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A traceless solid phase synthesis of thiomorpholin-3-ones

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Abstract

A novel synthesis of thiomorpholin-3-ones using a traceless solid phase approach is described, in which many kinds of thiomorpholin-3-ones were efficiently obtained in high purity based on an intramolecular alkylation of sulfides followed by an elimination of desired thiomorpholin-3-ones from the generated sulfonium salts.

Keywords: Traceless; Solid phase synthesis; Thiomorpholine-3-one

Compounds having a thiomorpholin-3-one (Fig. 1) skeleton have been known to show intriguing biological activities, for example, enhancement of brain noradrenaline and dopamine turnover,[1] hypnotic activity,[2] antagonism on 5-HT1b receptor[3] and EP4 receptor.[4] Therefore, this skeleton is very attractive as a template for chemical libraries to generate newly-bioactive compounds on high-throughput screenings.

Compounds **1** have been synthesized using conventional solution phase methods[2,5–7] and solid phase methods,[8–10] although both methods are problematic for synthesizing chemical libraries. Solution phase methods are not applicable or inappropriate for the multi-step syntheses of the libraries due to purification required in each step. Solid phase methods can omit the purification of synthetic intermediates but generate the final products with resin-tethering substituents, which are polar and often compromise bioavailability and reduce structural diversity of the chemical libraries. In addition, 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 relation to our research to find new drugs from the chemical library, we now report an efficient traceless solid phase synthesis of thiomorpholin-3-ones. In our strategy depicted in Scheme 1, and to shorten time for the library construction, we expected that the debenzylation of sulfonium salts by the S_N2 reaction could give the products in high purity without purification because by-products generated from incomplete and/or undesired reactions remain on solid supports.[11] While the last debenzylation step might accompany the S_N2 reaction at the α-position of the carbony group or β-elimination of the acyclic sulfides, the by-products generated from such undesirable reactions remain bound to the solid supports and never reduce the purity of the products. In addition,

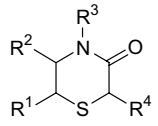
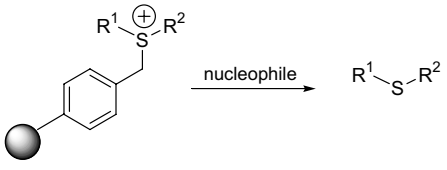


Fig. 1. Thiomorpholin-3-one.



Scheme 1.

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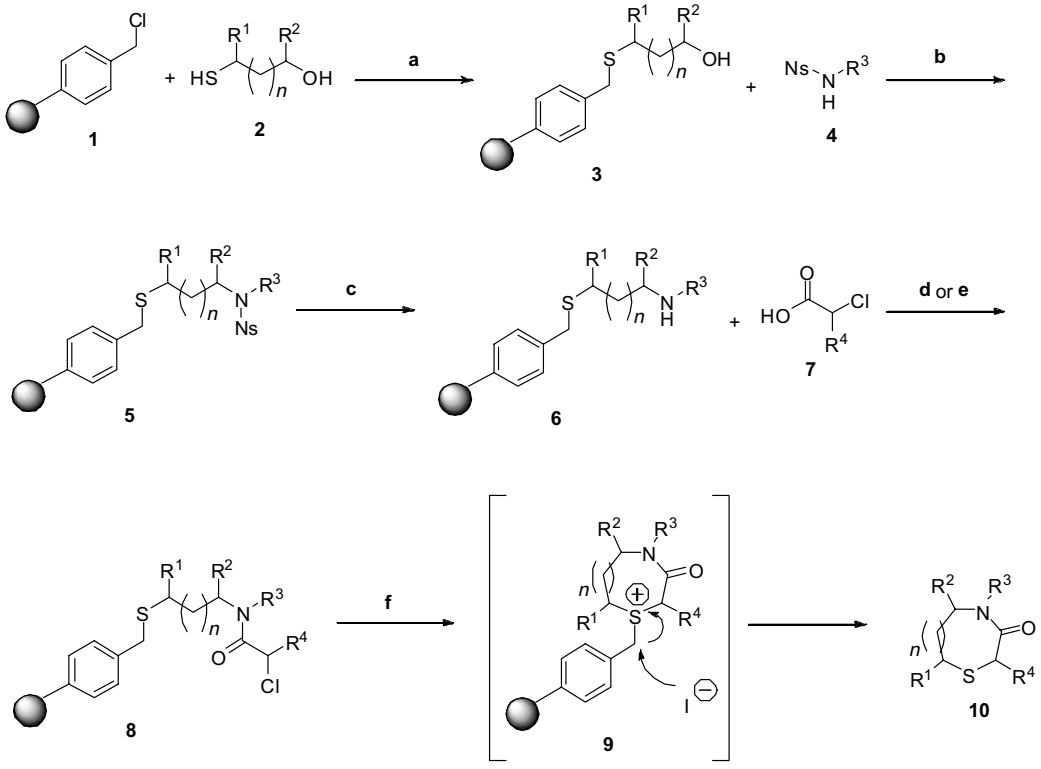
most of the assumed unreacted intermediates are not detached from solid supports at the end of the reaction scheme.[12]

