A Traceless Solid-phase Synthesis of 1,4-Diazepan-2-ones

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A novel synthesis of 1,4-diazepan-2-ones using a traceless solid-phase approach is described, in which many kinds of 1,4-diazepan-2-one have been efficiently obtained in high purity. The strategy is based on intramolecular alkylation of tertiary amines, followed by elimination of the desired tertiary amines from the generated quarternary ammonium salts.

Compounds having a 1,4-diazepan-2-one (**1**) skeleton have been known to show intriguing biological activities, e.g., antagonism on muscarinic receptors, inhibition of platelet aggregation, antibacterial activity, inhibition of HIV protease, etc.[1] Therefore, this skeleton is very attractive as a template of chemical libraries to generate new bioactive compounds in high-throughput screenings. Compounds **1** (Chart 1) have been synthesized using conventional solution-phase methods,[2] although these methods are not applicable or are inappropriate for multistep syntheses of libraries, owing to the purification required in each step. On the other hand, efficient traceless syntheses of tertiary amines on polymer supports suitable for library syntheses have been reported.[3] However, no library synthesis of tertiary amines having the 1,4-diazepan-2-one skeleton has been reported. In relation to our research to find new drug candidates from chemical libraries, we now report an efficient traceless solid-phase synthesis of 1,4-diazepan-2-one derivatives via elimination of tertiary amines from quarternary ammonium salts on a polymer support.

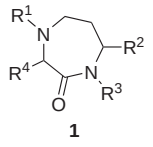

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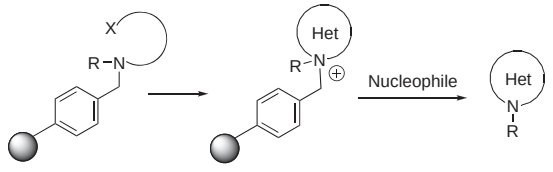
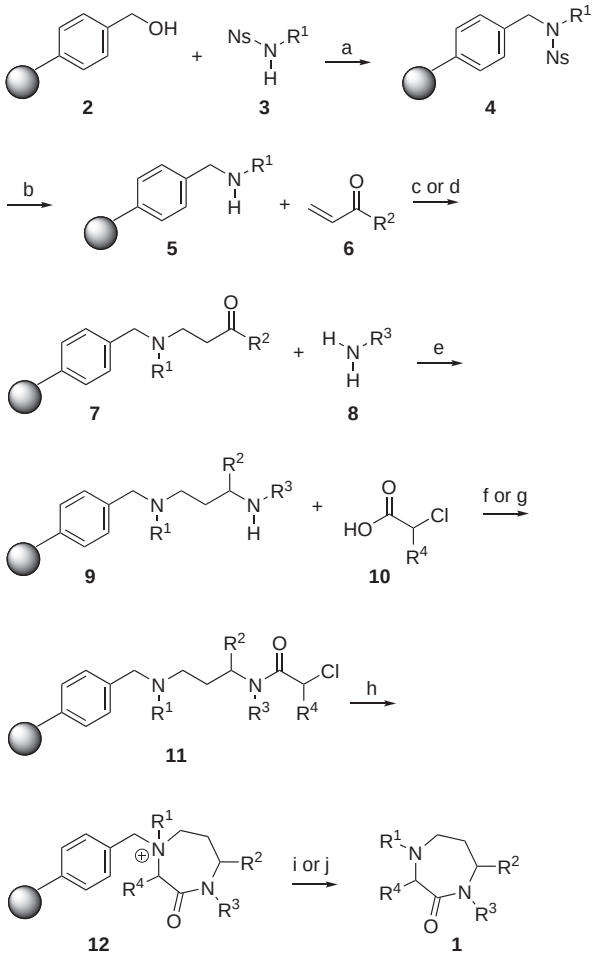
Chart 1.

In many cases of multi-step solid-phase syntheses, products obtained by cleavage of the resin in the final step are often mixtures of the desired compounds, along with many impurities generated by incomplete reactions on the polymer support in the previous steps. In our strategy depicted in Scheme 1, we expected that the debenzylation of quarternary ammonium salts by an S_N2 reaction could afford products in high purity without time-consuming purification steps such as column chromatography. By-products generated from incomplete and/or undesired reactions would remain on the solid support.[4,5] For instance, while the last debenzylation step might be accompanied by an S_N2 reaction at the α-position of the carbonyl group, the by-products generated from such an undesirable reaction would remain bound to the solid support and not reduce the purity of the products. In addition, all of the assumed unreacted intermediates would not be detached from the solid support at the end of the reaction scheme.



Scheme 1.

