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Graphical Abstract:

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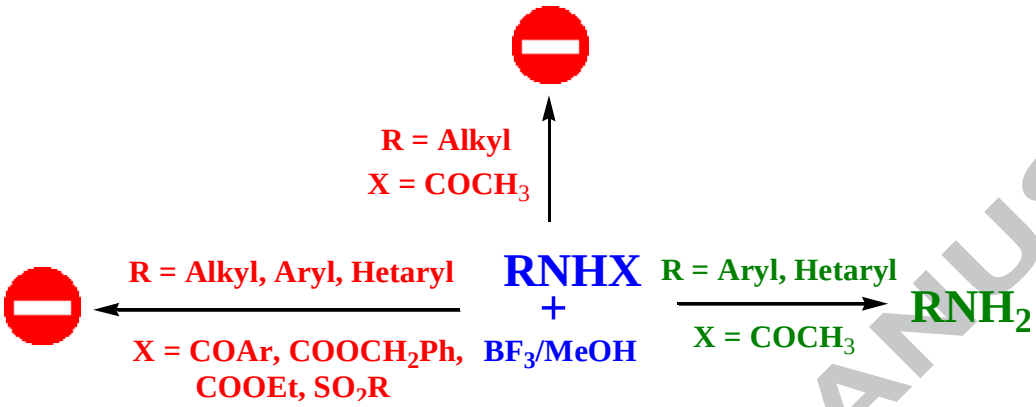

Boron trifluoride-methanol complex. Mild and powerful reagent for deprotection of acetylated amines. Scope and selectivity.

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A boron trifluoride–methanol complex demonstrated remarkable deprotection selectivity against commonly used amino-protecting groups in the deacetylation of acetanilides and high sensitivity to the steric hindrance of substrates. The scope and limitations of the reaction were explored.

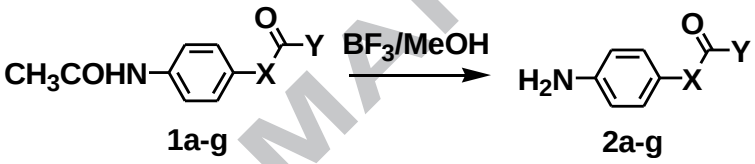
1. Introduction

Acetylation by the derivatives of acetic acid (acetic anhydride, acetyl chloride) can be considered as the most inexpensive and simple way to protect the amino group in multistep organic synthesis. The advantage of this approach is the ease of the protection step, that can be carried out at room temperature. Unfortunately the deprotection step often requires rather harsh conditions (highly acidic or basic media and elevated temperatures) causing side-reactions. It is therefore interesting to study mild deacetylation reactions to make this protecting group more attractive. For instance, Sihlbom[1] proposed a procedure consisting of heating acetanilides at reflux in methanol in the presence of boron trifluoride. During the course of our research regarding the synthesis of long-wave absorbing dyes we successfully used this procedure for the deprotection of highly labile acetylated aminocyanines.[2,3] Later on it was also used in the synthesis of azidofluoresceins[4] and in the final step for the preparation of nonnatural amino

acids,[5] where aromatic and heteroaromatic amines were simultaneously used as protecting groups for the carboxylic functional group and as directing groups for the coupling reaction. It is also noteworthy that the use of boron trifluoride did not cause racemization in the derivatives of chiral α-acids in the latter synthetic application. Herein we establish the scope and limitations of this highly promising synthetic method.

2. Results and Discussion

In order to study the relevance for the use of BF_3 in the deprotection of acetylated amines, we first examined the behavior of amides prepared from various aliphatic and aromatic amines and common acylating agents using the previously reported conditions employed for the deprotection of acetylated cyanine dyes.[2,3] The reaction was carried out for 3h with 6 equivalents of BF_3 and the composition of the reaction mixture was examined by NMR or GC.
Suprisingly, the deprotection procedure was very selective. Acetylated aliphatic amines ($PhCH_2NHCOCH_3$, $PhCH_2CH_2NHCOCH_3$, *n*-$BuNHCOCH_3$, *N*-acetylpyrrolidine) as well as benzoylated amines ($PhCH_2NHCOPh$, $PhCH_2CH_2NHCOPh$, PhNHCOPh) remained unchanged and only acetanilides appeared to be reactive. The selectivity of the process towards the nature of the amine was also proved by the selective removal of the acetyl protecting group when treating a series of amides of 4-acetylaminophenylacetic and 4-acetylamino-(*E*)-cinnamic acids **1a-g** with the above reagent (Table 1).



