# Polymer-Supported IBX-Amide Reagents: Significant Role of Spacer and Additive in Alcohol Oxidation

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**Abstract:** We found that the spacer and additive play a significant role in the oxidation of alkyl alcohols using polymer-supported IBX-amide reagents. The introduction of the spacer between the polymer support and IBX-amide group improved the initial conversion rate (up to 60% conversion). Furthermore, various alcohol compounds, when reacted with IBX-amide resin in the presence of BF<sub>3</sub>·OEt<sub>2</sub>, were effectively converted into the corresponding aldehydes or ketones within 5–30 minutes in high purities (>94%) at room temperature.

Key words: spacer, additive, IBX-amide resin

Polymer-supported reagents have gained wider acceptance in organic synthesis since the development of the solid-phase and combinatorial high throughput synthesis techniques.<sup>1</sup> The application of polymer-supported reagents to solution-phase organic synthesis combines the advantages of simple work up by filtration and fast reaction optimization.<sup>2</sup>

The oxidation of alcohols to ketones or aldehydes is an important process in organic chemistry, because these compounds represent important intermediates for the preparation of various other compounds.<sup>3</sup> The ensuing continuous interest in developing new methods of mildly and selectively oxidizing alcohols has prompted numerous reports on solid-supported reagents.<sup>4</sup> Especially, several solid-supported o-iodoxybenzoic acid (IBX) reagents have been developed, and these reagents were shown to convert a series of alcohols to the corresponding aldehydes and ketones in excellent yield with high purity.<sup>5</sup> In contrast to most of the previously reported supported oxidants, these IBX reagents do not rely on heavy metal salts or additional co-oxidants, therefore meeting the industrial needs for environment-friendly chemistry. However, their preparation necessitates several elaborate or time-consuming steps.

Accordingly, we previously reported a very simple method of preparing polymer-supported IBX amides (IBX-amide resin) in two steps, involving the coupling of 2-iodobenzoic acid to amino functionalized polystyrene beads, followed by their subsequent activation.<sup>6</sup> Also, we proved that these polymer-supported reagents were mild and efficient oxidants by the successful conversion of a

SYNLETT 2005, No. 14, pp 2175–2178 Advanced online publication: 03.08.2005 DOI: 10.1055/s-2005-872259; Art ID: U10605ST © Georg Thieme Verlag Stuttgart · New York series of alcohols to the corresponding aldehydes or ketones. However, as in previous studies, the oxidation of long chain alkyl alcohols proved to be more difficult than that of electronically active alcohols such as benzyl alcohol derivatives. In this regard, we suspected that the polymer matrix suppressed the diffusion of long chain alkyl alcohols into the reactive sites (IBX reagents), or that the hydroxy group of the alcohols was not so reactive to the electrophilic iodine center of the IBX reagents. Despite these plausible postulations, to the best of our knowledge, there have been no previous reports on attempts to enhance the reactivity of supported IBX reagents.

Herein, we report on the significant role of spacers in increasing the reactivity of IBX-amide resins in the oxidation of 1-decanol as a model substrate. In addition, we investigated whether additives such as trifluoroacetic acid (TFA),<sup>7</sup> BF<sub>3</sub>·OEt<sub>2</sub><sup>7,8</sup> and tetraethylammonium bromide (TEAB)<sup>9</sup> could promote the oxidation of the alcohol, since these agents were previously reported to activate conventional hypervalent iodine reagents by polarizing the I=O bond and facilitating the nucleophilic attack of the substrate to the polarized iodine center.

Firstly, we prepared four types of IBX-amide resin with spacers of different lengths between the polymer matrix and the IBX-amide group (Figure 1).  $\beta$ -Alanine ( $\beta$ -Ala),  $\epsilon$ -aminohexanoic acid ( $\epsilon$ -ACA) or  $\omega$ -aminoundecanoic acid ( $\omega$ -AUA) were separately employed as a spacer that contains amino-group via Fmoc chemistry.



mmol/g). The loading levels of the prepared IBX-amide resins were in the range of 0.54–0.60 mmol/g, so that the amount of resin needed for the oxidation became similar in each

resin needed for the oxidation became similar in each case. The swelling volume of each resin was in the range of 3.4-4.2 mL/g in CHCl<sub>3</sub>. We found that the swelling volume slightly decreased as the spacer was introduced (IBX-amide resins **2–4**).<sup>10</sup>

Prior to the thorough experiment, we performed oxidation of 1-decanol using IBX-amide resin **1** in the presence of amide compound in the solution to investigate any feasible role of additional amide bond in the spacer in indirect manner.<sup>11</sup> We found there were no significant differences between the results of oxidation with and without additional amide compound. Moreover, the amide compound was not affected by the oxidation using IBX-amide resins. With these results, we considered that additional amide bond in the spacer would not play a significant role in alcohol oxidation.

