A Traceless Solid-phase Synthesis of 1,4-Diazabicyclo[3,3,1]octan-3-ones

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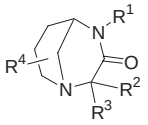
A novel synthesis of 1,4-diazabicyclo[3,3,1]octan-3-one derivatives using a traceless-solid-phase approach is described, in which many kinds of 1,4-diazabicyclo[3,3,1]octan-3-one derivatives have been efficiently obtained in high purity, based on an intramolecular alkylation of tertiary amines followed by an elimination of desired tertiary amines from the generated quarternary ammonium salts.

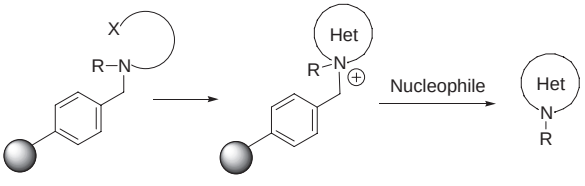
1,4-Diazabicyclo[3,3,1]octan-3-one (**1**) skeleton is very attractive as a template of a chemical library for drug discovery because the structure is unique and can be easily functionalized to provide a diverse library. Recently, compounds having this skeleton have been reported to show antagonism on the substance P receptor.[1] Compounds **1** have been synthesized using conventional-solution-phase methods,[1,2] although these methods are not inappropriate for multi-step syntheses of libraries owing to purification in each step. On the other hand, efficient traceless syntheses of tertiary amines on polymer support suitable for library syntheses have been reported.[3] However, no library synthesis of bicyclic tertiary amines having the 1,4-diazabicyclo[3,3,1]octan-3-one skeleton has been reported. In relation to our research to find new drugs from the chemical library, we now report an efficient-traceless-solid-phase synthesis of 1,4-diazabicyclo[3,3,1]nonane derivatives via an elimination of cyclic tertiary amines from quarternary ammonium salts on polymer support.



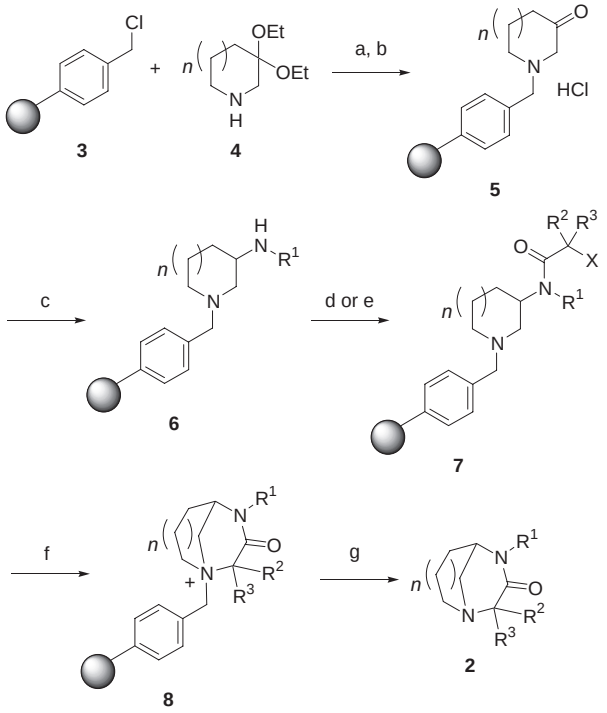
1

In many cases of multi-step solid-phase syntheses, products obtained by the cleavage of the resin in the final step are often mixtures of desired compounds, with many kinds of impurities generated by incomplete reactions on the polymer support in the previous steps. In our strategy depicted in Scheme 1, we expected that only desired heterocycles were detached from the polymer support by debenzylation of cyclic quarternary ammonium salts via S_N2 reaction[4] and the byproducts generated from incomplete and/or undesired reactions remained on the polymer support.

