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Chemoselective N-deacetylation under mild conditions†

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A mild and efficient chemoselective N-deacetylation using the Schwartz reagent at room temperature in rapid time is described. The mild and neutral conditions enable orthogonal N-deacetylation in the presence of some of the common protecting groups (*viz*. Boc, Fmoc, Cbz, Ts). The deprotection conditions did not induce any epimerization at the chiral amino centre.

Organic compounds with amine functionality are widespread in many natural products, bioactive compounds and pharmaceuticals.[1] However, due to their remarkable nucleophilicity quite often amines are protected to carry out a series of organic transformations. Though protecting group free synthesis is highly desirable and demanding,[2] in many instances the protection of amines is unavoidable, thus making the reaction reliable for obtaining the target compound efficiently without any side reactions.

The acetyl moiety is one of the widely employed protecting group for amines in organic synthesis and also it is one of the most common protecting groups used by nature in natural product synthesis.[1,3] Acetylated amines (acetamides) have a remarkably reduced nucleophilic character in comparison to amines. Acetylated amines have been explored for the catalytic asymmetric hydrogenations of enamides.[4] Acetylated amines such as acetamides have been successfully utilized as directing groups in C–H activation.[5] In spite of the wide utility of acetyl protection for amines in organic synthesis, acetyl deprotection (N-deacetylation) is practically limited to the traditional harsh deprotecting conditions. As the amide bond is robust, N-deacetylation usually requires the use of a strong base or acid at a high temperature.[3] These deprotective conditions limit the scope of acetylated amines along with the variety of functional groups which are sensitive to acid and base. N-deacetylation under harsh conditions may lead to racemization in certain cases. Nevertheless, efforts have been made in recent times to overcome this limitation. Some of the available protocols utilize moisture sensitive and corrosive reagents such as oxalyl chloride,[6] and a triphenyl phosphite complex[7] under basic conditions at lower temperatures. Recently an elegant method has been described by employing transamidation using an ammonium salt.[8] However, this protocol demands the sacrifice of a stoichiometric equivalent of another amine for the transamidation. While searching through the literature, we learnt that the Schwartz reagent has been elegantly and effectively employed for the conversion of carboxamides to imines, and also for the conversion of amides to aldehydes.[9] However to the best of our knowledge, the Schwartz reagent has not been exploited for a straight forward N-deacetylation protocol. Also there are not many standard protocols for N-deacetylation under mild conditions. Based on this consideration it would be valuable to develop a method for N-deacetylation under mild conditions that can tolerate a variety of functional groups. We envisioned that the Schwartz reagent can be utilized for N-deacetylation and the protocol would particularly be very useful for laboratory scale reactions.

Herein, we wish to report a convenient selective N-deacetylation protocol using the Schwartz reagent at room temperature in a very short time (2–5 min). Moreover, we demonstrate the selective (orthogonal) deprotection by carrying out competition experiments. The methodology proved to be very efficient for aromatic, heteroaromatic and aliphatic amides and also no epimerization was observed during the N-deacetylation of chiral acetamides.

In order to demonstrate the utility of the Schwartz reagent we began our study with the synthesis of various *N*-acetamides (**1a–1t**) starting from the corresponding amines with varying electronic and steric properties (Table 1). In our initial experiment, compound **1a** was treated with the Schwartz reagent in anhydrous THF at room temperature. The turbid reaction mixture changed into a clear solution in a very short time (3 min). The completion of the reaction was monitored by TLC and the reaction was quenched by the addition of water and

