed and isolated as carboxylic acid **2a**.

These results clearly demonstrate that the monosubstituted (hetero)aromatic hydrazines easily undergo hydrazine cleavage under treatment with TMSOK.

Obviously, once the (hetero)aromatic hydrazine is protected, the dehydrazination does not work properly. No conversion during the treatment with TMSOK was observed in the case of Fmoc protected derivatives **1b**, **1f** and partially **1j**, where also the products of decomposition were observed. Although dehydrazination was observed in the case of mesyl-protected hydrazines **1c** and **1k**, the yields were low because of the formation of a number of side products. In the case of compound **1g** no study of the cleavage was performed because it was possible to prepare the starting material only with very low purity. Surprisingly, when the hydrazine is substituted with an acetyl group, the removal of this moiety proceeds with good conversion as is shown in the case of derivatives **1h** and **1l**. The low reactivity of Fmocylated hydrazines can be advantageously used for selective protection of the hydrazine group against trimethylsilanolate treatment. If hydrazine removal is intended, no protection is necessary. However, if we want to preserve the hydrazine, *e.g.*, during ester hydrolysis mediated by using TMSOK, we can avoid the cleavage by facile Fmoc protection.

Table 1 Synthesis of derivatives **2** *via* dehydrazination of compounds **1**



1	R^1	R^2	2	Yield of 2 [a] (%)
1a		-H	**2a**	20[b]
1b		-Fmoc	**2a**	[c]
1c		-Ms	**2a**	16[b]
1d		-COMe	**2a**	19[b]
1e		-H	**2e**	53
1f		-Fmoc	**2e**	[c]
1g		-Ms	**2e**	[d]
1h		-COMe	**2e**	54
1i		-H	**2i**	58
1j		-Fmoc	**2i**	[c]
1k		-Ms	**2i**	17
1l		-COMe	**2i**	57

[a] Overall yield determined by ^{1}H NMR spectroscopy after HPLC purification and calculated to initial loading of the resin. [b] Product was isolated as a carboxylic acid. [c] Product was not observed. [d] Reaction was not studied because the preparation of **1g** proceeded with very low purity.

Table 2 Optimization of the reaction conditions for derivative **1i** using different bases in THF

Entry	Base	*t* (h)	*c* (mmol)	Conversion[a] (%)
1	NaOH	0.5	500.0	27
2	NaOH	1.5	500.0	70
3	LiOH	0.5	500.0	34
4	LiOH	1.5	500.0	62
5	*t*-BuONa	0.5	500.0	27
6	*t*-BuONa	1.5	500.0	70
7	MeONa	0.5	500.0	9
8	MeONa	1.5	500.0	62
9	DBU	0.5	500.0	36
10	DBU	1.5	500.0	82
11	TMSOK	0.5	200.0	74
12	TMSOK	0.5	100.0	69
13	TMSOK	0.5	50.0	76
14	TMSOK	0.5	25.0	57
15	TMSOK	1.0	12.5	100
16	TMSOK	1.0	6.2	100
17	TMSOK	1.0	3.1	88
18	TMSOK	1.0	1.6	38

[a] Conversion was determined by HPLC with PDA detection.

We were also interested in knowing whether TMSOK is the specific base responsible for the cleavage or if it could be replaced by another base. We therefore selected one model compound **1i** and extended the study to a wider range of bases, replacing TMSOK with sodium hydroxide (NaOH), lithium hydroxide (LiOH), sodium *tert*-butoxide (*t*-BuONa), sodium methoxide (MeONa) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 2). At the same time, the influence of the TMSOK concentration on reactivity was studied as well. The reactions were monitored by LC/MS.

The results indicate that hydrazine can be cleaved from the aromatic compound by treatment with different bases. However, in many cases the remaining starting material decreases the conversion. The best results, requiring the shortest reaction times as well as providing the highest product purities, are achieved using TMSOK.

It is worth highlighting the TMSOK concentration necessary for successful performance of the reaction. The reaction still proceeds satisfactorily with a concentration as low as 3 mM (Fig. 1).