The synthesis began with the nucleophilic displacement of benzyl chloride on Merrifield resin **1** with the sulfanylethanols **2** (Scheme 2). Next, under the Mitsunobu conditions with N-monosubstituted 2-nitrobenzenesulfonamides **4**,[13] the polymer-supported alcohols **3** were converted to the *N*,*N*-disubstituted 2-nitrobenzenesulfonamides **5**, which provided the secondary amines **6** by the deprotection of the 2-nitrobenzenesulfonyl (Ns) group. Then **6** were transformed into the key intermediates **8** by acylation with chloroacetic acids **7**. The intramolecular cyclization of **7** and the debenzylation of the sulfonium salts **9** were carried out in the presence of CsI, providing product **10** in high purity without purification by column chromatography.

To demonstrate the usefulness of this approach, several thiomorpholin-3-one derivatives were synthesized.[14] The representative results are shown in Table 1. The alkyl and aryl groups can be introduced in R^1–R^4 with high purities and moderate total yields (entries 1–6), while compounds with functional groups such as ester and basic nitrogen could be obtained (entries 4 and 5). Construction of a 7-membered and an 8-membered ring (entries 7 and 8)



Scheme 2. (a) Compound **2** (3 equiv), DBU (4 equiv), DMF, rt, 24 h; (b) **4** (2 equiv), PPh_3 (2 equiv), DEAD (2 equiv), THF, rt, 16 h; (c) $HOCH_2CH_2SH$ (10 equiv), DBU (10 equiv), DMF, rt, 1 h; (d) DIC (12 equiv), **7** (12 equiv), DMF, rt, 20 h; (e) PyBrop (12 equiv), **7** (12 equiv), *i*-Pr_2NEt (24 equiv), rt, 20 h; (f) CsI (1 equiv), dioxane, water, 95 °C, 1–2 h.

Table 1
Syntheses of thiomorpholin-3-one derivatives **10**

Entry	**10**	R^1	R^2	R^3	R^4	*n*	Yield[a] (%) (Purity[b] (%)) of **10**
1	**10a**	H	H	(4-Br)$PhCH_2CH_2$–	H	0	65 (99)
2	**10b**	Me	Me	(4-Br)$PhCH_2CH_2$–	H	0	58 (100)
3	**10c**	H	H	(4-Br)Ph–	H	0	72 (100)
4	**10d**	H	H	(4-Me_2N)$PhCH_2$–	H	0	50 (97)
5	**10e**	H	H	(4-MeOCO)$PhCH_2$–	H	0	47 (100)
6	**10f**	H	H	(4-Br)$PhCH_2CH_2$–	Me	0	49 (96)
7	**10g**	H	H	(4-Br)$PhCH_2CH_2$–	H	1	74 (99)
8	**10h**	H	H	(4-Br)$PhCH_2CH_2$–	H	2	53 (95)

[a] Isolated overall yields (six steps) based on Merrifield resin **1**.
[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 or 220 nm.

was also possible, and this result would expand diversity of the libraries based on this synthetic route. It is generally known that solution phase constructions of medium-sized rings containing 8-membered rings are often attended with undesirable intermolecular reactions and therefore result in low yields or failure. By contrast, our method could give the 8-membered ring in comparable yield to those of 6- and 7-membered rings. We assume that the pseudo high-dilution condition on the solid supports favored the intramolecular cyclization over the intermolecular side reaction.[15]

In conclusion, a novel traceless solid phase synthesis of thiomorpholin-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.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.117.

