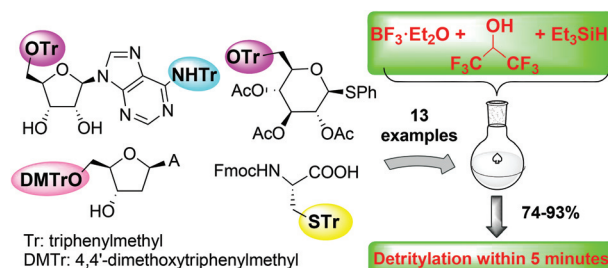


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**A three-component reagent system for rapid and mild removal of *O*-, *N*- and *S*-trityl protecting groups**

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A synergistic effect of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , hexafluoroisopropanol and triethylsilane led to efficient detritylation of nucleoside, monosaccharide and amino acid derivatives.



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## COMMUNICATION

### A three-component reagent system for rapid and mild removal of *O*-, *N*- and *S*-trityl protecting groups†

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Zoltán Kupihár,<sup>b</sup> Lajos Kovács,<sup>b</sup> Anikó Borbás\*<sup>a</sup> and Pál Herczegh\*<sup>a</sup>

**A new reagent system consisting of a Lewis acid such as BF<sub>3</sub>·Et<sub>2</sub>O or Cu(OTf)<sub>2</sub>, the mild protic acid hexafluoroisopropanol and the reducing quenching agent triethylsilane was elaborated for *O*-, *N*- and *S*-deprotection of nucleoside, carbohydrate and amino acid derivatives. The method is compatible with acetyl, silyl, acetal and Fmoc groups.**

*O*-, *N*- and *S*-triphenylmethyl groups as well as their methoxy derivatives are widely used in organic synthesis.<sup>1,2</sup> Detritylation is conveniently achieved under acidic conditions using either strong protic acids or different Lewis acids. The trityl ethers are especially important tools in nucleic acid synthesis for the protection of 5'-hydroxyl of nucleosides, and deprotection is generally accomplished with dichloroacetic acid in dichloromethane.<sup>3</sup> Recently, we have also used trityl and 4,4'-dimethoxytrityl ethers for the protection of new nucleoside analogues.<sup>4</sup> However, our nucleoside derivatives having an acid-sensitive double amination structure proved to be sensitive to the influence of protic acids which prompted us to find a mild, Lewis acid-mediated detritylation method.

Several examples have been known for the use of Lewis acids for detritylation such as ferric chloride,<sup>5</sup> ytterbium triflate,<sup>6</sup> cerium triflate,<sup>7</sup> indium triflate,<sup>8</sup> boron trichloride,<sup>9</sup> zinc bromide,<sup>10</sup> boron trifluoride diethyl etherate,<sup>10</sup> magnesium bromide<sup>10</sup> or triethylsilyl triflate.<sup>11</sup> Some of these reagents act under mild conditions but we realized that in most cases the reaction time was too long. Since during a long reaction course side reactions can occur, these conditions were unsatisfactory to our purposes. One of the possibilities of increasing the rate of detritylation is the reductive quenching of the intermediate trityl cation with a trialkylsilane. According

to literature data, combination of trialkylsilane with a Lewis acid<sup>11</sup> has not accelerated the reaction sufficiently.

To achieve a mild and rapid detritylation, we decided to use a new reagent system including both Lewis and protic acids and a quenching agent expecting a synergistic behavior of the three components.‡ First, deprotection of 5'-*O*-trityl uridine **1** was studied using a reagent cocktail including boron trifluoride diethyl etherate as the Lewis acid, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a mild protic acid and the reducing agent triethylsilane (Table 1). Noteworthy, HFIP is capable of slowly removing 4,4'-dimethoxytrityl groups when it is used as a single agent.<sup>12</sup> The complete cleavage of the protective group using the three-component reagent has taken place in 2–3 minutes (entry 1). Omitting either component from the cocktail resulted in a moderate to drastic increase of the reaction time and imperfect conversion of the trityl derivative. In a second set of experiments, boron trifluoride diethyl etherate was substituted by copper(II) triflate (Table 1, entries 7–10). In order to work with a homogeneous solution, the copper salt was dissolved in nitromethane prior to adding it to **1a**. We have found that Cu(OTf)<sub>2</sub> was an efficient Lewis acid component of the detritylating cocktail as BF<sub>3</sub>·Et<sub>2</sub>O.

