Pergamon

Tetrahedron Letters 40 (1999) 8563–8566

TETRAHEDRON LETTERS

# Solid-phase synthesis of 2-methoxyaniline derivatives by the traceless silicon linker strategy

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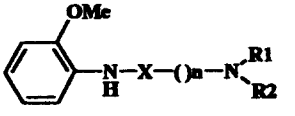
Received 20 August 1999; accepted 21 September 1999

**Abstract**

Application of the silicon linkage strategy to the solid-phase synthesis of the rich-electron *o*-anisidine derivatives is described. The protective *t*-Boc group was easily removed with B-catechol borane and the isocyanate was successfully prepared with the mild reagent $(t\text{-Boc})_2O$/DMAP. Carbamates, ureas or amides were prepared and released by cleavage with TFA at room temperature. This method can be used to prepare small focused libraries with biological activity at serotonin receptors. © 1999 Elsevier Science Ltd. All rights reserved.

Derivatives of 2-methoxyaniline such as carbamates, ureas and amides are a promising class of compounds with biological properties.[1] Thus, we demonstrated the interest of the arylcarbamates of aminoalkanol as potent ligands for the 5-$HT_4$ receptor subtype.[2] Recently, several isoforms of this receptor have been characterised[3] and they differ only by the length of the terminal peptidic chain.[4] Selective ligands for these isoforms cannot be designed using a classical approach because of the strong similarity of the binding sites. Consequently, the synthesis of a large number of molecules sharing a common pharmacophore and possessing molecular diversity in the secondary sites seemed an appropriate strategy. For this purpose, the synthesis of a focused small-molecule library with the formula **1** was undertaken.




**1** X = CO, CO-O, CO-NH

Such a molecule can be easily synthesised from the aromatic amines by introducing the different building blocks in three or four steps, giving diversity in the length of the chain and the nature of the basic nitrogen substituents. Solid-phase synthesis where the aromatic amine was attached to the polymer by a traceless linker seemed to be the appropriate strategy. This was developed recently by several teams who took advantage of the propensity of the silicon or germanium–aromatic carbon bond to be

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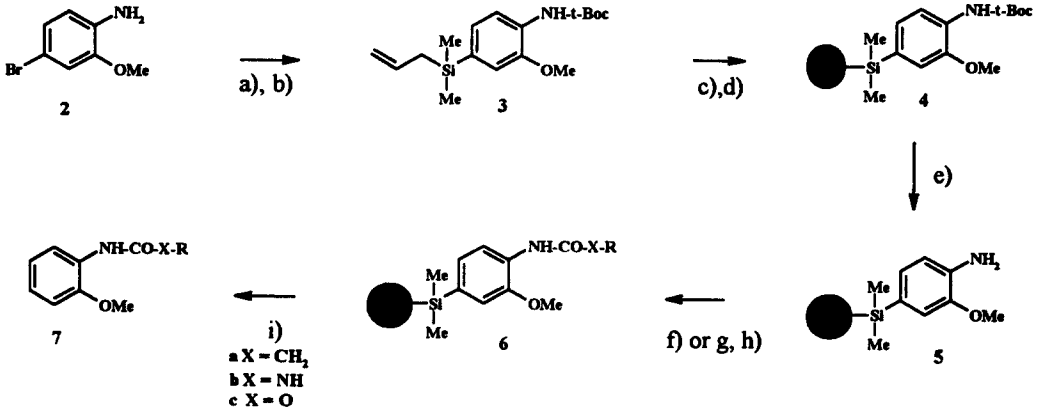
*PII:* S0040-4039(99)01817-1

easily cleaved by fluoride ions or $H^+$.[5–11] Ellman reported the synthesis of a series of benzodiazepine derivatives using this method. Two synthetic pathways were described: aromatic carbon–silicon or germanium bonds were formed by the reaction of protected bromoaniline in the presence of *t*-BuLi with dimethylchloro derivatives of silicon or germanium and linkage on the (aminomethyl)polystyrene resin.[5,8] Then the benzodiazepine derivatives were synthesised from the solid support by the introduction of three components: acid chlorides, amino acids and alkylating agents. The C–Si bond of the deficient-electron ring was cleaved by HF or $Me_2S$/TFA treatment. A simplified strategy[9] was presented more recently where the advantage was to load any bromo aromatic moiety onto the silyl-substituted support.

