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# A versatile method for the preparation of 2,2-disubstituted morpholine analogues

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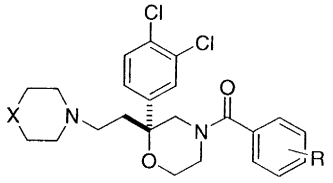
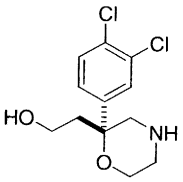
**Abstract**

We describe a versatile synthetic method for the preparation of 2,2-disubstituted morpholine analogues. Iodoetherification of 1,1-disubstituted olefin with *N*-Boc-aminoethanol using NIS proceeded smoothly in a regioselective manner and the following cyclization was accomplished in good yield. We successfully applied this method for the preparation of the key intermediate **2** of tachykinin receptor antagonist. 

In the course of our studies on tachykinin receptor antagonist, we have already reported that morpholine derivative **1** exhibited high binding affinities for tachykinin receptors.[1] For the synthesis of these morpholine derivatives, 2-[(2*R*)-(3,4-dichlorophenyl)morpholin-2-yl]ethanol (**2**) is recognized as a key intermediate. We previously reported an asymmetric synthetic method for the preparation of **2** using the Sharpless asymmetric dihydroxylation and the Mitsunobu reaction.[2] Although this method is useful for the preparation of an optically active form, it is not suitable for large-scale synthesis because of the difficulties in handling osmium and multi steps. Therefore we focused our attention on an alternative synthetic strategy.




**1**




**2**

To the best of our knowledge, the general synthetic method for the construction of the 2,2-disubstituted morpholine ring from olefin can be classified into the two main routes depicted in Scheme 1. In route A, epoxide **4** is opened by aminoethanol, and the following cyclization under dehydration conditions yields morpholine **6**.[3] Route B proceeds via 3-oxomorpholine **9** and involves α-bromoacetylation of the aminoalcohol **7** derived from epoxide **4**.[4]

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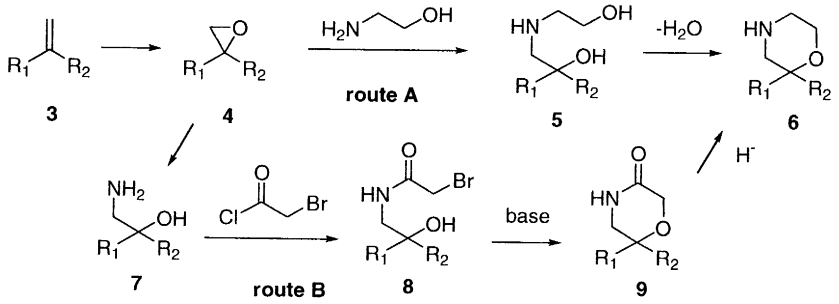
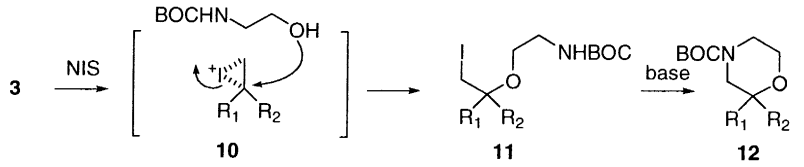



Scheme 1. General method for the synthesis of morpholine ring

As a part of our ongoing research concerned with the construction of morpholine ring, we focused our attention on the use of haloetherification, a process which has been extensively used for the functionalization on olefin.[5] Here we report a versatile short-step method for the synthesis of 2,2-disubstituted morpholine via iodoetherification. Our proposed strategy is illustrated in Scheme 2. Initial formation of an iodonium ion intermediate **10** is generated using *N*-iodosuccinimide (NIS), and then the resulting iodonium ion reacts with *N*-Boc-aminoethanol in a regioselective manner to afford the iodoether **11**. Cyclization of **11** by base treatment leads to the desired 2,2-disubstituted morpholine analogue **12**. We conjecture that this methodology could be a useful general procedure for the synthesis of a variety of 2,2-disubstituted morpholines from a 1,1-disubstituted olefin.