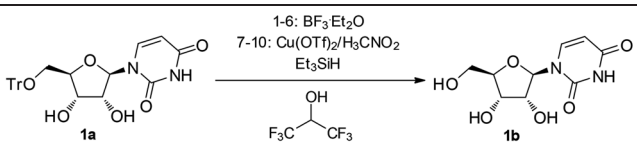
Applying the optimized conditions, detritylation of **1a** was carried out on a preparative scale (0.50 mmol) with both the BF<sub>3</sub>·Et<sub>2</sub>O- and Cu(OTf)<sub>2</sub>-containing mixtures to afford **1b** in 87% and 90% yields, respectively. The silyl-protected **2a** turned out to be sensitive towards the reagent mixtures containing 0.2 equiv. of either of the Lewis acids and the detritylated **2b** could only be isolated in moderate yields. Clean and fast deprotection of **2a** was achieved using the Lewis acids in a decreased amount (0.065 equiv.) and the yields reached 88% and 66%, respectively.

We were pleased to find that adenosine **3a** containing both *N*- and *O*-trityl protecting groups could completely be deprotected with the BF<sub>3</sub>·Et<sub>2</sub>O reagent within 5 minutes to provide the *N,O*-detritylated **3b** in 84% yield. Interestingly, attempted detritylation of **3a** using Cu(OTf)<sub>2</sub> was unsuccessful. Partial deprotection (presumably *O*-detritylation) was observed in a very low extent even in an overnight reaction.

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† Electronic supplementary information (ESI) available: Experimental details, and <sup>1</sup>H and <sup>13</sup>C spectra of compounds. See DOI: 10.1039/c6ob00067c

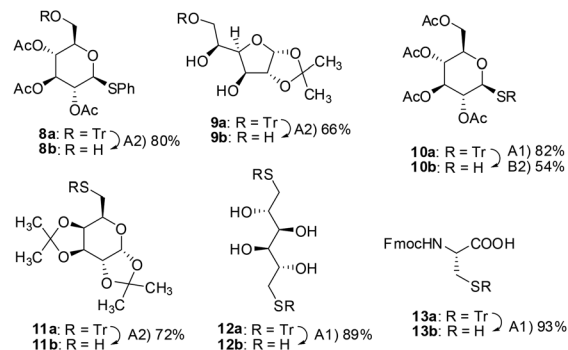
**Table 1** Optimization of the reaction conditions for detritylation of **1a**


Entry	Reagents (1 ml/0.1 mmol)	Lewis acid (0.2 equiv.)	Et <sub>3</sub> SiH (3.8 equiv.)	Detritylation time (min)	Conversion
1	+	BF <sub>3</sub> ·Et <sub>2</sub> O	+	3	~100%
2	—	BF <sub>3</sub> ·Et <sub>2</sub> O	+	10	~100%
3	+	BF <sub>3</sub> ·Et <sub>2</sub> O	—	30	~50%
4	+ <sup>a</sup>	BF <sub>3</sub> ·Et <sub>2</sub> O	+	10	~100%
5	+	BF <sub>3</sub> ·Et <sub>2</sub> O <sup>b</sup>	+	5–10	~100%
6	—	BF <sub>3</sub> ·Et <sub>2</sub> O	—	30	~70%
7	+	Cu(OTf) <sub>2</sub>	+	5	~100%
8	—	Cu(OTf) <sub>2</sub>	+	10	~100%
9	+	Cu(OTf) <sub>2</sub>	—	30	~100%
10	—	Cu(OTf) <sub>2</sub>	—	30	~75–80%
11	+	None	+	30	~5–10%