In order to investigate the effect of the spacers, the time courses of the 1-decanol oxidation reactions using each IBX-amide resin with spacers of different lengths were evaluated under the same conditions (oxidant:alcohol = 1:1; Figure 2). The comparison experiment with the IBX-amide resins with different spacers **2–4**, showed that the introduction of the spacer increased the conversion rate compared to that of the IBX-amide resin without a spacer, **1**. In particular, while a moderate rate enhancement was observed for the IBX-amide resins with a short spacer ( $\beta$ -Ala, **2**) and longer spacer ( $\omega$ -AUA, **4**) in the case of the IBX-amide resin with the  $\varepsilon$ -ACA spacer (**3**) the conversion was significantly increased from 17% to 63% when the oxidation reaction was performed for 12 hours.



**Figure 2** Time courses for the oxidation of 1-decanol to 1-decanal using IBX-amide resin with spacers of different lengths, 1-4 (1 equiv) in CHCl<sub>3</sub> (1 mL/100 mg of resin) at 25 °C. The conversions were determined by GC-MS: ( $\blacklozenge$ ) 1, ( $\blacktriangle$ ) 2, ( $\blacksquare$ ) 3, (X) 4.

Thus, we confirmed that the observed spacer effects were consistent with the hypothesis that the accessibility of the IBX-amide toward 1-decanol is an important factor in increasing the reaction rate.

However, despite the significant increase in the initial conversion rate (<6 h), which was dependent on the length of the spacer, it seemed that the reactive sites located at

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the inner part of the polymer-supports still have less chance to react with the substrate in solution, considering that the conversion did not exceed 42–71%, even two days after the initial burst reaction.

In an additional attempt to improve the reactivity of the IBX-amide resins, we investigated the effect that an additive such as TFA,  $BF_3 \cdot OEt_2$  and TEAB would have on 1-decanol oxidation under the same reaction conditions as those described above (Figure 3).



**Figure 3** Time courses for the oxidation of 1-decanol to 1-decanal with IBX-amide resin 1 (1 equiv) and additive (1 equiv) in  $CHCl_3$  (1 mL/100 mg of resin) at 25 °C. The conversions were determined by GC-MS: ( $\blacklozenge$ ) without additive ( $\blacktriangle$ ) TFA, ( $\blacksquare$ ) BF<sub>3</sub>-OEt<sub>2</sub>, (O) TEAB.

The results of the 1-decanol oxidation reactions proved that the addition of a Brønsted and Lewis acid such as TFA and  $BF_3$ ·OEt<sub>2</sub> significantly increased the conversion rate. In particular, we were surprised to find that when  $BF_3$ ·OEt<sub>2</sub> was added, IBX-amide resin converted 1-decanol to 1-decanal quantitatively within one hour at 25 °C. To our knowledge, this is the first report of a significant enhancement of the oxidation rate being obtained when supported IBX reagents were used with an additive.

The bromide ion has previously been used as an effective catalyst in the oxidation of alcohols with PhI=O,<sup>12</sup> and sulfides with IBX.<sup>9</sup> However, in contrast to the remarkable rate enhancement effected by TFA and BF<sub>3</sub>·OEt<sub>2</sub>, no such result was observed when TEAB was used as an additive. On the contrary, the addition of TEAB strongly retarded the oxidation of 1-dencaol. Instead we found that the IBX-amide resin facilitated the oxidation of the bromide ion, leading to the formation of the tribromide ion ( $\lambda_{max} = 266 \text{ nm}$ ).<sup>13,14</sup>

Inspired by the positive effect of  $BF_3 \cdot OEt_2$  on alcohol oxidation with IBX-amide resins, we thoroughly investigated the effects of the addition of  $BF_3 \cdot OEt_2$  on other alcohol oxidations. As shown in Table 1, all of the tested alkyl and benzylic alcohols were cleanly converted to the

corresponding aldehydes or ketones within 5–30 minutes at room temperature.

In particular, we found that the conversion was completed within five minutes when benzyl alcohol was subjected to the oxidation reaction (Table 1, entry 4). In contrast, without additive the conversion of benzyl alcohol was completed after 90 minutes under the same condition (data not shown), thereby we confirmed that  $BF_3 \cdot OEt_2$  also significantly increased the conversion rate of benzylic alcohol.

In addition, the IBX-amide resin **1** consumed in oxidation with  $BF_3 \cdot OEt_2$  was collected and reactivated using the previously reported procedure<sup>6</sup> affording the resins with a restored oxidation activity.<sup>15</sup>

In conclusion, we presented two methods of improving the oxidation of long chain alkyl alcohols by IBX-amide resins, which was known to be difficult to accomplish using conventional polymer-supported IBX reagents. Firstly, we found that extending the chain length of the spacer between the polymer-support and IBX-amide group improved the initial conversion rate. Secondly, the combination of an IBX-amide resin and an additive such as  $BF_3 \cdot OEt_2$  and TFA resulted in a further rate enhancement. Furthermore, we expect that the two methods presented herein will extend the range of application of supported IBX reagents.