Similar synthetic pathways could be used for the preparation of compound **1** from the protected 4-bromo-2-methoxyaniline. However, the use of the inexpensive *t*-Boc as the protecting group, few building steps for the linker and an easy cleavage with TFA were considered as essential for the development of this synthesis. In particular, it was of great interest to condense (Scheme 1) the allyldimethylsilyl derivative **3** prepared from *N*-*t*-Boc-4-bromo-2-methoxyaniline **2**, according to the process already reported,[10] with the bromo-substituted polystyrene. Hydroboration followed by the Suzuki coupling[11,12] provided the resin **4** characterised by the carbonyl function (C=O, FT-IR spectra) and microanalysis of the nitrogen atom. However, the protective *t*-Boc group could not be removed by TFA as preliminary attempts showed that the C–Si bond was totally or partially cleaved regardless of the experimental conditions. The presence of MeO, an electronic donor group, on the aromatic ring was implicated in the acid susceptibility of this bond.[13]




Scheme 1. (a) $(t\text{-Boc})_2O$, THF; (b) KH, *t*-BuLi, THF, –78°C; $C_3H_5(Me)_2SiCl$; (c) THF, 9-BBN; (d) $Pd(Ph_3)_4$, $Na_2CO_3$, bromo-polystyrene; (e) B-chlorocatecholborane, $CH_2Cl_2$; (f) R-$CH_2$-COCl, $NEt_3$, $CH_2Cl_2$; (g) $(t\text{-Boc})_2O$, DMAP, $CH_2Cl_2$; (h) R-OH or $RNH_2$, $CH_2Cl_2$, Δ; (i) TFA, 18 h, rt

Only the Lewis acid B-catecholborane[14] rapidly removed the *t*-Boc group without any formation of 2-methoxyaniline, the resin **5** being characterised by the lack of the carbonyl function band in the IR spectra. It was condensed directly with various acid chlorides (R-$CH_2$-COCl) in the presence of $Et_3N$ to provide the amido derivatives **6a** which was easily cleaved by treatment with pure TFA at room temperature for 18 h. Compounds **7a** (Table 1) were isolated (57–90% yield) as pure compounds. They were characterised, using NMR spectra, by comparison with authentic samples. The amino function could also be transformed into an isocyanate group by a very mild method using $(t\text{-Boc})_2O$ in the presence of DMAP.[15] The addition of alcohol ROH such as bromoethanol, 3-chloropropanol or 4-chlorobutanol, gave the corresponding carbamates **7b** with good yields (85–53%) after cleavage with TFA at room temperature. No traces of *o*-anisidine could be detected in the compounds indicating the insensitivity of the carbamate bond to the acidic treatment conditions. This was an essential point in our strategy for the

Table 1
Synthesis of compounds **7** using the solid-phase synthesis with the silicon–aryl bond

| **7a** | **Me** | **Et** | **$CH_2Cl$** | **$(CH_2)_3Cl$** | **$C_6H_5$** |
|---|---|---|---|---|---|
| **entry 1** | **(57%)** | **(80%)** | **(74%)** | **(67%)** | **(90%)** |
| **7b** | **$O(CH_2)_2Br$** | **$O(CH_2)_3Cl$** | **$O(CH_2)_4Cl$** | | |
| **entry 2** | **(85%)** | **(53%)** | **(68%)** | | |
| **7c** | **NH-Pr-*n*** | **NH-$C_6H_4$-oMeO** | **NH-$(CH_2)_2$-Ph** | | |
| **entry 3** | **(72%)** | **(64%)** | **(83%)** | | |

synthesis of the carbamate libraries **1**. Similarly, ureas **7c** were obtained with good yields by the reaction of amines such as propylamine, *o*-anisidine or phenethylamine and the compounds were compared with authentical samples. The different compounds are reported in Table 1.

