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Boron trifluoride–methanol complex—mild and powerful reagent for deprotection of labile acetylated amines

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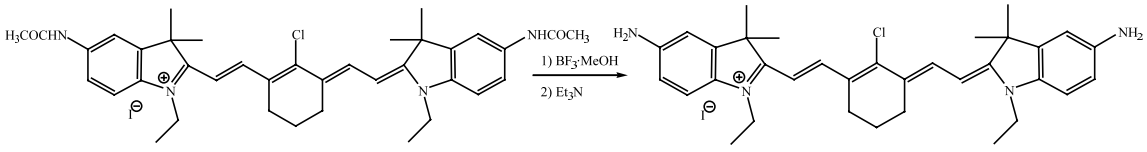
Abstract—A set of amino-group possessing cyanine dyes is obtained from their *N*-acetyl derivatives via deprotection with boron trifluoride–methanol complex in good yields.

Protection and subsequent deprotection of amino group are processes of great importance for all fields of organic synthesis. Numerous reagents and methods are developed now for these purposes, especially in peptide chemistry.[1] At the same time, the most simple and cheap way of protection–acetylation by derivatives of acetic acid (acetic anhydride, acetyl chloride) is not widely used, mainly due to the fact that the deprotection step requires rather severe reaction conditions (highly acidic or basic media, elevated temperatures), causing a lot of side reactions. In this way, development of mild deacetylation procedures can greatly enlarge the application scope of this very attractive protecting group.

Lately, there has been a considerable interest in cyanine-type dyes, possessing amino groups, because of their use as NIR-absorbing labels for proteins,[2–4] as well as pH-sensitive ionophores for analytical applications.[5] The synthesis of quaternary salts of nitrogen heterocycles needs protection–deprotection steps of amino groups. Earlier, this procedure was undertaken by using di-*t*-butylcarbonate for protection of initial amine followed by cleavage of resulting N-BOC-protected dyes by iodotrimethylsilane.[2,3] Both these reactions require rather expensive reagents and final purification of dyes by column chromatography.

In literature a single report about deacetylation of acetanilides by boron trifluoride–methanol complex is found.[6] We attempted to use this reagent for the synthesis of amino group-containing cyanine dyes of different types (indotricarbocyanine **1**, norindosquarocyanine **2**, *meso*-substituted indotricarbocyanine **3** and ketocyanines **4**–**6**) (Scheme 1).[7] It appeared that this reagent easily cleaves acetylated dyes resulting products with free amino groups in good yields (Table 1). The reaction is carried out in boiling methanol with 6-fold excess of reagent. Nearly quantitative yields of crude products are obtained.[8] On the final stage of liberation of free amino dyes we used triethylamine instead of aqueous ammonia, which was employed by the authors of the original article, improving significantly the yields.

Finally, we believe that boron trifluoride–methanol complex is a reagent of great potential and are looking forward to establish the scope of its synthetic utility.



Scheme 1. Representative deprotection of an acetylated amine with boron trifluoride–methanol complex. Here dye **1** is shown.

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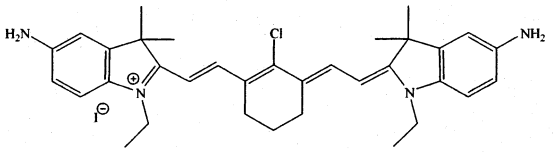
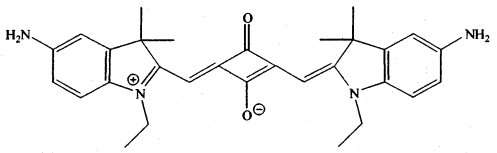
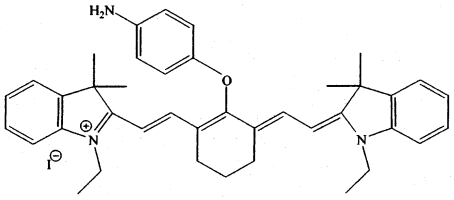
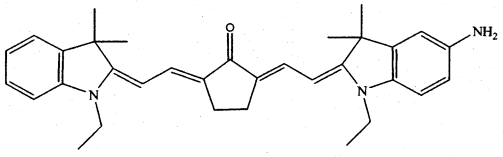
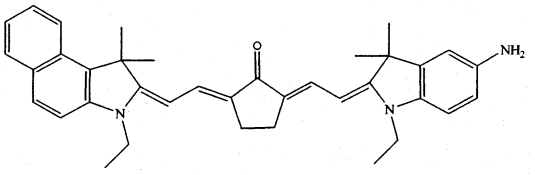
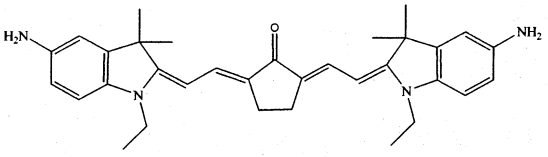
Table 1. Amino group-containing cyanine dyes obtained by deprotection of their *N*-acetyl derivatives with boron trifluoride–methanol complex and yields

Number	Product	Yield (%)
1		95
2		67
3		75
4		64
5		71
6		78

Acknowledgements

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Chem. **1992**, *57*, 4578; dyes **4**–**6**: Miltsov, S.; Encinas, C.; Alonso, J. *Tetrahedron Lett*. **2001**, *42*, 6129–6131.

8. Representative procedure for **1**: 752 mg (1 mmol) of acetylated dye **1** in 30 ml of dry methanol were treated with 1.35 ml (12 mmol) of BF_3 as boron trifluoride–methanol complex (50% BF_3, Aldrich®) and the reaction solution was kept under reflux for 5 h. After completion of the reaction, 2.5 ml of triethylamine were added drop by drop on cooling and the resulting mixture was evaporated to dryness in vacuum. The remaining solid was stirred with 50 ml of water and filtered. After drying the crude, product was recrystallized from methanol containing sodium iodide. Yield: 634 mg (95%). ^{1}H NMR (250 MHz, DMSO-d_6): 1.27 (t, $J=7.3$ Hz, 6H), 1.60 (s, 12H), 1.83 (br, 2H), 2.56 (br, 4H), 4.13 (br, 4H), 6.13 (d, $J=14$ Hz, 2H), 6.60 (d, $J=8$ Hz, 2H), 6.74 (d, $J=8$ Hz, 2H), 7.13 (s br, 2H), 8.08 (d, $J=14$ Hz, 2H). FABMS: 541 ($M^+(Cl^{35})$, 100), 542 ($M^+(Cl^{35}+H)$, 30). VIS-NIR (CH_3OH): $\lambda_{max}=835$ nm.