The synthesis began with the amination of the Merrifield resin in **3** with the cyclic amines **4** (Scheme 2). Next, the polymer-supported products were converted to the corresponding ketones **5**, which provided the diamine **6** by reductive amination. Then, **6** were transformed into the key intermediates **7** by acylation with α-halo-acetic acids. The intramolecular cyclization, quaternization of the tertiary nitrogen of the piperidine ring was carried out in the presence of n-Bu_4NI in DMF at 120 °C. The products **8** were treated with sulfanylethanol under reported conditions to provide the desired compounds **2** in high purity without time-consuming purification steps like column chromatography.[5]



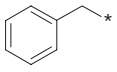
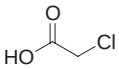
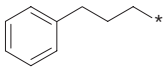
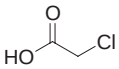
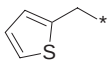
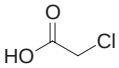
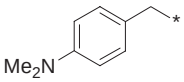
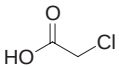
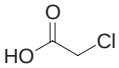
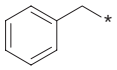
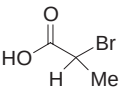
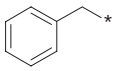
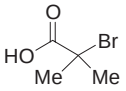
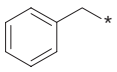
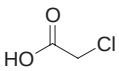
Scheme 1.



Scheme 2. (a) **4** (2 equiv.), Et_3N (3 equiv.), n-Bu_4I (0.2 equiv.), DMF, 60 °C, 24 h; (b) 6 M HCl aq, dioxane, rt, 2.5 h; (c) $NaBH(OAc)_3$ (5 equiv.), R^1NH_2 (4 equiv.), CH_2Cl_2, rt, 48 h; (d) DIC (12 equiv.), $XCR^2R^3CO_2H$ (12 equiv.), DMF, rt, 20 h; (e) PyBrop (12 equiv.), $XCR^2R^3CO_2H$ (12 equiv.), i-Pr_2NEt (24 equiv.), rt, 20 h; (f) n-Bu_4NI (3 equiv.), DMF, 120 °C, 5.5 h; (g) $HOCH_2CH_2SH$ (3.6 equiv.), 2 M NaOH aq (3 equiv.), EtOH, 70 °C, 3 h.

To demonstrate the usefulness of this approach, several 1,4-diazabicyclo[3,3,1]octan-3-one derivatives were synthesized and characterized by ^1H NMR and MS.[6] The representative results are shown in Table 1. Alkyl and aryl groups can be introduced in R^1 with high purities (>95%) and moderate or low total yields (5–51%) (Entries 1, 2, 3, and 5), while a compound with basic nitrogen could be obtained (Entry 4). Effect of bulkiness of

Table 1. Syntheses of 1,4-diazabicyclo[3,3,1]octan-3-one derivatives **2**

Entry	**2**	*n*	R^1	R^2	R^3	Amide formation	Yield/%[a] (purity/%[b])
1	**2a**	1		H	H	d, 	51 (99.3)
2	**2b**	1		H	H	d, 	46 (97.7)
3	**2c**	1		H	H	d, 	47 (99.7)
4	**2d**	1		H	H	d, 	26 (92.3)
5	**2e**	1		H	H	e, 	5 (97.0)
6	**2f**	1		H	Me	e, 	41 (97.0)
7	**2g**	1		Me	Me	e, 	0
8	**2h**	0		H	H	d, 	6 (95.2)

[a]Isolated overall yields (6 steps) based on the Merrifield resin **3**. [b]Reverse-phase HPLC was carried out using CH_3CN/20 mM phosphate buffer (pH 6.5). Flow rate: 1 mL/min. Column: ODS. HPLC purities were determined by summation of integrated HPLC peak areas at 210 nm.

the substituents on α-position (R^2 and R^3) of the carbonyl group on the yield was clearly observed (Entries 6 and 7), where monosubstitution is only successful, although disubstituted halide did not give the product. Construction of 1,4-diazabicyclo[3,2,1]octan-3-one skeleton (Entry 8) was also possible and this result would expand the diversity of the libraries based on this synthetic route.

In conclusion, a novel traceless solid-phase syntheses of 1,4-diazabicyclo[3,3,1]octan-3-one derivatives based on the Merrifield resin has been developed. Using this approach, we are currently constructing novel and diverse chemical libraries for high throughput screening. The information of biological activities will be reported in due course.

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4 Simple synthetic examples of tertiary amines based on debenzylation of resin-bound quarternary ammonium salts were reported on Ref. 3d.

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6 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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