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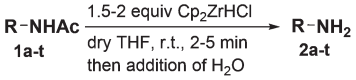
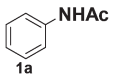
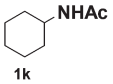
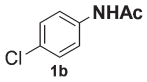
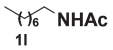
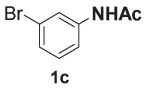
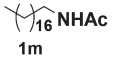
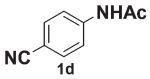
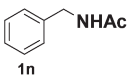
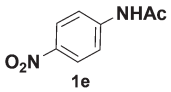
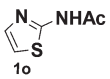
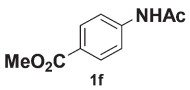
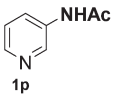
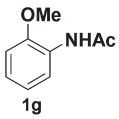
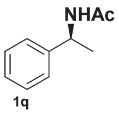
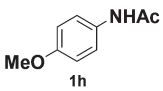
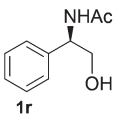
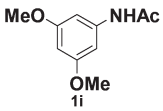
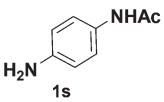
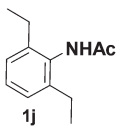
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data and copies of ^{1}H-NMR for compounds **1a–1t**, **3**, **4**, **5**, **6**, **7**, **8**, **11**. ^{1}H and ^{13}C-NMR spectra for the compounds **2a–2t**, **9**, **10**, **12**. See DOI: 10.1039/c3ob41971a

Table 1 The deprotection of various acetamides by the Schwartz reagent[a]

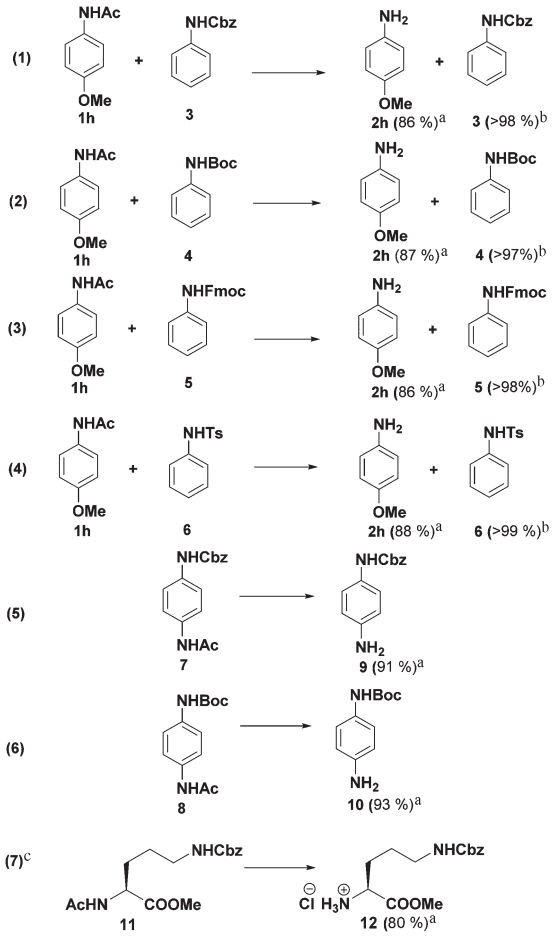


Entry	Substrate	Time (min)	Product yield[b] (%)	Entry	Substrate	Time (min)	Product yield[b] (%)
1	 1a	3	**2a** (94)	11	 1k	2	**2k** (91)
2	 1b	3	**2b** (92)	12	 1l	2	**2l** (93)
3	 1c	3	**2c** (90)	13	 1m	2	**2m** (91)
4	 1d	4	**2d** (84)	14	 1n	2	**2n** (91)
5	 1e	4	**2e** (89)	15	 1o	3	**2o** (88)
6	 1f	4	**2f** (87)	16	 1p	3	**2p** (89)
7	 1g	4	**2g** (86)	17	 1q	2	**2q** (93)
8	 1h	2	**2h** (88)	18	 1r	4	**2r** (89)
9	 1i	3	**2i** (86)	19	 1s	5	**2s** (90)
10	 1j	5	**2j** (87)	20	 1t	3	**2t** (94)

[a] A maximum of 1.5–2 equiv. of the Schwartz reagent is required for the complete conversion. [b] The yield of the isolated products.

worked up to afford the corresponding **2a** in an excellent yield (94%, Table 1).