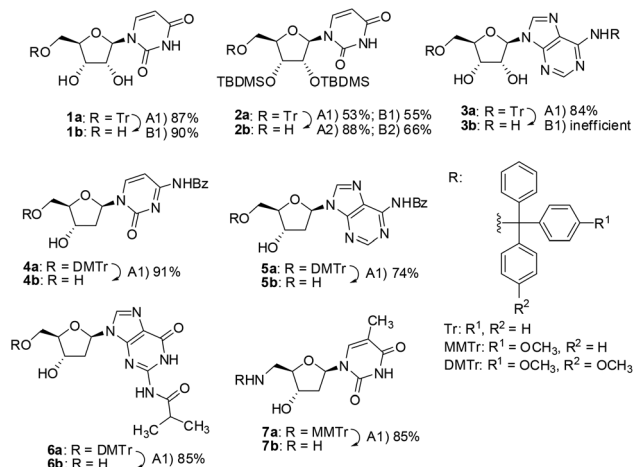
<sup>a</sup> 0.5 ml/0.1 mmol. <sup>b</sup> 0.05 equiv.

For further experiments the BF<sub>3</sub>·Et<sub>2</sub>O-containing mixture was used. Cleavage of the 4,4'-dimethoxytrityl groups of 2'-deoxynucleosides **4a**, **5a** and **6a** also proceeded rapidly, without depurination. The removal of the 5'-N-4-monomethoxytrityl group of **7a** with the cocktail took place completely within 5 minutes as well, furnishing 5'-amino-5'-deoxythymidine **7b** in 85% yield (Scheme 1).

Next, the efficacy of the cocktail was studied on carbohydrate derivatives (Scheme 2). Detritylation of the 6-O-trityl thioglucoside **8a** resulted in the expected product in 80% yield. Importantly, acyl-migration side reaction which often



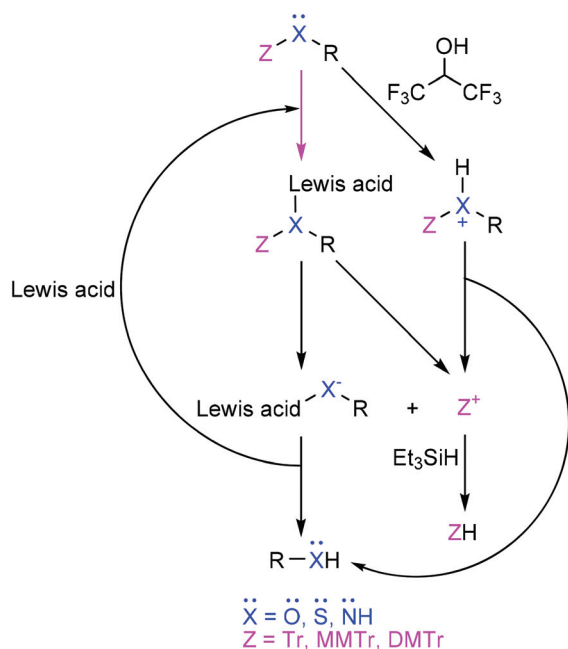
**Scheme 2** O- and S-Detritylation of sugar and amino acid derivatives. Reagents and conditions: (A1) BF<sub>3</sub>·Et<sub>2</sub>O (0.2 equiv.), HFIP, Et<sub>3</sub>SiH; (A2) BF<sub>3</sub>·Et<sub>2</sub>O (0.065 equiv.), HFIP, Et<sub>3</sub>SiH; (B1) Cu(OTf)<sub>2</sub> (0.065 equiv.), HFIP, Et<sub>3</sub>SiH.