## Preparation of IBX-Amide Resin with Spacers of Different Lengths

Amino PS resin (BTCore EM NH<sub>2</sub> 100–200 mesh, 1.5 mmol/g, from BeadTech, Inc.) was pre-swollen with *N*-methylpyrrolidone (NMP) at r.t. for 30 min. Various Fmoc-protected spacers (2 equiv), viz. *N*-Fmoc- $\beta$ -alanine, *N*-Fmoc- $\epsilon$ -ACA or *N*-Fmoc-undecanoic acid, BOP (2 equiv), HOBt (2 equiv), and DIEA (2.5 equiv) were added to the resin suspension in NMP (10 mL per 1 g of resin). The resultant mixture was shaken at r.t. for 2 h (2×). The resins were filtered, washed with NMP, MeOH, and CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL each) and treated with 20%(v/v) piperidine/NMP (30 min) to afford the amino-alkylated resins. To the spacer containing resins or initial resins suspension in NMP, 2-iodobenzoic acid (2 equiv), BOP (2 equiv), HOBt (2 equiv), and DIEA (2.5 equiv) were added and the suspension mixture was shaken at r.t. for 2 h (2×). The resins were filtered, washed with NMP, MeOH, and CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL each) and dried

0

 Table 1
 Oxidation of Alcohols Using IBX-Amide Resin 1–4 with BF<sub>3</sub>·OEt<sub>2</sub> in CHCl<sub>3</sub><sup>a</sup>

OH

|       | R                       | R' CHC     | l <sub>3</sub> , r.t. R R' |                         |
|-------|-------------------------|------------|----------------------------|-------------------------|
| Entry | IBX-amide resin (equiv) | Time (min) | Product                    | Purity (%) <sup>b</sup> |
| 1     | <b>1</b> (1.1)          | 30         |                            | >97                     |
| 2     | 1 (1.5)                 | 30         |                            | 99                      |
| 3     | <b>1</b> (1.1)          | 30         | 0                          | 94                      |
| 4     | 1 (2.0)                 | 5          | 0                          | 99                      |
| 5     | 1 (1.1)                 | 10         | NO                         | >95 (91)°               |
| 6     | <b>2</b> (1.5)          | 20         |                            | 98                      |
| 7     | <b>3</b> (1.1)          | 10         | CI                         | 99                      |
| 8     | <b>4</b> (1.5)          | 20         | 0                          | 99                      |

IDV amida reain DE OEt

<sup>a</sup> Reactions run at r.t. using an equimolar mixture of IBX-amide resin and BF<sub>3</sub>·OEt<sub>2</sub> in CHCl<sub>3</sub>.

<sup>b</sup> Determined by GC-MS.

<sup>c</sup> Yield of isolated product.

overnight under vacuum at 30 °C. The completion of each coupling step was confirmed by the ninhydrin color reaction.<sup>16</sup> The resins were activated by reacting them with an equimolar mixture of tetrabutylammonium oxone (5 equiv) and methylsulfonic acid in CHCl<sub>3</sub> at r.t., for 18–20 h. The activated resins were washed several times with CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, and dried overnight under vacuum at 30 °C. The loading levels of the resulting resins were determined by benzyl alcohol oxidation.<sup>6</sup>

#### Time Courses of 1-Decanol Oxidation

1-Decanol (1 equiv) and each IBX amide resin (1 equiv) were mixed in  $CHCl_3$  (1 mL/100 mg of resin) and shaken at 25 °C for a designated time. When investigating their effect, the additives (1 equiv) were also added to the reaction mixture. The reaction was terminated by filtration and the filtered resin was washed (5 × 1 mL) with  $CH_2Cl_2$ . The final conversion was determined from the combined reaction and wash solution by GC-MS.

### Long Alkyl Alcohol Oxidation Using IBX-Amide Resin and $BF_3{\cdot}OEt_2$

The alcohol (1 equiv), IBX-amide resin **1** (1.1 equiv), and BF<sub>3</sub>·OEt<sub>2</sub> (1.1 equiv) were mixed in CHCl<sub>3</sub> (3 mL/300 mg of resin) and shaken at 25 °C for a designated time. Thereafter, the reaction was terminated by filtration and the filtered resin was washed (5 × 2 mL) with CH<sub>2</sub>Cl<sub>2</sub>. The reaction and wash solution were combined, passed through the short silica column, and analyzed by GC-MS.

