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Practical Synthesis of Ethyl 1-(*tert*-Butoxycarbonyl)-4-(1-pyrrolidinyl)-4-piperidineacetate, an Intermediate of a Novel Antiarteriosclerotic, Utilizing Aza-Michael Addition Promoted by LiBr

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The aza-Michael addition of pyrrolidine to β,β-dialkylated unsaturated ester **6** utilizing LiBr proceeded smoothly to give the inaccessible ethyl 1-(*tert*-butoxycarbonyl)-4-(1-pyrrolidinyl)-4-piperidineacetate (**7**), which is an intermediate of novel antiarteriosclerotic **1**.

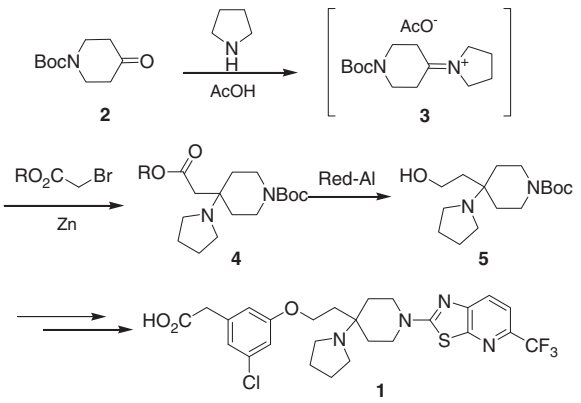
Novel antiarteriosclerotic **1** was discovered by IMMD Inc. and Shionogi & Co., Ltd.[1] Recently, our group developed a pilot plant preparation method for *tert*-butyl 4-(2-hydroxyethyl)-4-(1-pyrrolidinyl)-1-piperidinecarboxylate (**5**), which is an intermediate of **1**, via unstable iminium salt **3** by a Reformatsky-type reaction (Scheme 1).[2] However, scale-up of the Reformatsky reaction lacks reproducibility because agglomeration of the zinc powder is likely to occur. In fact, our first trial pilot production was unsuccessful (500 L scale).

Here we report a new practical synthetic route to key intermediate ester **7** via the aza-Michael addition of pyrrolidine to α,β-unsaturated ester **6** (Scheme 2). The practical preparation of ester **6** from ketone **2** using the Horner–Wadsworth–Emmons reaction was reported by the Merck group.[3]

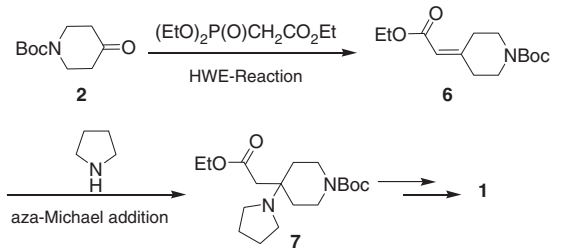
The aza-Michael addition, that is, addition of nitrogen nucleophilies to α,β-unsaturated carbonyl compounds, is recognized as a simple and useful method for preparing β-aminocarbonyl derivatives.[4] Much effort has been invested in the development of efficient methods; e.g., using lanthanoid triflate,[5] $InCl_3$,[6] $FeCl_3$,[7] KF/Al_2O_3,[8] $CeCl_3/NaI$,[9] silica gel,[10] lipase,[11] clay,[12] ultrasound,[13] and microwave.[14] Recently, environmentally benign protocols using water solvent were reported.[15] These methods, however, are limited to reactions of β-non or monoalkylated unsaturated ester substrates and cannot be applied to β,β-dialkylated unsaturated esters as a Michael acceptor because this reaction is susceptible to steric factors.[16] As far as we know, the use of high pressure is the only effective way to achieve the aza-Michael addition of this type.[5a,17] However, the need remains for a method offering improved efficiency for pilot plant preparation from the recently recognized standpoint of process chemistry.

