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Improved procedure for the synthesis of thiazolium-type peptide coupling reagents: BMTB as a new efficient reagent☆

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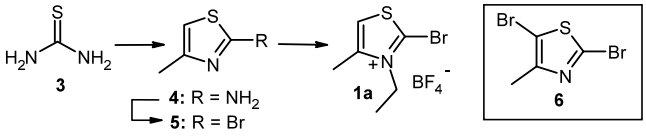
Abstract—An efficient scalable synthesis of 2-halothiazolium-type peptide coupling reagents has been developed. The key step is the formation of the 2-bromothiazole scaffold through cyclization of α-thiocyanato ketones with hydrogen bromide. Using this method, the new coupling reagent 2-bromo-*N*-methylthiazolium bromide (BMTB) was synthesized. BMTB was tested in a difficult model coupling reaction of two sterically hindered *N*-methylated amino acids and showed higher activity than the well-established peptide coupling reagent HATU. © 2003 Elsevier Science Ltd. All rights reserved.

The coupling of sterically hindered *N*-alkylated amino acids is a challenge in peptide chemistry for which a satisfactory solution has not been found.[1] Use of a conventional peptide coupling reagent in such cases often results in poor yields that are frequently associated with racemization. The finding that HOAt-based coupling reagents such as HATU are superior to HOBt-type reagents represented an important improvement. However, these reagents do not provide a general solution for difficult coupling reactions.[2,3] In addition, HOAt is expensive, and safety concerns with this reagent have recently been raised.[4] In the past years, considerable efforts to find new improved coupling reagents and procedures have been observed in the literature.[5]

One of these efforts yielded the new peptide coupling reagent 2-bromo-3-ethyl-4-methyl thiazolium tetrafluoroborate (BEMT, **1a**) which was introduced by Xu in 1999. Together with the coupling reagent 2-bromo-1-ethyl pyridinium tetrafluoroborate (BEP, **2**), BEMT is described to work well for sterically hindered amino acid peptide couplings, particularly for the case of *N*-alkylated amino acids.[6,7] As an experimental demonstration for the potency of these reagents, the authors published the first chemical synthesis of the copiously *N*-methylated cyclic undecapeptide cyclosporin O.[8]

Due to our interest in the synthesis of peptides consisting of multiple *N*-alkylated amino acids,[5a] we were in need of BEMT which has not been commercially available to date. According to the previously described procedure, BEMT is synthesized starting from thiourea **3** which is converted to the aminothiazole **4**. Compound **4** is then transformed into the corresponding bromothiazole **5** which is subsequently *N*-ethylated using Meerwein reagent.[6] In our efforts to repeat the described synthesis, we encountered difficulties in the transformation of the aminothiazole into the corresponding bromothiazole **5**, namely the formation of considerable amounts of dibrominated compound **6** as side product (Scheme 1). Our attempts to improve the selectivity of this step were unsuccessful. In addition, purification of **5** via distillation proved to be difficult and not suitable for large-scale application.



Scheme 1. Synthesis of BEMT following a protocol by Xu.[6]

☆ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)00928-6

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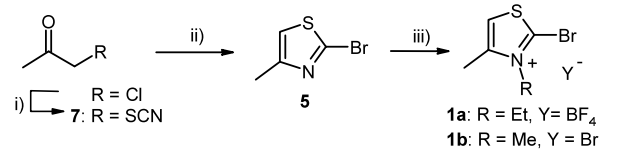
We therefore needed a new strategy to access the key compound **5**.