1a-g **2a-g**

Compound	X	Y	Yield, % [a]
2a	$-CH_2-$	$-NHCH_2Ph$	76 (94)
2b	$-CH_2-$	$-N(CH_2)_4$	(92)
2c	$-CH_2-$	$-NHCH_2CH=CH_2$	63
2d	-CH=CH-	$-NHCH_2Ph$	71
2e	-CH=CH-	$-N(CH_2)_4$	(93)
2f	-CH=CH-	$-NHCH_2CH=CH_2$	72
2g	-CH=CH-	$-NHCH_2CH_2OCH_3$	(84)

[a] Parenthesis refer to amine complexes with BF_3

Table 1. Deacetylation of amides of 4-acetylaminophenylacetic and 4-acetylamino-(*E*)-cinnamic acids.

Upon NMR-monitoring of the reaction mixture, complete cleavage of the acetanilide group was demonstrated and no traces of destruction of the phenylacetamide or cinnamide moieties were detected after 3 hours. In the latter case, we observed insignificant amounts (< 5%) of *Z*-isomerized products. Some products, such as free amines, which were low-melting point substances, were difficult to separate in their pure form. Therefore, we isolated the amines as their boron complexes instead, which were the primary reaction products by evaporating the volatiles *in vacuo* and triturating the residue with Et_2O to give fine non-hydroscopic powders. The ^1H NMR-spectra of the complexes agreed with those of protonated aniline derivatives. The ^{19}F spectra showed two close singlets near -148 ppm, independent of the aniline structure. The relation of integral intensities corresponded to the natural relation of ^{11}B and ^{10}B isotopes (4.05).

To further demonstrate the reaction selectivity, we used 4-aminoacetanilides, acylated with different acylating agents as model compounds (**3a-e**). The protective groups that remained unaltered during the course of the deacetylation reaction were benzoyl, methanesulfonyl, ethoxycarbonyl and benzyloxycarbonyl groups. In order to examine the role of steric hindrance in the acyl fragment we tested deprotection of *N*-acetyl-*N'*-pivaloyl-*p*-phenylenediamine (**3e**) and observed only the removal of the acetyl group (Table 2).

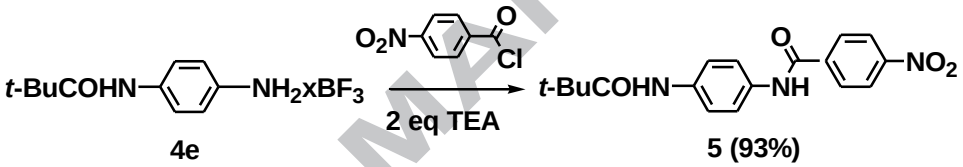
3a-e **4a-e**

X = a) PhCO-, b) EtOOC-, c) $PhCH_2OOC$-, d) CH_3SO_2-, e) *t*-BuCO-

Compound	Yield (free amine),%	Yield (BF_3-complex)%
4a	83	95
4b	71	90
4c	78	94
4d	84	94
4e	87	97

Table 2. Deprotection of acylated 4-aminoacetanilides using BF_3-MeOH.

Reaction products as well as their complexes with BF_3 were separated, with the latter showing considerably higher yields (Table 2). The acylation reaction of **4e·BF$_3$** with 4-nitrobenzoyl chloride using 2 equivalents of Et_3N in CH_2Cl_2 yielded **5** in 93% yield, demonstrating that complexes of aromatic amines with BF_3 could be used for further manipulation in the same manner as their hydrochlorides (Scheme 1).

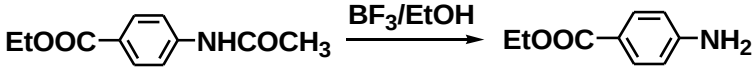


4e **5 (93%)**

Scheme 1. Acylation of 4e-BF_3 complex with 4-nitrobenzoyl chloride.