In this study, we investigated the aza-Michael addition between β,β-dialkylated unsaturated ester **6** and pyrrolidine using various additives ($PdCl_2$, $Pd(OAc)_2$, TMSOTf, $MnSO_4$, Bu_4NI, $Sc(OTf)_3$, $Yb(OTf)_3$, $ZrCl_4$, $Al(O\textit{i}\text{-}Pr)_3$, CuI, $Bi(OTf)_3$, $BF_3\text{-}Et_2O$, $MgBr_2$, $FeCl_3$, $CeCl_3$, $LiClO_4$, $B(OH)_3$, $NiCl_2$, AgOTf, ZnCl, $TiCl_4$, $Ti(O\textit{i}\text{-}Pr)_4$, $AlCl_3$, $Cu(OTf)_2$, $HClO_4$, $Mg(ClO_4)_2$, CsF, SmI_2, $Sn(OTf)_2$, $SnCl_4$, $In(OTf)_3$, $Eu(hfc)_3$, $GaCl_3$, $FeCl_2$, $CoCl_2$, MS4A, SiO_2, and H_2O) (Scheme 3). Among the 38 additives screened, $LiClO_4$ promoted the desired addition, although the yield was low (31%). The main by-products in this reaction were ester **8** (migration of the double bond of starting material **6**) and amide **9** (1,2-adduct from **8**). The 1,2-adduct of **6** was not observed. Based on this result, we attempted optimization of the reaction conditions. The use of 1.0 equiv of $LiClO_4$ at 20–25 °C gave the desired ester **7** in good yield (82%). Although the $LiClO_4$-promoted aza-Michael addition was reported by Saidi and co-wokers, the use of β,β-dialkylated unsaturated ester as a Michael acceptor has not been described.[18]

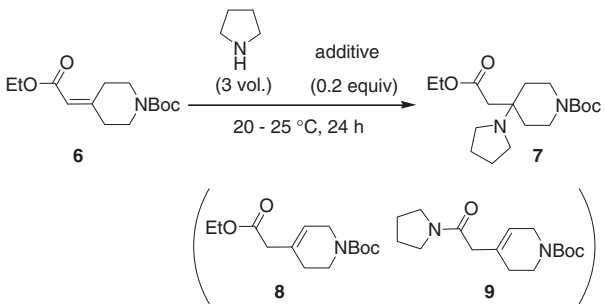
From the viewpoint of process chemistry, a safer and more inexpensive reagent than $LiClO_4$ is needed. We focused on the ability of the Li salt to promote the reaction. Table 1 lists the



Scheme 1.



Scheme 2.

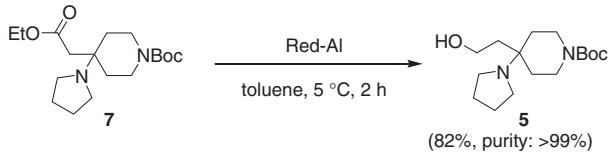


Scheme 3.

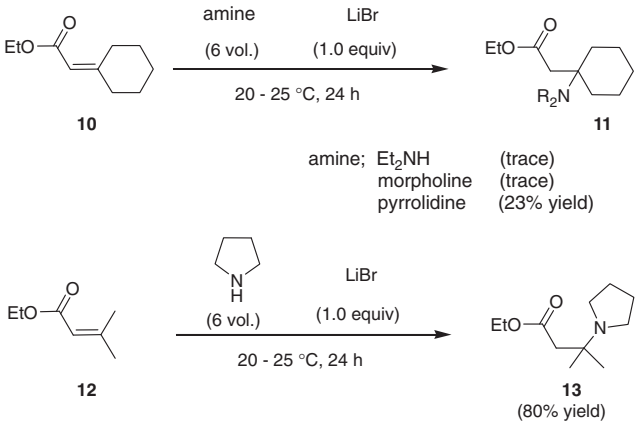
Table 1. Screening of Li salts

Entry	Li salt[a]	Yield/%[b]	Ratio **7**/**8**/**9**[b]
1	$LiClO_4$	82	84/2/14
2	LiCl[c]	76	76/1/23
3	LiBr	81	82/1/17
4	LiI[c]	76	78/4/18
5	LiOTf	73	76/3/21
6	LiOAc	16	27/69/4
7	Li_2CO_3	15	26/70/4
8	Li_2SO_4	14	25/72/3
9	LiPF6	trace	—
10	$LiBr \cdot H_2O$	71	72/3/25
11	LiBr (54% aq.)	51	53/4/43

[a]1.0 equiv was used. [b]Determined by HPLC analysis. [c]Reaction time was 30 h.



