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Straightforward synthesis of (*R*,*R*/*S*,*S*)-2-[2-(2-aryl)-1-phenyl-ethyl]-morpholines: a new class of inhibitors of the norepinephrine transporter

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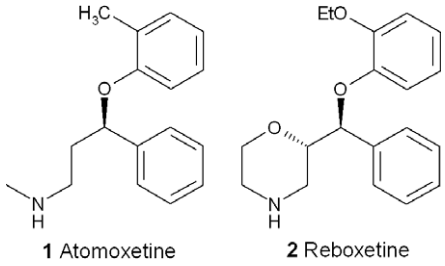
Abstract—Diastereoselective synthesis of (*R*,*R*/*S*,*S*)-2-[2-(2-aryl)-1-phenyl-ethyl]-morpholines **6** has been achieved through the preparation of key *E*-enol-triflate **4** and its further coupling with benzylzinc reagents and final hydrogenation.

Norepinephrine (NE) plays a very important role in the central nervous system.[1] Selective inhibitors of norepinephrine transporter (NET) like Atomoxetine (**1**) (Strattera™) and Reboxetine (**2**) (Edronax™) are marketed for the treatment of affective disorders (Fig. 1).[2]

In our continued exploration of new inhibitors,[3,4] we targeted the family of compounds **6**. This series features the same 2,2′-*anti* stereochemistry as Reboxetine, which is critical for the inhibitory activity. In this context, the main synthetic challenge we faced was the stereoselective preparation of these analogs. For this purpose, we envisaged that morpholine **4** could serve as key intermediate. This compound features two valuable characteristics: (a) the triflate group, which allows a palladium cross-coupling with benzylzinc halides and (b) the right *E* stereochemistry, which yields, after single final hydrogenation, the desired 2,2′-*anti* analogs **6**. Finally, **4** would be prepared from ketone **3**, which was available on a large scale in our laboratory[4] (Fig. 2).



1 Atomoxetine **2** Reboxetine

Figure 1.

The preparation of the desired *E*-enol-triflate **4** required considerable experimental optimization. Firstly, deprotonation of ketone **3** with bases such as LiHMDS or KHMDS in THF at −78 °C gave predominantly the undesired *Z*-enol-triflate **7**.[5] This may be due to the formation of highly stabilized metal chelate **I** by coordination of the metal cation with the oxygen of the morpholine ring (Fig. 3).

Taking these findings into account, we turned our attention to the search of conditions in which the formation of this highly stabilized internal chelate could be avoided. Addition of 18-crown-6 could trap the metal from the reaction (especially potassium[6]) and, thus, prevent formation of the internal chelate. Using ^{t}BuOK (1.1 equiv), 18-crown-6 (1.1 equiv), $PhN(SO_2CF_3)_2$ (1.2 equiv) in THF, the desired *E*-enol-triflate **4** was obtained in 70% yield and 10:1 ratio of *E*- to *Z*-enol-triflate (1–7 mmol scale). To our surprise, the isolated yields and the observed stereoselectivity were much lower when we used a new batch of ^{t}BuOK rather than the bottle which had been in our laboratory for some time. With a freshly opened bottle of the base, **4** was isolated only in 40–45% yield and poor 1.1:1 ratio of *E*- to *Z*-enol-triflate. As ^{t}BuOK is known to be hygroscopic, we hypothesized that the older bottle might contain

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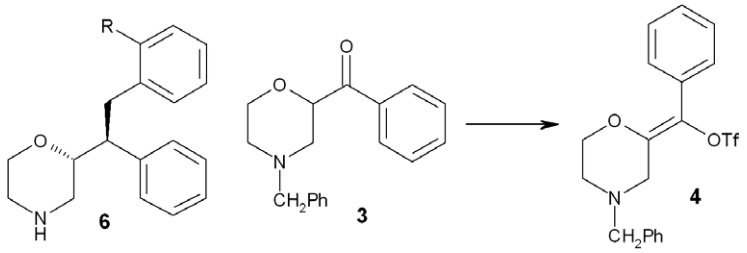


Figure 2.

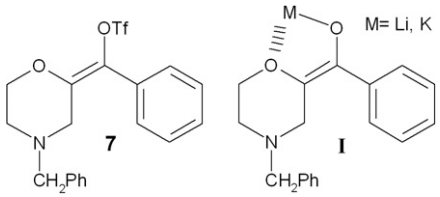


Figure 3.

more water and that the presence of water might cause a change of the reaction mechanism favoring the formation of the desired *E*-enol-triflate. To test this hypothesis, we screened the effect of varying equivalents of water on the reaction mechanism. From this study, we found the optimal conditions for the formation of **4** to be 1 equiv of **3**, 1.3 equiv of ^{t}BuOK, 1.3 equiv of 18-crown-6, 1.4 equiv of $PhN(SO_2CF_3)_2$ and just 0.5 equiv of water. Under these conditions, yields of 65–70% and stereoselectivity ratios of 8–10:1 were consistently achieved.