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11. Some other examples of the solid phase syntheses accompanying the cyclization on the solid supports revealed that the objective heterocycles showed high purities without any further post-cleavage purification, see: (a) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090–6092; (b) Tietze, L. F.; Steinmetz, A. *Synlett* **1996**, 667–668; (c) Saruta, K.; Ogiku, T. *Chem. Lett.* **2007**, *36*, 1430–1431.
12. If the polymer-supported alcohols **3** did not react with N-monosubstituted 2-nitrobenzenesulfonamides **4** completely, the esters composed of residual **3** and chloroacetic acids **7** might be provided in the amide formation steps (step **d** or **e** on Scheme 2), which might lead to the formation of the lactones as impurities at the cleavage steps. Fortunately, such by-products have not been identified so far and the desired products were provided with high purities, because the Mitsunobu reactions proceeded perfectly. The proceeding of these reactions was confirmed with the elemental analysis of the *N*,*N*-disubstituted 2-nitrobenzenesulfonamides **5** (data not shown).
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14. *Typical experimental procedure is as follows*: To Merrifield resin **1** (20.0 g, 38.8 mmol, Polymer Laboratories; 1.94 mmol/g) in DMF (200 ml) were added DBU (23.2 ml, 155 mmol) and sulfanylethanol **2** (8.17 ml, 117 mmol) at 0 °C. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with DMF (×5), water (×5), MeOH (×5), THF (×5) and Et_2O (×5), and was dried in vacuo (**3**: 22.3 g; 100%; equivalent to 1.74 mmol/g). To a mixture of resin **3** (3.45 g, 6 mmol), *N*-[2-(4-bromophenyl)ethyl]-2-nitrobenzenesulfonamide **4** (925 mg, 2.4 mmol) and PPh_3 (3.15 g, 12 mmol) in THF (100 ml) was added a 40% toluene solution of DEAD (5.56 ml, 12 mmol) at 0 °C. After stirring for 2 min, the whole was allowed to stir at room temperature for 16 h. The resin was washed with CH_2Cl_2 (×5), THF (×5), MeOH (×5), THF (×5), and Et_2O (×5) to give **5**. To resin **5** (3.45 g, 6 mmol) in DMF (10 ml) were added DBU (1.79 ml, 12 mmol) and sulfanylethanol (842 μl, 12 mmol) at 0 °C. After stirring for 2 min, the whole was allowed to stir at room temperature for 1 h. The resin was washed with Et_3N–water (1:9, ×3), DMF (×3), water (×5), MeOH (×5), THF (×5), and Et_2O (×5) to give **6**. The obtained resin **6** was swollen with a mixture of chloroacetic acid (1.36 g; 14.4 mmol), diisopropylcarbodiimide (2.23 ml, 14.4 mmol), DMF (12 ml) and the mixture was agitated for 20 h at room temperature. The resin was then washed with DMF (×5), Et_3N–water (1:9, ×5), THF (×5), and MeOH (×5) to give **8**. Resin **8** was swollen with a mixture of CsI (624 mg, 2.4 mmol), dioxane (8 ml) and water (2 ml) and stirred at 95 °C for 1 h. The resin was washed with MeOH–$CHCl_3$ (1:4, ×3) and MeOH (×5) and the filtrate was evaporated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ and brine and dried with Na_2SO_4. The solvent was evaporated to provide product **10** as a pale yellow solid (235 mg, 65%).
    All products gave satisfactory 400 MHz ^1H NMR, 100 MHz ^{13}C NMR, IR and MS spectra. The spectral data of **10** are given below: Compound **10a**: 4-[2-(4-bromophenyl)ethyl]-1,4-thiazaperhydroin-3-one: ^1H NMR (400 MHz, DMSO-d_6): δ 2.80–2.74 (4H, m), 3.20 (2H, s), 3.54–3.50 (4H, m), 7.21 (2H, d, $J = 8.45$ Hz), 7.48 (2H, d, $J = 8.45$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 30.3, 3.33, 50.1, 50.2, 120.4,130.6, 131.6, 137.8, 166.3; IR (KBr) ν_{max}: 2933, 1652, 1484, 1425, 1362, 809, 515; MS: *m*/*z* 300/302 $[M+H]^+$. Compound **10b**: 4-[2-(4-bromophenyl)ethyl]-5,6-dimethyl-1,4-thiazaperhydroin-3-one: ^1H NMR (400 MHz, DMSO-d_6): δ 1.08 (0.8H, d, $J = 6.40$ Hz), 1.20 (0.8H, d, $J = 6.40$ Hz), 1.27 (2.2H, d, $J = 6.40$ Hz), 1.33 (2.2H, d, $J = 6.40$ Hz), 2.91–2.71 (2H, m), 3.18–3.03 (2H, m), 3.32 (2H, s), 3.60–3.53 (1H, m), 3.85–3.75 (1H, m), 7.25–7.20 (2H, m), 7.52–7.47 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 17.3, 20.5, 20.8, 26.5, 30.2, 33.3, 33.4, 38.2, 39.1, 49.3, 49.9, 60.3, 61.4, 120.3, 130.6, 131.6, 131.7, 137.7, 138.0, 165.1, 165.2; IR (KBr) ν_{max}: 2975, 2930, 1628, 1488, 1428, 1404, 1072, 1012, 807, 510; MS: *m*/*z* 328/330 $[M+H]^+$. Compound **10c**: 4-(4-bromophenyl)-1,4-thiazaperhydroin-3-one: ^1H NMR (400 MHz, DMSO-d_6): δ 3.03 (2H, t, $J = 5.63$ Hz), 3.42 (2H, s), 3.96 (2H, t, $J = 5.63$ Hz), 7.29–3.26 (2H, m), 7.60–7.56 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 30.6, 52.1, 120.6, 127.8, 132.4, 141.6, 166.8; IR (KBr) ν_{max}: 3056, 2930, 1656, 1489, 1396, 1011, 825, 551; MS: *m*/*z* 272/274 $[M+H]^+$. Compound **10d**: 4-{[4-(dimethylamino)phenyl]methyl}-1,4-thiazaperhydroin-3-one: ^1H NMR (400 MHz, DMSO-d_6): δ 2.75 (2H, t, $J = 5.89$ Hz), 2.86 (6H, s), 3.29 (2H, s), 3.48 (2H, t, $J = 5.89$ Hz), 4.42 (2H, s), 6.69–6.67 (2H, m), 7.10–7.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 30.4, 40.6, 48.0, 50.0, 112.6, 124.4, 129.3, 150.1, 166.4; IR (KBr) ν_{max}: 2932, 2812, 1648, 1533, 1442, 1365, 1189, 807, 586; MS: *m*/*z* 251 $[M+H]^+$. Compound **10e**: methyl 4-[(3-oxo-1,4-thiazaperhydroin-4-yl)methyl]benzoate: ^1H NMR (400 MHz, DMSO-d_6): δ 2.84 (2H, t, $J = 5.63$ Hz), 3.36 (2H, s), 3.57 (2H, t, $J = 5.63$ Hz), 3.85 (3H, s), 4.64 (2H, s), 7.40 (2H, d, $J = 8.19$ Hz), 7.94 (2H, d, $J = 8.19$ Hz); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 26.4, 30.5, 49.0, 50.6, 52.1, 127.8, 129.7, 130.1, 142.0, 166.6, 166.7; IR (KBr) ν_{max}: 2988, 2948, 1726, 1649, 1436, 1416, 1282, 1112, 744; MS: m/z 266 $[M+H]^+$.