As previously stated, the deacetylation of acetanilides[1] is rather sensitive to steric hindrance on the benzene moiety. In this sense, we examined the influence of *N*-substitution in acetanilide on the rate of reaction. It was observed that during the examined reactions, the time for the complete deprotection of acetanilide (3 hours), the conversion of *N*-methylacetanilide was only achieved in 10% yield and that *N*-ethylacetanilide remained unreacted. This result indicates the selective deprotection of acetylated primary arylamines in the presence of similarily protected secondary amino groups.

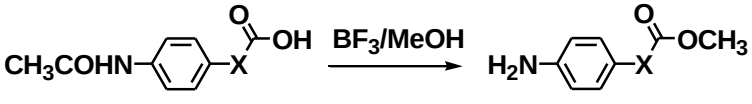
It was reasonable to expect that acetanilides posessing ester groups can be deprotected while leaving the ester group unaltered, which is not possible when performing any hydrolytical method. The ethyl ester of 4-acetaminobenzoic acid **6** was converted to ethyl *p*-aminobenzoate **7** containing about 10% of the corresponding methyl ester, even when the reaction was carried out in ethanol. In order to avoid transesterification the complex of boron trifluoride with ethanol, which was prepared by carefully adding boron trifluoride etherate to absolute ethanol, was used and pure ethyl *p*-aminobenzoate was obtained in nearly quantitive yield.



6 **7**

Scheme 2. Reaction of ethyl 4-acetylaminobenzoate with the boron trifluoride–ethanol complex.

Furthermore it was possible to combine the acetanilide deprotection and carboxyl group esterification reactions in a one-step synthesis.



8a-b **9a-b**

X = a) OCH_2, b) CH_2.

Scheme 3. Reaction of 4-acetylaminophenyl-substituted acids with the boron trifluoride–methanol complex.

Some aromatic and heterocyclic amines can be synthesized by condensation only as acetylated derivatives and their deacetylation by hydrolytical methods sometimes meets problems caused by the instability of the heterocyclic moieties in highly acidic or basic media. Using our approach we obtained amino-substituted 3,5-dihydro-2,3-diphenyl-5-(phenylmethylene)-3,5-dihydro-4*H*-imidazol-4-ones **10** and **11** from their respective acetamides in good yields. Amino-derivatives of 1*H*-pyrido[2,1-*b*]benzoxazole **12**, 5*H*-3,4-thiadiazolo[3,2-*a*]pyrimidine **13** and 4*H*-pyridino[1,2–*a*]pyrimidine **14** were also successfully prepared from readily available acetylated species, synthesized according to literature procedures[7,8] (Figure 1). Compounds **13** and **14** were isolated as complexes with BF_3 because of the high solubility of the free amines in water. Earlier it was shown that 5*H*-3,4-thiadiazolo[3,2-*a*]pyrimidines, which have structures very similar to compound **13,** underwent cleavage of the thiadiazole ring both in acidic[9] (5% HCl) and basic[10] (5% NaOH) media. This fact ensures that the conventional hydrolytical deprotection of acetylated **13** is hardly possible. It is also worth noting that deprotection of benzyloxycarbonyl-protected compound **14** was previously achieved[18] by catalytic hydrogenation but only with the simultaneous saturation of the pyridine ring.

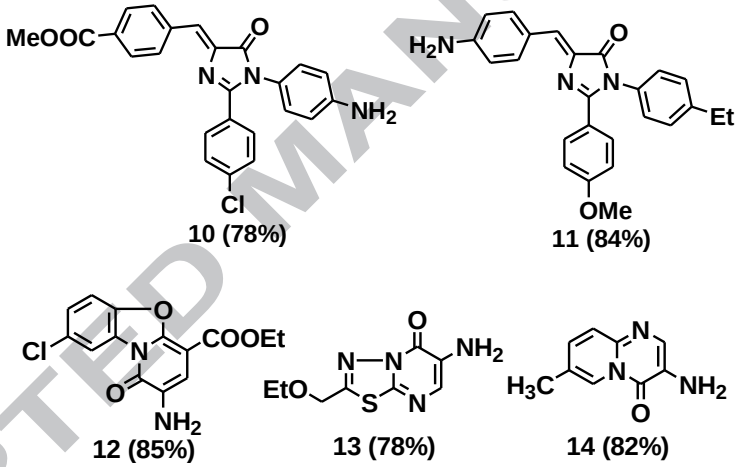


Figure 1. Heterocyclic and aromatic amines, prepared from acetamides.