As solid-phase synthesis is not always applicable in organic synthesis, we examined the possibility of hydrazine cleavage in solution as well. Twelve simple (hetero)aromatic hydrazines were chosen as model substrates, including both electron-donating as well as electron-withdrawing substituents (Table 3) in various positions of the aromatic ring, and they were treated with 0.15 M solution of TMSOK in *N*,*N*-dimethylformamide-d_7 (d_7-DMF). d_7-DMF was chosen due to its better solubilization of the selected substrates and a possibility of direct yield determination using ^{1}H NMR by comparison with

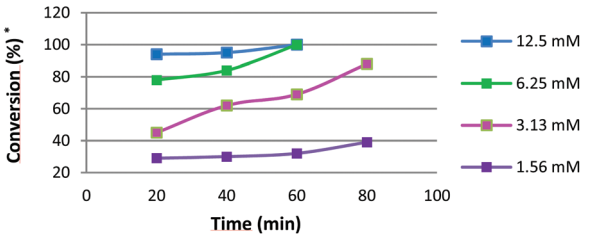
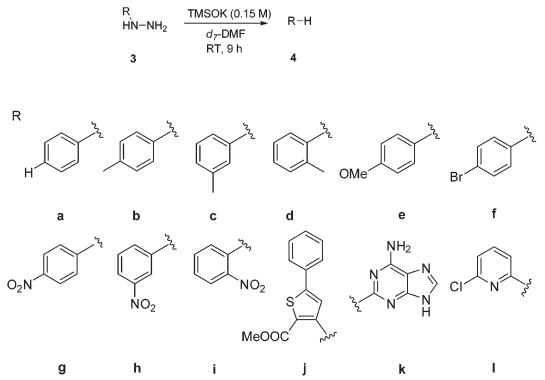


Fig. 1 Optimization of the TMSOK concentration for reaction of **1i**. *Conversion was determined by HPLC with PDA detection.

Table 3 Hydrazine cleavage in solution with the corresponding yields in d_7-DMF



Compound **3**	Yield of **4** [a] (%)	Yield of **4** at 70 °C, 48 h [a] (%)
3a	99	—
3b	95	—
3c	35	70
3d	SM	51
3e	89	—
3f	81	—
3g	55	—
3h	85	—
3i	90	—
3j	69	—
3k	Insoluble	50
3l	42	97

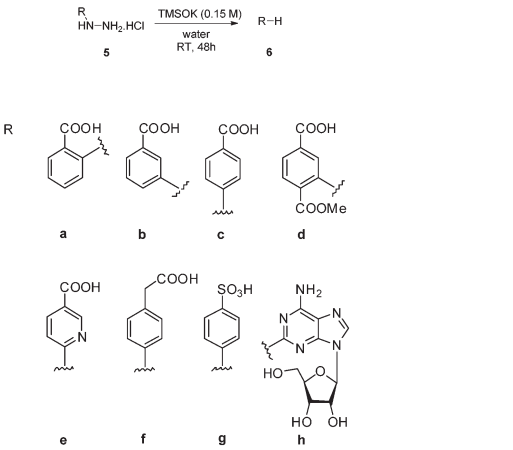
[a] Yield determined by ^{1}H NMR spectroscopy.

the residual solvent signal.[20] The concentration of TMSOK was optimized, and the best results were obtained when the concentration of TMSOK was 0.15 M. For four derivatives the general reaction conditions afforded lower yield, therefore the temperature was increased to 70 °C (Table 4).

The dehydrazination works very well for phenylhydrazine and substrates with electron-donating groups. Lower yields must be expected for substrates bearing electron-withdrawing groups. The good conversion is exemplified by the change in the NMR spectra as shown in Fig. 2 for derivative **3b** (for other crude NMR spectra see the ESI†).

Although THF and DMF are acceptable solvents from their toxicity point of view,[21] water is still the first choice for "green chemistry". We therefore selected another eight water-soluble

Table 4 Hydrazine cleavage in solution with the corresponding yields in water



Entry	Compound **5**	Yield of **6** [a] (%)	Yield of **6** at 70 °C, 48 h [a] (%)
1	**5a**	99	—
2	**5b**	64	—
3	**5c**	77	—
4	**5d**	81	—
5	**5e**	71	—
6	**5f**	90	—
7	**5g**	98	—
8	**5h**	40	89
9	**3k**	49	45

[a] Yield determined by ^{1}H NMR spectroscopy.

substrates **5a–h** and hydrazine **3k** and examined their reactivity under the treatment of 0.15 M solution of TMSOK in water (Table 4). For most substrates the dehydrazination works quantitatively within 48 hours in all cases with excellent yields. For two substrates the temperature had to be increased to achieve higher yields (Table 4).

Finally we tried to suggest a mechanism for hydrazine group removal (Scheme 2).