Scheme 2. Regioselective iodoetherification and cyclization to form morpholine ring

Table 1 shows a number of examples of this chemistry.[6] A variety of 2,2-disubstituted morpholine analogues could be prepared readily in this procedure. Iodoetherification employed with NIS and *N*-Boc-aminoethanol in $CH_3CN$ at 25°C.[7] A screening of appropriate solvents for iodoetherification showed a dramatic solvent effect, and the best solvent was $CH_3CN$. Other solvents such as THF, 1,4-dioxane, and $CH_2Cl_2$ gave poor results (5–10% yield). Attempts at haloetherification via bromonium ion using *N*-bromosuccinimide were unsatisfactory due to diminished yield. As can be seen in entries 1–3, α-methylstyrene substrate gave good results (89–96% yield). We also investigated the substrate in this reaction, which had aliphatic substituents. In this case, both acyclic and cyclic substrate reacted to afford the product in 54–72% yield (entries 4–7). All these 1,1-disubstituted olefins yielded the product regioselectively.

In the ensuing step of the morpholine ring formation, we examined various combinations of base and solvent. Treatment of a DMF solution of iodide **14a**–**g** with NaH resulted in good yield of the morpholine **15a**–**g**, as shown in Table 2.[6]

With the technology in hand to synthesize 2,2-disubstituted morpholine analogues, we directed our efforts to the completion of the synthesis of **2**, a key intermediate of the tachykinin receptor antagonist. The synthetic route to optically active (2*R*)-**2** is outlined in Scheme 3. Styrene derivative **16** was treated with *N*-Boc-aminoethanol (10 equiv.) and NIS (4 equiv.) in $CH_3CN$ at 70°C to obtain iodide **17** in 72% yield. Treatment of **17** with NaH in DMF at 70°C cleanly provided morpholine **18** in 77% yield. Deprotection of both the triphenylmethyl (Tr) group and Boc group of **18** by 4*N* HCl proceeded smoothly in 79% yield after recrystallization. Next, the resulting racemic (*RS*)-**2** was resolved with D-(−)-tartaric

Table 1
Iodoetherification of *exo*-olefin with *N*-Boc-aminoethanol using NIS

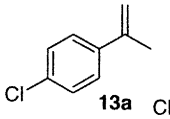
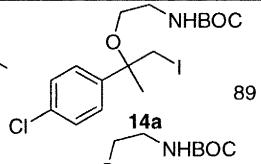
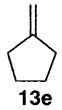
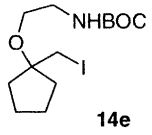
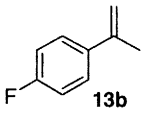
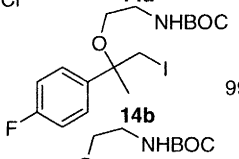
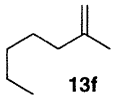
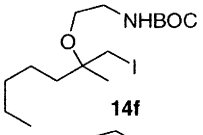
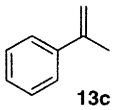
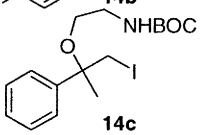
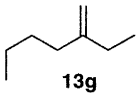
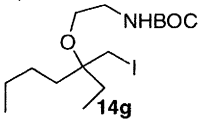
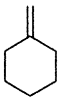
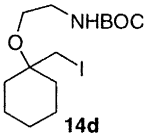
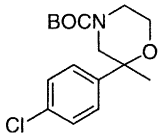
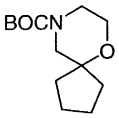
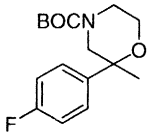
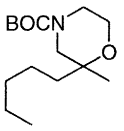
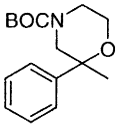
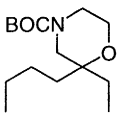
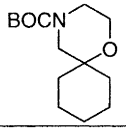
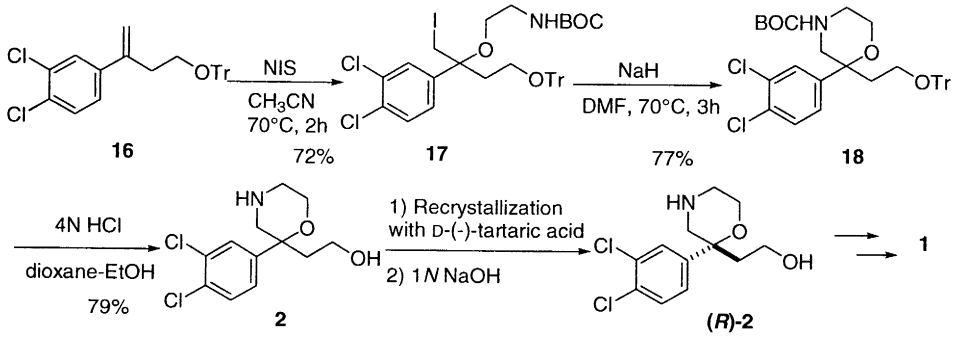
| Entry | Substrate | Product | Yield (%) | Entry | Substrate | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **13a** |  **14a** | 89 | 5 |  **13e** |  **14e** | 72 |
| 2 |  **13b** |  **14b** | 99 | 6 |  **13f** |  **14f** | 69 |
| 3 |  **13c** |  **14c** | 96 | 7 |  **13g** |  **14g** | 54 |
| 4 |  **13d** |  **14d** | 54 | | | | |