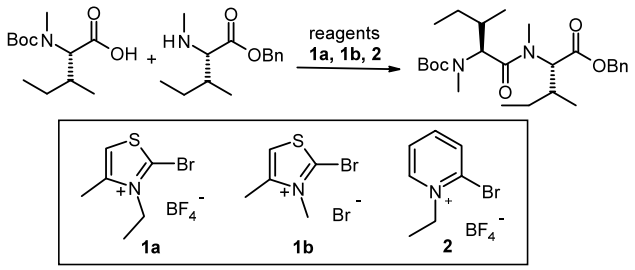
Starting from commercially available chloroacetone or other α-chloroketones, thiocyanatopropan-2-one **7** was synthesized following the procedure by Hantzsch.[9] We found that treatment of **7** with HBr in dichloromethane resulted, after neutralization, in quantitative formation of the free thiazole **5**.[10] Distillation provided the pure final product in >80% yield. Finally, alkylation using Meerwein salt gave the desired product BEMT **1a**. With this efficient process in hand, BEMT was synthesized on a 0.5 kg scale. However, the use of Meerwein salt is not recommended for large-scale applications due to safety and environmental concerns. In our efforts to identify a less expensive and less toxic alkylating source which would lead to an equally potent coupling reagent, we employed methylbromide which furnished the thiazolium salt **1b** (Scheme 2).[11]

To evaluate the coupling activity of these reagents we performed a comparison study. 1 Equiv. of the amino acid *N*-Boc-MeIle was coupled with 1 equiv. of MeIle-OBn using 1.5 equiv. of reagent **1a**, **1b** and **2**, respectively (Scheme 3). This reaction is known to proceed very poorly using classical coupling reagents, since the *N*-methyl groups as well as bulky side chains contribute to substantial steric hindrance.

As shown in Figure 1, all three reagents **1a**, **1b**, and **2** were superior to PyBop or the combination EDC/HOBt which both failed to show any activity in this case. More importantly, the new reagent **1b** (2-bromo-3-methyl-4-methyl thiazolium bromide, BMTB) demonstrated higher conversion rates than the powerful coupling reagent HATU.



Scheme 2. New general synthesis of thiazolium type peptide coupling reagents. (i) NaSCN, EtOH; (ii) HBr, CH_2Cl_2; (iii) alkylating reagent.



Scheme 3. Model reaction for the comparison of the peptide coupling reagents **1a**, **1b**, and **2**. *Reaction conditions*: 1 equiv. of each amino acid, 2 equiv. DIPEA, 1.5 equiv. reagent, CH_2Cl_2, rt, 2 h.

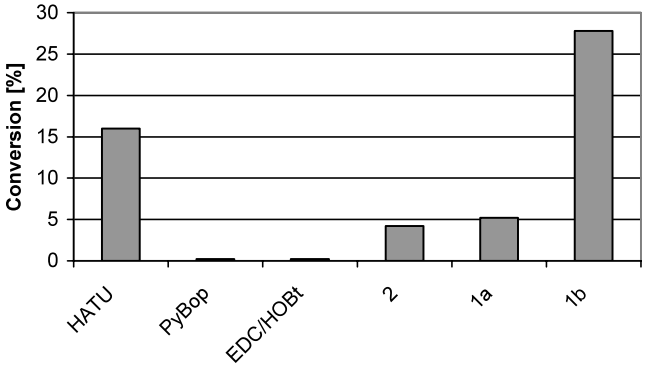


Figure 1. Conversion for the reaction shown in Scheme 3 using the coupling reagents **1a**, **1b**, and **2**.

In none of the model reactions investigated so far we found any significant levels of racemization, and coupling additives such as HOBt are therefore unnecessary.[12] Overall, we recommend BMTB as an attractive alternative for known peptide coupling reagents.[13] BMTB is crystalline and non-hygroscopic, easy to handle and stable at room temperature for months. The scope of this and similar reagents for other condensation reactions is currently being investigated in our laboratories.

Supplementary material

The following supplementary material is available online: experimental procedure for the coupling experiments; general procedure for the synthesis of 2-halo-1,3-thiazoles; general procedure for the *N*-alkylation of 2-halo-1,3-thiazoles; analytical data for the reagent BMTB.

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12. Racemization studies are described in a pending patent application: Wischnat, R.; Rudolph, J., Bayer AG.
13. For the purchase of BMTB, please contact Johannes Heckmann, Bayer AG, Chemicals Division, Marketing, Building B106, D-51368 Leverkusen, Germany. Tel.: +49-214-30-33095; fax: +49-214-3025336. E-mail: johannes.heckmann.jh@bayer-ag.de.