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### References

- (a) McNamara, C. A.; Dixon, M. J.; Bradley, M. Chem. Rev. 2002, 102, 3275. (b) Hodge, P. Curr. Opin. Chem. Biol. 2003, 7, 362.
- (2) (a) Bhattacharyya, S. Comb. Chem. High Throughput Screening 2000, 3, 65. (b) Patchornik, A. H. Polym. Adv. Technol. 2002, 13, 1078. (c) Nam, N.-H.; Sardari, S.; Parang, K. J. Comb. Chem. 2003, 5, 479.
- (3) (a) Hudlicky, M. Oxidation in Organic Chemistry; American Chemical Society: Washington, DC, 1990, 114– 163. (b) Lou, J. D.; Lou, W. X. Synth. Commun. 1997, 27, 3697. (c) Mirafzal, G. A.; Lozera, M. Tetrahedron Lett. 1998, 39, 7263.

- (4) (a) Fréchet, J. M. J.; Darling, P.; Farrall, M. J. J. Org. Chem. 1981, 46, 1728. (b) Mohanazadeh, F.; Ghamsari, S. React. Funct. Polym. 1996, 29, 193. (c) Hinzen, B.; Ley, S. V. J. Chem. Soc., Perkin Trans. 1 1997, 1907. (d) Kessat, A.; Babadjamian, A.; Iraqi, A. Eur. Polym. J. 2001, 37, 131. (e) Tamami, B.; Karimi Zarchi, M. A. Eur. Polym. J. 1995, 31, 715.
- (5) (a) Mülbaier, M.; Giannis, A. Angew. Chem. Int. Ed. 2001, 40, 4393. (b) Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. Angew. Chem. Int. Ed. 2001, 40, 4395. (c) Reed, N. N.; Delgado, M.; Hereford, K.; Clapham, B.; Janda, K. D. Bioorg. Med. Chem. Lett. 2002, 12, 2047. (d) Lei, Z.; Denecker, C.; Jegasothy, S.; Sherrington, D. C.; Slater, N. K. H.; Sutherland, A. J. Tetrahedron Lett. 2003, 44, 1635.
- (6) Chung, W.-J.; Kim, D.-K.; Lee, Y.-S. Tetrahedron Lett. 2003, 44, 9251.
- (7) Zhdankin, V. V.; Litvinov, D. N.; Koposov, A. Y.; Luu, T.; Ferguson, M. J.; McDonald, R.; Tykwinski, R. R. *Chem. Commun.* 2004, 106.
- (8) (a) Moriarty, R. M.; Vaid, R. K.; Ravikumar, V. T.; Vaid, B. K.; Hopkins, T. E. *Tetrahedron Lett.* **1988**, *44*, 1603.
  (b) Ochiai, M.; Miyamoto, K.; Shiro, M.; Ozawa, T.; Yamaguchi, K. J. Am. Chem. Soc. **2003**, *125*, 13006.
- (9) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. J. Org. Chem. 2003, 68, 5422.
- (10) Swelling volume was determined using a column (ID 0.9 cm, length 40 cm) with sintered glass filter. Each resin (500 mg) was swollen in CHCl<sub>3</sub> for 2 h. Thereafter, the solvent was removed by filtration, and the swelling volume of each resin was determined as: resin 1 (4.2 mL/g); resin 2 (3.9 mL/g); resin 3 (3.4 mL/g); resin 4 (3.8 mL/g).
- (11) Oxidation of 1-decanol (1 equiv) was performed using IBXamide resin 1 (1.3 equiv) with *N*-methyl hexanamide (1.3 equiv) in CHCl<sub>3</sub> at r.t. The reaction mixture was analyzed by GC-MS after 3 h and 6 h. The conversion of 1-decanol was compared with that from the oxidation of 1-decanol without *N*-methyl hexanamide (NMH) under the same condition; 37% (with NMH) and 34% (without NMH) after 3 h, 43% (with NMH) and 44% (without NMH) after 6 h. No reaction between NMH and IBX-amide resin 1 was detected.
- (12) (a) Tohma, H.; Takizawa, S.; Watanabe, H.; Kita, Y. *Tetrahedron Lett.* **1998**, *39*, 4547. (b) Tohma, H.; Maegawa, T.; Takizawa, S.; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328.
- (13) Soulard, M.; Block, F.; Hatterer, A. J. Chem. Soc., Dalton. Trans. 1981, 2300.
- (14) Kim, D.-K.; Chung, W.-J.; Lee, Y.-S. Synlett 2005, 279.
- (15) Three cycles of oxidations with the condition employed in entry 1 (in Table 1) and reactivations were investigated. The oxidation capacity was maintained in the range of 0.55–0.59 mmol/g. The conversions of 1-decanol were determined as >97 (run 1), >97 (run 2), and 95% (run 3).
- (16) Kaiser, E.; Colescott, R. L. C.; Bossinger, D.; Cook, P. I. Anal. Biochem. 1970, 34, 595.