Using our proposed deprotection procedure, we were also able to synthesize styryl dyes bearing free amino groups, which are formally the products of the condensation of heterocyclic salts with an active methyl group and 4-aminobenzaldehyde **20**-**24**. The obtained diamino-substituted dyes **21** and **24** have been demonstrated to be suitable for incorporation in the main chain of polyamides.[11,12] The obtained yields of free amines for the deprotection step was 72 – 85% **(** Figure 2).

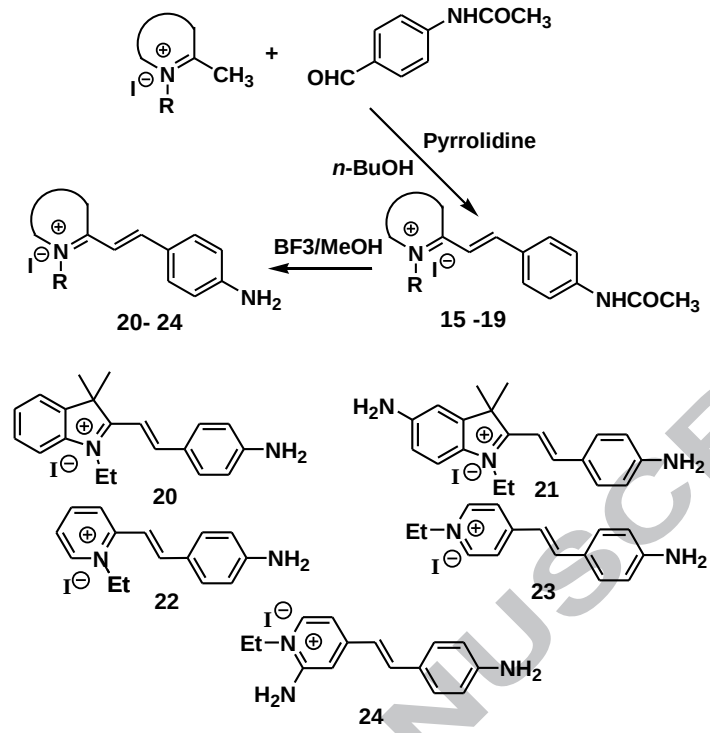
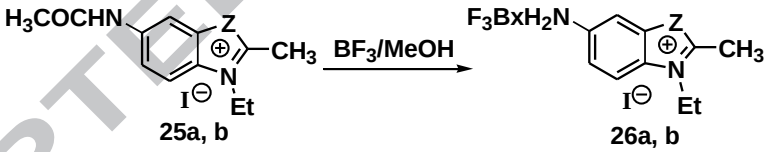


Figure 2. Amino-substituted styryl dyes.

The final model reaction using this deprotection method was the synthesis of functionalized cyanine dyes. In this case, it is desirable to start with amino-substituted heterocyclic salts which can be prepared by reduction of the corresponding nitrated salts with $SnCl_2$ and the separation of the water-soluble products from aqueous reaction mixtures.[13] We obtained amino-salts **26a,b** from acetylated precursors in high yields as complexes with BF_3 (Scheme 4).



a) Z = S (92%); b) Z = $C(CH_3)_2$ (95%).

Scheme 4. Preparation of amino-substituted heterocyclic salts.

All our attempts to perform the elementary analysis of boron complexes failed. Assuming that the products represent 1:1 amine-BF_3 complexes we examined the ^1H and ^{19}F NMR spectra of their mixtures with 4-bromoanisole and CF_3CONEt_2 as standard substances and observed sufficient concordance of the defined molar relations of amine-BF_3 complexes and standards with those evaluated from spectral data (Table 3).