The reaction of unprotected arylhydrazine $\mathbf{A_H}$ starts probably by dissociation of an acidic NH proton. The possibility of conjugation in the system $\mathbf{C_H}$ is the stimulation for oxidation of intermediate $\mathbf{B_H}$ with air. The air oxidation assistance was proved by performing the experiment under an inert atmosphere, where no reaction was observed. Decomposition of diazene $\mathbf{C_H}$ to hydrocarbon **E** *via* anion **D** is included in other published mechanisms.[11] A similar process can be expected for acetylated hydrazine $\mathbf{A_{Ac}}$, probably when the amide NH proton is removed first. The analogous acetyl diazene $\mathbf{C_{Ac}}$ formed by air oxidation can be then hydrolyzed by trimethylsilanolate to give intermediate **D** again, which is further stabilized by a proton to the final hydrocarbon **E**. The bulky Fmoc and strong electronegative mesyl group analogues of hydrazine $\mathbf{A_{Ac}}$ are probably more resistant to proton removal and/or oxidation because of steric hindrance and/or the increased electron withdrawing effect. The suggested mechanism is probably involved also in cleavage of a hydrazone linker published recently.[22]

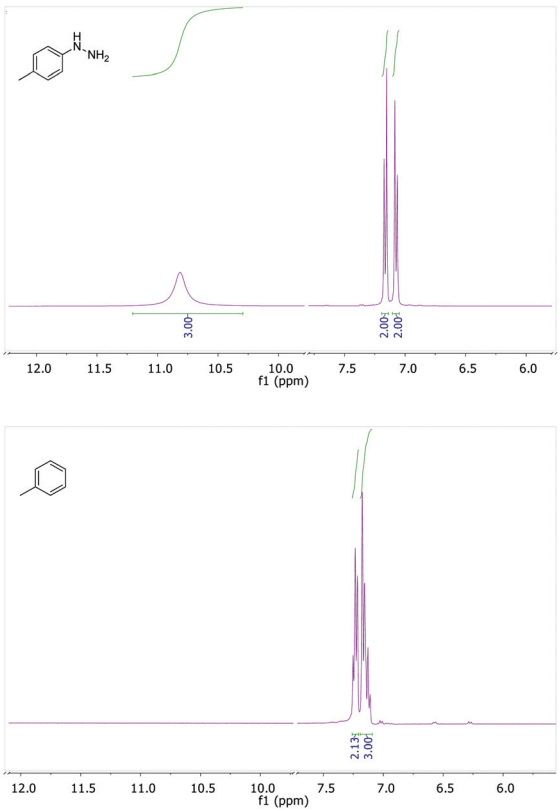
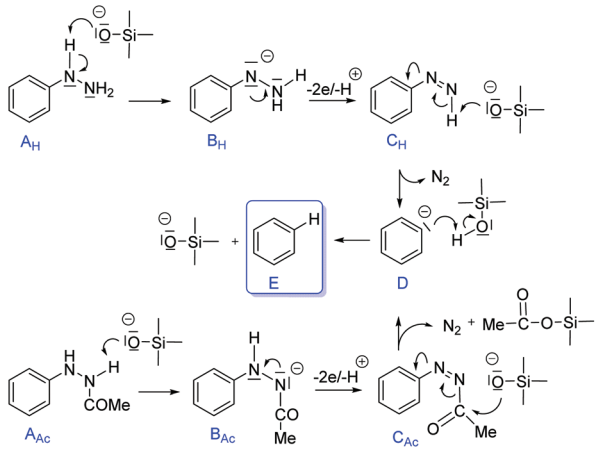


Fig. 2 ^{1}H NMR spectra of starting tolylhydrazine **3b** (upper spectrum) and crude product **4b** after its treatment with TMSOK (lower spectrum) in d_7-DMF.



Scheme 2 The supposed mechanism of dehydrazination.

In conclusion, we introduced a new methodology for hydrazine cleavage from aromatic substrates. The reaction is wide in scope and usually occurs at RT in acceptable reaction times. The reaction requires only low concentrations of TMSOK in THF or DMF frequently used in chemical research as well as production. Significantly, for water-soluble substrates, the reaction can be successfully performed even in water, which fully respects "green chemistry" principles.

Moreover, such a simple methodology works in solution as well as on a solid support, and thus it is easily applicable in industrial production of active pharmaceutical ingredients *via* both methodologies, where SPOS is also established for commercial production on a kilogram scale in addition to traditional solution-phase synthesis.[18]

Hydrazine removal can be avoided by using a suitable protecting group, and thus the removal of a hydrazine group can be directed.

Acknowledgements

This research project was supported by the Ministry of Education, Youth and Sports of the Czech Republic (project IGA_PrF_2016_020) and by the European Social Fund (CZ.1.07/2.3.00/30.0060 and CZ.1.07/2.3.00/20.0009). The infrastructure of this project (Institute of Molecular and Translation Medicine) was supported by the National Program of Sustainability (project LO1304).

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