Scheme 4.



Scheme 5.

results of the screening of Li salts. We found that LiBr was as effective as $LiClO_4$ (Entry 3). The selectivity and reaction velocity of LiCl and LiI were somewhat inferior to LiBr (Entries 2 and 4). The use of LiBr has some merits, i.e., it is, safe, easy to handle, inexpensive, and easily available.

These results prompted us to synthesize the amino alcohol **5**, which is an intermediate of **1**. The amino ester **7** was prepared using the present aza-Michael addition as crude product (78%, **7**:**8**:**9** = 98:0:2).[19] By-product isomer **8** and amide **9** could mostly be removed by extraction. The obtained ester **7** was subjected to the subsequent Red-Al reduction (Scheme 4). The reduction proceeded successfully with 95% conversion. After crystallization, the desired amino alcohol **5** was obtained in 82% yield without purification via silica gel column chromatography (purity, >99% by HPLC analysis).[20]

Finally, we investigated the substrate generality of the present aza-Michael addition (Scheme 5). Unexpectedly, the aza-Michael addition between cycloalkylidenic ester **10** and amine had a poor yield due to the generation of by-products (double bond isomer and 1,2-adduct). Although the low yield of β-amino ester is not well understood yet, optimization of the reaction conditions needs to be attempted. In contrast to cases in which β,β-dimethyl acrylate **12** was used, the desired β-amino ester **13** was obtained in good yield (80%).

In conclusion, we developed a safe, practical, and robust synthesis of less accessible ethyl 1-(*tert*-butoxycarbonyl)-4-(1-pyrrolidinyl)-4-piperidineacetate (**7**), which is an intermediate of novel antiarteriosclerotic **1**, utilizing the aza-Michael addition promoted by LiBr.

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19 Unsaturated ester **6** (2.69 g, 10.0 mmol) was added to a stirred solution of LiBr (868 mg, 10.0 mmol) in pyrrolidine (8.1 mL) at 20–25 °C, followed by being stirred at the same temperature for 24 h. After removing pyrrolidine from the reaction mixture of amino ester **7** by evaporation, toluene (35.0 mL) and aqueous 10% citric acid (40.0 mL) were added to the residue at 0–5 °C. The pH of the aqueous layer was adjusted to 10 with aqueous 20% NaOH, which was extracted with toluene (30.0 mL). The organic layer was washed with aqueous 1% NaOH (14.0 mL) and water (14.0 mL). The desired amino ester **7** was obtained as a crude product (2.67 g, 78%).
20 Red-Al 70% in toluene (3.11 g, 10.8 mmol) was added to a stirred solution of ester **7** (2.67 g) in toluene (10.0 mL) at 0–5 °C, followed by being stirred at the same temperature for 3 h. Acetone (0.7 mL) was added to the reaction mixture, which was then poured into aqueous 10% citric acid (35.0 mL). The pH of the aqueous layer was adjusted to 10 with aqueous 48% NaOH, which was extracted with ethyl acetate (15.0 mL). The organic layer was washed with water (10.0 mL) and evaporated. After MeOH (8.0 mL) was added to the residue, water (15.0 mL) was added slowly to the solution at 20–25 °C, and precipitation of the amino alcohol **5** was observed. This slurry was cooled to 5 °C and aged for 1 h. The crystals were obtained by filtration, washed with water and dried. By this procedure, the desired amino alcohol **5** was obtained (1.91 g, 82%).