Encouraged by the initial result a variety of substrates were examined for the N-deacetylation. Substrates with both electron withdrawing and donating functional moieties (**1b–1i**) underwent N-deacetylation in a very rapid time affording the corresponding amines (**2b–2i**) in excellent yields (Table 1). The electronic properties of the functional groups did not have any significant impact on the reaction time and yield. The steric factor in substrate **1j** did not have any impact on the rate of deprotection. The N-deacetylation of aliphatic and heteroaromatic substrates was very efficient in a short time affording the corresponding amines (**2k–2p**) in excellent yields. The N-deacetylation was highly chemoselective. Substrates with an α-chiral centre were chosen for the study to investigate the possibility of epimerization during the N-deacetylation. Chiral substrates (**1q** and **1r**) underwent facile N-deacetylation in a short time to afford the corresponding amines (**2q** and **2r**) without any



Scheme 1 Chemoselective N-deacetylation in a series of competition experiments. The substrates were treated in an equimolar ratio (1 : 1). The reactions were carried out using the Schwartz reagent (2.5 equiv.) at room temperature in dry THF for 5 min and then the reaction was quenched with H_2O. The same reaction mixtures were stirred overnight to study the reactivity profile of other protecting groups under the reaction conditions. [a]The values in brackets show the yields of the isolated products. [b]The yield of the recovered substrates. [c]The reaction was quenched with HCl in 1,4-dioxane to make a stable salt.

epimerization.[10] We observed that even the tertiary acetamide (**1t**) was equally susceptible to the deacetylation conditions to afford the free amine (**2t**) in an excellent yield (Table 1).

In order to have a wider application of this protocol we carried out a series of competition experiments (Scheme 1).

Initially, for the competition experiments substrates (**3–6**) containing commonly used protecting groups such as Cbz, Boc, Fmoc, Ts were considered (Scheme 1).

Compound **1h** was treated with the competitive substrates (**3–6**) in an equimolar ratio under the optimized reaction conditions (Schwartz reagent 2.5 equiv., THF, room temperature, 3–5 min, then water). It is very remarkable that **1h** alone underwent N-deacetylation chemoselectively in just 3–5 minutes affording the corresponding amine **2h** in an excellent yield and the competitive substrates were recovered in almost quantitative amounts (Scheme 1). In order to substantiate any possible reactivity of the reagent on the competitive substrates, the reactions were stirred overnight. However, all of the competitive substrates (carbamates **3–6**) were unreactive and were recovered in almost quantitative yields.

Also, when compounds (**7** and **8**) containing both *N*-Ac and *N*-Boc, or *N*-Cbz moieties were treated with the reagent in THF followed by the addition of water, the corresponding amines (**9** and **10**) were afforded *via* chemoselective N-deacetylation in excellent yields (Scheme 1). Furthermore, the application of this method was demonstrated on an amino acid derivative: L-N^{δ}-Cbz-N^{α}-acyl ornithine methyl ester **11**. On treatment with the Schwartz reagent (5 min) followed by the addition of HCl in 1,4-dioxane compound **11** afforded the corresponding L-N^{δ}-Cbz-ornithine methyl ester hydrochloride **12**.[10] It is particularly important to note that the reagent is highly preferential to amides. This result would be synthetically very useful and can be utilized in the orthogonal deprotection of the *N*-acetyl moiety in the presence of various other protecting groups under mild conditions. The protocol does not demand the use of any quenching or scavenging agents.[6,11] Also, generally N-deacetylation requires harsh acidic or basic conditions in which protection groups such as Boc, Fmoc, Ts would be highly labile.

Conclusions

In summary we have described an efficient and facile method for N-deacetylation. The method has several distinct advantages. The deprotection requires a very short reaction time (2–5 min) at room temperature affording amines in excellent yields with a great chemoselectivity. The reaction conditions are very mild and many of the conventional protecting groups of amines were stable under the reaction conditions. Furthermore, the reaction conditions enable the deprotection of chiral acetamides without any epimerization. The protocol may provide an advantage to remove the acetyl group at any convenient stage of the natural product synthesis. Further study of the Schwartz reagent and its utility is under progress.

Acknowledgements

P. R. S. and T. B. M. thank CSIR, New Delhi for the fellowship. Financial support from IISER-Pune is gratefully acknowledged by the authors to carry out this research work.

Notes and references

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10 The observed optical rotation of the products were in agreement with the literature values (please see ESI†).

11 The reaction was quenched with water without the aid of any acid.