The next step was the palladium catalyzed coupling of **4** with *ortho*-substituted benzylzinc derivatives.[7,8] Thus, when commercially available 2-ethoxybenzylzinc chloride (1.2 equiv), **4** (1 equiv), and $Pd(PPh_3)_4$ (5 mol %) were refluxed for 1 h in anhydrous THF, we obtained the desired compound **5a** in an excellent 80% yield (Scheme 1; Table 1, entry **a**). Similarly, very good yields were achieved under these conditions for other analogs listed in Table 1, including sterically hindered ones (entries **c**, **d**, **f**). Furthermore, these conditions were compatible with the presence of halogens (entries **g**,[9] **h**), which allows further functionalization at that position.

Finally, standard palladium-catalyzed hydrogenation of compounds **5** in methanol afforded the desired analogs **6** in good yields and with the required 2,2′-*anti* stereochemistry (Scheme 1; Table 1).

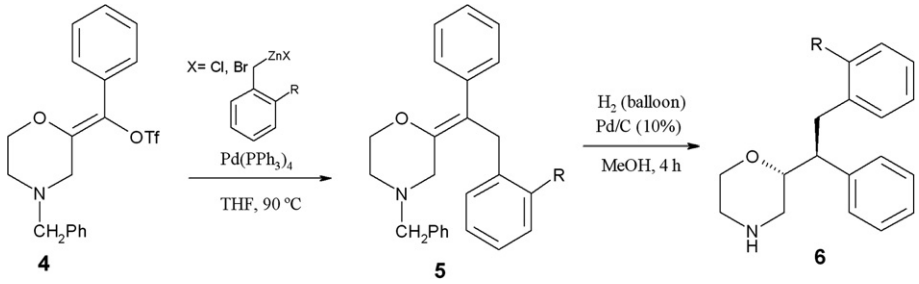
Table 1.

Entry	R	**5**, Yield[a] (%)	**6**, Yield[a] (%)
a	OEt	80	80
b	OMe	85	81
c	Ph	88	80
d	^{i}Pr	88	82
e	OPh	87	85
f	OTBDMS	76	72
g	Br	84	—[b]
h	Cl	85	—[b]

[a] Isolated yield.
[b] The reaction was not done.

In summary, we report herein a highly efficient route to (*R*,*R*/*S*,*S*)-2-[2-(2-aryl)-1-phenyl-ethyl]-morpholines **6**. The biological activity of the target compounds will be communicated in due course.

Preparation of **4**: To a solution of ^{t}BuOK (95% from Aldrich, 110 mg, 0.93 mmol) and water (0.5 equiv) in anhydrous THF (4.2 ml/mmol) were added, at 0 °C under nitrogen atmosphere, 18-crown-6 (246 mg, 0.93 mmol) and **3** (200 mg, 0.71 mmol, a single portion as solid) and the mixture was stirred at this temperature for 15 min and, then, at room temperature for 45 min. Next, *N*-phenyltrifluoromethanesulfonimide was added (357 mg, 1 mmol, a single portion as solid) and the final mixture was stirred overnight at room temperature. The solvent was removed and Et_2O was added to the residue. The mixture was filtered off and the solid was washed twice with Et_2O. The combined filtrated was evaporated and the crude was purified by column chromatography on silica gel eluting with hexane–dichloromethane 1:1 to afford 210 mg of **4** as a pale yellow oil (71% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.57 (dd, $J = 1.3$ and 8.2 Hz, 2H), 7.43–7.26 (m, 8H), 4.02 (t, $J = 4.8$ Hz, 2H), 3.67 (s, 2H), 3.45 (s, 2H), 2.68 (t, $J = 4.8$ Hz, 2H). LC–MS (*m*/*z*): 414 (M^{+}+1).



Scheme 1.

General method for the synthesis of **5**: Compound **4** (1 equiv) and $Pd(PPh_3)_4$ (5 mol %) were added to a solution of benzylzinc reagent (1.2 equiv) in anhydrous THF (7.5 ml/mmol) under nitrogen atmosphere and the mixture was stirred at 95 °C for 1 h. The reaction was allowed to reach room temperature and quenched with water. Then, it was filtered through Celite, dried over anhydrous sodium sulfate, filtered again, and the solvent removed. The residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol 98:2 yielding the title compounds **5**. Example **5a**: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.31–7.09 (m, 11H), 6.90–6.75 (m, 3H), 4.00–3.81 (m, 4H), 3.63 (s, 2H), 3.54 (s, 2H), 3.24 (s, 2H), 2.58–2.54 (m, 2H), 1.35 (t, $J = 7$ Hz, 3H). LC–MS (*m*/*z*): 400 (M^++1).

General method for the synthesis of **6**: To a 1:1 weighting ratio of **5** and Pd/C (10%) in methanol (10 ml/mmol) was bubbled hydrogen with a balloon. Then, the mixture was stirred under this atmosphere, keeping the balloon, at room temperature for 4 h. The reaction was filtered through Celite and washed twice with methanol. The solvent was removed and the residue was purified by chromatography on silica gel eluting with dichloromethane–methanol 9:1 affording the title compounds **6**. Example **6a**: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.22–6.99 (m, 6H), 6.88 (dd, $J = 1.9$ and 7.8 Hz, 1H), 6.74–6.67 (m, 2H), 3.96–3.60 (m, 5H), 3.42 (dd, $J = 3.5$ and 12.5 Hz, 1H), 3.12 (bs, 1H), 3.03–2.80 (m, 4H), 2.68–2.43 (m, 2H), 1.34 (t, $J = 6.9$ Hz, 3H). LC–MS (*m*/*z*): 312 (M^++1).

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