Table 2
Cyclization of iodoether compound using NaH

| Entry | Substrate | Product | Yield (%) | Entry | Substrate | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **14a** |  **15a** | 92 | 5 | **14e** |  **15e** | 79 |
| 2 | **14b** |  **15b** | 90 | 6 | **14f** |  **15f** | 83 |
| 3 | **14c** |  **15c** | 91 | 7 | **14g** |  **15g** | 85 |
| 4 | **14d** |  **15d** | 80 | | | | |

acid in EtOH to give (*R*)-**2** with high enantiomeric purity. Treatment of an EtOH solution of racemic (*RS*)-**2** with 0.5 equiv. of D-(−)-tartaric acid resulted in 86% yield, from tartaric acid, of (*R*)-**2**/ D-(−)-tartaric acid salt with 91% *ee*. Recrystallization with EtOH–$H_2O$ gave white crystals, and a subsequent base treatment gave (*R*)-**2** of >99% *ee* in 95% yield.[6]

In conclusion, a potentially useful and versatile method for the preparation of 2,2-disubstituted




Scheme 3. Synthesis of key intermediate for tachykinin receptor antagonist

morpholine analogues has been achieved. The enantiomerically pure (*R*)-**2** prepared by the above method has been successfully incorporated into a number of tachykinin receptor antagonists.

## References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5. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.
6. All new compounds are fully characterized by their spectroscopic and analytical data.
7. Typical procedure: Preparation of **14c** (Table 1, entry 3): A round-bottomed flask was charged with α-methylstyrene (71 mg, 0.60 mmol), *N*-Boc-aminoethanol (145 mg, 0.72 mmol), and $CH_3CN$ (4.0 mL). NIS (162 mg, 0.72 mmol) was successively added. The reaction mixture was vigorously stirred at room temperature for 2 h. The solution was poured into brine and extracted with EtOAc. The combined EtOAc layer was washed with water and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by preparative TLC (*n*-hexane:EtOAc 5:1) and yielded as a colorless oil (234 mg, 96% yield): FT-IR (neat) $\nu_{max}$ 3430, 3363, 2978, 2933, 1714, 1506, 1448, 1392, 1366, 1273, 1251, 1170, 1093, 1079, 764, 401 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.24 (m, 5H), 5.03 (bs, 1H), 3.53 (d, *J*=10.4 Hz, 1H), 3.45 (d, *J*=10.4 Hz, 1H), 3.38–3.17 (m, 4H), 1.71 (s, 3H), 1.45 (s, 9H); HRMS (FAB) calcd for $C_{16}H_{25}O_3NI$ ($M+H^+$) 406.0879, found 406.0872. Preparation of **15c** (Table 2, entry 3): A round-bottomed flask was charged with **14c** (234 mg, 0.56 mmol) and DMF (4.0 mL). NaH (30 mg, ca. 60% mineral oil suspension, 0.75 mmol) was successively added. The reaction mixture was vigorously stirred at room temperature for 3 h. The solution was poured into brine and extracted with EtOAc. The combined EtOAc layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the desired product was purified by preparative TLC (*n*-hexane:AcOEt 4:1) and yielded as a colorless oil (145 mg, 91% yield): FT-IR (neat) $\nu_{max}$ 2976, 2929, 2869, 1699, 1449, 1425, 1366, 1281, 1242, 1172, 1137, 1095, 868, 764, 701 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.53–7.21 (m, 5H), 4.40–4.27 (m, 1H), 3.73–3.44 (m, 3H), 3.28–3.10 (m, 2H), 1.51 (bs, 3H), 1.41 (bs, 9H); HRMS (EI) calcd for $C_{16}H_{23}O_3N$ ($M^+$) 277.1674, found 277.1679.