Compound **10f**: 4-[2-(4-bromophenyl)ethyl]-2-methyl-1,4-thiazaperhydroin-3-one: ^1H NMR (400 MHz, DMSO-d_6): δ 1.21 (3H, t, $J = 6.91$ Hz), 2.79–2.70 (3H, m), 2.90–2.87 (1H, m), 3.68–3.47(5H, m), 7.21 (2H, d, $J = 8.19$ Hz), 7.48 (2H, d, $J = 8.19$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 26.4, 33.7, 36.1, 49.5, 50.3, 120.3, 130.6, 131.6, 137.9, 170.3; IR (KBr) ν_{max}: 2977, 2933, 1655, 1488, 1451, 1425, 1072, 1011, 811, 508; MS: m/z 314/316 $[M+H]^+$.

Compound **10g**: 4-[2-(4-bromophenyl)ethyl]-1,4-thiazaperhydroepin-3-one: ^1H NMR (400 MHz, DMSO-d_6): δ 1.80–1.75 (2H, m), 2.73 (2H, t, $J = 7.94$ Hz), 2.80 (2H, t, $J = 5.63$ Hz), 3.32 (2H, s), 3.46–3.44 (4H, m), 7.21 (2H, d, $J = 8.45$ Hz), 7.47 (2H, d, $J = 8.45$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.1, 32.9, 33.8, 34.9, 50.1, 50.5, 120.2, 130.6, 131.6, 137.9, 172.6; IR (KBr) ν_{max}: 2931, 1642, 1486, 1448, 1422, 1133, 1011, 803, 512; MS: m/z 314/316 $[M+H]^+$.

Compound **10h**: 4-[2-(4-bromophenyl)ethyl]-1,4-thiazaperhydroocin-3-one: ^1H NMR (400 MHz, DMSO-d_6): δ 1.68–1.62 (2H, m), 1.87–1.81 (2H, m), 2.64 (2H, t, $J = 5.12$ Hz), 2.77 (2H, t, $J = 7.94$ Hz), 3.35 (2H, s), 3.47–3.39 (4H, m), 7.21 (2H, d, $J = 8.45$ Hz), 7.48 (2H, d, $J = 8.45$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 29.2, 29.8, 32.8, 33.3, 46.9, 47.2, 120.2, 130.6, 131.6, 138.1, 171.1; IR (KBr) ν_{max}: 2937, 1600, 1485, 1469, 1430, 1234, 1129, 1070, 1010, 806, 516; MS: m/z 328/330 $[M+H]^+$.

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