The synthesis began with the Mitsunobu reaction on 4-hydroxymethyl polystyrene **2** with N-monosubstituted 2-nitrobenzenesulfonamides **3** (Scheme 2).[6,7] Next, *N*,*N*-disubstituted



Scheme 2. (a) **3**, PPh_3, DEAD, THF, rt, 16 h; (b) $HOCH_2CH_2SH$, DBU, DMF, rt, 1 h; (c) **6**, $ClCH_2CH_2Cl$, 40 °C, 72 h; (d) **6**, $ClCH_2CH_2Cl$, 80 °C, 96 h; (e) $NaBH(OAc)_3$, **8**, CH_2Cl_2, rt, 48 h; (f) DIC, **10**, DMF, rt, 20 h; (g) PyBrop, **10**, *i*-Pr_2NEt, rt, 20 h; (h) CsI, dioxane, water, 95 °C, 3 h; (i) $HOCH_2CH_2SH$, 2 M NaOH aq, EtOH, 70 °C, 3 h; (j) $HSCH_2CO_2H$, 2 M NaOH aq, EtOH, 70 °C, 3 h.

Table 1. Syntheses of 1,4-diazepan-2-one derivatives **1**

Entry	**1**	R^1	R^2	R^3	R^4	**5 → 7**	**9 → 11**	**12 → 1**	Yield[a]/% (purity[b]/%)	dr[c]
1	**1a**	(4-Br)$PhCH_2CH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	44 (97)	—
2	**1b**	(4-Br)$PhCH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	45 (98)	—
3	**1c**	$PhCH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	33 (97)	—
4	**1d**	(4-MeO)$PhCH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	18 (95)	—
5	**1e**	Ph	Et	(4-F)$PhCH_2CH_2$	H	d	f	i	25 (98)	—
6	**1f**	(4-Br)$PhCH_2CH_2$	Me	(4-F)$PhCH_2CH_2$	H	c	f	i	48 (91)	—
7	**1g**	(4-Br)$PhCH_2CH_2$	H	(4-F)$PhCH_2CH_2$	H	c	f	i	0	—
8	**1h**	(4-Br)$PhCH_2CH_2$	Et	(4-CF_3O)Ph	H	c	g	i	27 (97)	—
9	**1i**	(4-Br)$PhCH_2CH_2$	Et	(4-NMe_2)$PhCH_2$	H	c	f	i	51 (95)	—
10	**1j**	(4-Br)$PhCH_2CH_2$	Et	H	H	c	f	j[d]	16 (92)	—
11	**1k**	(4-Br)$PhCH_2CH_2$	Et	(4-F)$PhCH_2CH_2$	Me	c	f	i	32 (97)	99:1
12	**1l**	(4-Br)$PhCH_2CH_2$	Et	(4-F)$PhCH_2CH_2$	Ph	c	f	i	23 (93)	95:5

[a]Isolated overall yields (7 steps) based on **2**. [b]HPLC was carried out using a reverse phase column [ODS, eluent: CH_3CN/20 mM phosphate buffer (pH 6.5)]. Purity was determined by summation of integrated HPLC peak areas at 210 nm. [c]HPLC was carried out using a column with a chiral stationary phase (Chiralpak IA, eluent: hexane/*i*-PrOH) because a reverse phase column (ODS) could not achieve separation of diastereomers. Ratio of the diastereomers was determined by summation of integrated HPLC peak areas at 210 nm. [d]Condition j gave a slightly higher purity of 92% than condition i (purity of 89%).

2-nitrobenzenesulfonamides **4** provided the secondary amines **5** by deprotection of the 2-nitrobenzenesulfonyl (Ns) group. Next, by the Michael addition, **5** were transformed into β-amino ketones **7**, which were then converted to the corresponding diamines **9** by reductive amination. Diamines **9** were transformed into the key intermediates **11** by acylation with α-haloacetic acids **10**. Intramolecular cyclization and the quaternization of the resin-bound tertiary nitrogen were carried out in the presence of CsI in dioxane–H_2O at 95 °C. The products **12** were treated with thiols under conditions reported in the literature[8] to provide the desired compound **1** in high purity without column chromatography purification.

To demonstrate the usefulness of this approach, several 1,4-diazepan-2-one derivatives were synthesized and characterized.[9] Representative results of these syntheses are shown in Table 1. Alkyl and aryl groups could be introduced at R^1–R^4 with high purities and moderate total yields, while compounds with functional groups such as basic nitrogen could also be obtained (Entry 9). It is worth noting that introduction of the benzyl groups at R^1 (Entries 2–4) was also possible, but the yields were relatively low (Entries 3 and 4) under these conditions because nucleophilic attack during the last step might have occurred at R^1 instead of the resin-bound benzyl group.[10] Introduction of substituents at R^4 gave mixtures of diastereomers. Unexpectedly, the major/minor diastereomer ratio exceeded 90:10 because epimerization might have occurred under the final cleavage conditions which were basic at 70 °C. Lack of substituents at R^3 and R^4 (Entry 10) was allowed, but the compound without substituents at R^2 (Entry 7) could not be prepared owing to the probable instability of the intermediate.

In conclusion, a novel traceless solid-phase synthesis of 1,4-diazepan-2-one derivatives based on 4-hydroxymethyl polystyrene has been developed. Using this approach, we are currently constructing novel and diverse chemical libraries for high-throughput screenings. Biological activity of the synthesized compounds will be reported in due course.

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10 Although 2-hydroxyethyl benzyl sulphides might be detached from solid supports under this cleavage condition, such impurities can be excluded by simple solid-phase extraction based on cation exchange.

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