X	[X]/[St], by weight	[X]/[St], ^1H NMR	[X]/[St], ^{19}F NMR
2e-BF_3[a]	0.98	0.87	
4b-BF_3[a]	0.77	0.69	
4c-BF_3[b]	0.63	0.56	0.61
4d-BF_3[b]	0.86	0.84	0.86
4e-BF_3[a]	1.13	0.97	
9a-BF_3[b]	0.65	0.62	0.64
9b-BF_3[b]	0.53	0.51	0.52
13-BF_3[a]	0.87	0.80	
14-BF_3[a]	1.21	1.24	
26a-BF_3[a]	0.55	0.56	
26b-BF_3[a]	0.69	0.71	

[a] Standard: 4-bromoanisole, [b] Standard: CF_3CONEt_2

Table 3. Determination of the composition of selected amine-BF_3 compounds.

3. Conclusions

We have reported a mild and highly selective method for the liberation of free aromatic and heterocyclic amines from their acetylated derivatives. Other amides such as benzamides, acylated aliphatic amines, some other commonly used amino group protections and ester groups remained unaltered in the reaction conditions.

Acknowledgements

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References and notes

1. Sihlbom, L. *Acta Chem. Scand*. **1954**, *8*, 529–530.
2. Miltsov S.; Rivera L.; Encinas C.; Alonso J. *Tetrahedron Lett.* 2003, 44, 2301-2303.
3. Miltsov S.; Karavan V.; Goikhman M.; Podeshvo I.; Gymez-de Pedro S.; Puyol M.; Alonso J. *Dyes and Pigments* **2014**, *109*, 34-41.
4. Shieh P.; Hangauer M.J.; Bertozzi C.R. *J. Am. Chem. Soc*, **2012**, *134*, 17428-17431.
5. Tran, L.D., Daugulis, O. *Angew. Chem. Int. Ed*. **2012**, *51*, 5188-5191.
6. Representative procedure for **4e**: **3e** (1.17 g, 5 mmol) in dry methanol (10 ml) was treated with BF_3 (3.4 ml, 30 mmol) as the boron trifluoride–methanol complex (50% BF_3, Aldrich®) and the reaction solution was heated at reflux for 3 h. After completion of the reaction, the reaction mixture was cooled, neutralized with 25% aqueous ammonia (2.5 ml) and evaporated to dryness in vacuum. The residue was treated with water (5 ml) and extracted with $CHCl_3$ (15 ml), then dried with Na_2SO_4. Evaporation of solvent yielded **4e** (835 mg, 87%). ^{1}H NMR (300 MHz, DMSO-d_6): 1.16 (s, 9H), 6.49 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 8.79 (s, 1H). Signal of NH_2-protons are overlapped with signals of water at 4.0. In order to obtain the complex of amine with BF_3 after completion of the reaction, the reaction mixture was evaporated to dryness in vacuum and the residue was washed with ether and dried on air. Yield of **4e-BF_3** – 97%. ^{1}H NMR (300 MHz, DMSO-d_6): 1.24 (s, 9H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 8.7 – 10.3 (br.s, NH_2 + H_2O), 9.37 (s, 1H).
7. Kralj L.; Hvala A.; Svete J.; Golic L.; Stanovnik B. *J. Het. Chem.* **1997**, *34*, 247-255.
8. Recnik S., Toplak R., Svete J., Pizzioli L., Stanovnik B. *J. Het. Chem.* **2000**, *37*, 783-790.
9. Tsuji T.; Otsuka Y. *Chem.Pharm.Bull.* 1978, 26, 2765–2767.
10. Okabe T.; Taniguchi E., Maekawa K. *Bull.Chem.Soc.Jap.* 1974, 47, 2813-2817.
11. Goikhman M. Ya.; Yevlampieva N.P.; Kamanina N.V.; Podeshvo I.V.; Gofman I.V.; Miltsov S.A. *Polym. Sci. Ser. A*, **2011**, *53*, 457-468.
12. Goikhman M. Ya.; Yevlampieva N.P.; Podeshvo I.V.; Miltsov S.A., Karavan V.S.; Gofman I.V.; Khurchak A.P.; Yakimansky A.V. *Polym. Sci. Ser. B*, **2014**, *56*, 352-359.
13. Berezin M.Y.; Guo K.; Teng B.; Edwards W.B.; Anderson C.J.; Vasalatiy O.; Gandjbakche A.; Griffits G.L.; Achilefu S. *J. Amer. Chem. Soc.* **2009**, *131*, 9198-9200.