**Scheme 1** O- and N-Detritylation of nucleosides. Reagents and conditions: (A1) BF<sub>3</sub>·Et<sub>2</sub>O (0.2 equiv.), HFIP, Et<sub>3</sub>SiH; (B1) Cu(OTf)<sub>2</sub> (0.2 equiv.), HFIP, Et<sub>3</sub>SiH; (A2) BF<sub>3</sub>·Et<sub>2</sub>O (0.065 equiv.), HFIP, Et<sub>3</sub>SiH; (B2) Cu(OTf)<sub>2</sub> (0.065 equiv.), HFIP, Et<sub>3</sub>SiH.

occurs under acidic conditions was not observed. Attempted removal of the 6-O-trityl group from the 1,2-O-isopropylidene-glucofuranose derivative **9a** with the reagent mixture containing 0.2 equiv. of BF<sub>3</sub>·Et<sub>2</sub>O led to partial loss of the acid sensitive cyclic acetal. The decomposition could be avoided successfully by decreasing the amount of Lewis acid to 0.065 equivalents. Although complete detritylation was observed, mono- and bis-triethylsilylated by-products were also formed eroding the yield of **9b**.

As triphenylmethyl is a common S-protecting group, the methods that are able to cleave the S-trityl group under mild conditions are very important for the thiol-containing compounds. Thus, applying the three-component reagent for S-detritylation was also studied. The removal of the anomeric S-trityl groups of **10a** with the BF<sub>3</sub>·Et<sub>2</sub>O-containing reagent



**Scheme 3** Possible mechanism for the three-component detritylation.

system under usual conditions produced **10b** in 82% yield. The *S*-detritylation reaction of **10a** using 0.2 equiv. Cu(OTf)<sub>2</sub> as the Lewis-acid component resulted in a nearly 1 : 1 mixture of the expected 1-thiosugar and its disulfide derivative. Decreasing the amount of Cu(OTf)<sub>2</sub> to 0.065 equivalent, the side reaction could be diminished, however, beside **10b**, its disulfide derivative was also isolated in 10% yield. Wang and coworkers reported<sup>13</sup> that Cu(I)chloride-mediated deprotection of the trityl thioethers led to the formation of the corresponding disulfide. In our case, similarly, the copper catalyst might have contributed to the oxidative transformation of **10b**.

The treatment of the acid sensitive **11a** with the cocktail containing the  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in a reduced amount led to efficient *S*-detritylation. Finally, the di-*S*-tritylated mannitol **12a** and the *S*-tritylated Fmoc-L-cysteine **13a** were reacted with the detritylating mixture producing the thiol derivatives **12b** and **13b** in excellent yields (Scheme 2).

It should be emphasized that in the presence of our detritylation reagent mixture the trityl group was cleaved completely in less than 5 minutes. The probable mechanism of synergistic detritylation reaction accomplished with our three-component reagent mixture can be seen in Scheme 3. In the case of **2a** → **2b** transformation the byproduct triphenylmethane was isolated from the reaction mixture which corroborates the proposed mechanism.

## Conclusions

In summary, we have elaborated a new, three-component reagent system for rapid and mild removal of *O*-, *N*- and *S*-triphenylmethyl, 4-methoxytriphenylmethyl and 4,4'-dimethoxy-

triphenylmethyl protective groups. Out of the Lewis acids tested,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  was superior to  $\text{Cu}(\text{OTf})_2$ . While the  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -containing reagent system led to very efficient *O*-, *N*- and *S*-deprotection,  $\text{Cu}(\text{OTf})_2$  showed only high efficacy in *O*-deprotection. The method was compatible with a wide range of protecting groups such as acetyl, TBDMS, cyclic acetal and Fmoc.

We assumed that similar new detritylating systems can be constructed by substituting  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  or copper(II) triflate for other Lewis acids.

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## Notes and references

‡ General procedure for detritylation: 0.500 mmol of trityl, monomethoxytrityl or dimethoxytrityl derivative was added to the mixture of hexafluoroisopropanol (0.5 mL), Lewis acid:  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (A1: 0.2 equiv., A2: 0.065 equiv.) or  $\text{Cu}(\text{TfO})_2$  (B1: 0.2 equiv., B2: 0.065 equiv., 100 mg in 50 mL  $\text{MeNO}_2$ ) and  $\text{Et}_3\text{SiH}$  (3.8 equiv., 300  $\mu\text{L}$ ). After complete conversion of the starting compound (cc. 5 min) the reaction was quenched with a saturated aqueous solution of  $\text{NaHCO}_3$ . The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography.

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