The amino carbamate **1** (X=CO-O, $n$=2, $NR_1R_2$=N-Me piperazine) was synthesised for evaluation of the efficiency of the synthetic pathway for the preparation of the derivatives **1**. It was obtained by the reaction of N-Me piperazine with the resin **6** (X-R=O-$(CH_2)_2$-Br) in methylene chloride and it was cleaved with TFA as a pure compound (yield: 48%).

In summary, the silicon-based linker for traceless solid-phase synthesis has been developed for the preparation of the amides, carbamates and ureas of *o*-anisidine as potential ligands for serotonin receptor subtypes. The resin was readily prepared and the *t*-Boc protecting group was chosen as it was easily removed with B-catechol borane without cleavage of the resin. Carbamates and ureas were obtained through the intermediate isocyanate prepared with the mild $(t\text{-Boc})_2O$/DMAP method. This process constitutes a promising method to prepare focused libraries derived from carbamates **1** of *o*-anisidine.[16]

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16. *General procedure*: **Preparation of the resin 4**: Allylsilane compound **3** (6 g) prepared according to the method reported[10] was stirred in 84 mL of dry THF and 33.6 mL of 0.5 M 9-BBN solution in THF under an argon atmosphere at room temperature for 5 h. $Pd(PPh_3)_4$ (0.4 g), 2M aqueous $Na_2CO_3$ solution (9 mL) and bromo-polystyrene resin (2.8 g) were added, then the mixture was refluxed for 40 h. An additional quantity of $Pd(PPh_3)_4$ (0.4 g) was then added and heating continued for 24 h. The mixture was filtered and the resin was washed successively with THF, MeOH, DMF and $CH_2Cl_2$ and then dried under a high vacuum. CO carbonyl stretch absorption (1730 $cm^{-1}$) was observed in IR spectra (KBr). The loading of the resin was indicated by nitrogen determination (1.3 mmol/g). Anal. found: N, 1.9. **Preparation of the resin 5, cleavage of the *t*-Boc group**: The resin (0.1 g) was treated with B-chlorocatecholborane solution (5 mL, 0.2 M $CH_2Cl_2$) at room temperature. After stirring for 10 min, the mixture was diluted with $H_2O$ (16 mL), stirred for 20 min and filtered. The resin was washed successively with $H_2O$, NaOH 10%, $CH_2Cl_2$, MeOH and dried under vacuum. IR spectra indicated

the total disappearance of the CO absorption. Anal. found: N: 2.21. **Preparation of the carbamates 6b and ureas 6c**: The suspension of resin **5** (1 equiv.) in $CH_2Cl_2$ was added to a solution of di-*tert*-butyldicarbonate (14 equiv.) in $CH_2Cl_2$ and DMAP (4-dimethylaminopyridine). The mixture was stirred for 30 min at room temperature. Alcohol ROH or amine $RNH_2$ (14 equiv.) in $CH_2Cl_2$ was added and refluxed overnight. The resin was filtered, washed several times with $CH_2Cl_2$ and MeOH and dried under high vacuum. CO carbonyl stretch absorption (1740–1730 $cm^{-1}$ for the carbamates and 1660 $cm^{-1}$ for the ureas) were observed in the IR spectra (KBr). **Preparation of the amides 6a**: $Et_3N$ (10 equiv.) and acid chloride RCOCl (10 equiv., 0.5 M in $CH_2Cl_2$) were added to the suspension of resin **5** (1 equiv.) in $CH_2Cl_2$. The mixture was stirred overnight at room temperature. The resin was filtered, washed several times with $CH_2Cl_2$ and MeOH and dried under high vacuum. Strong CO carbonyl stretch absorption (1660–1715 $cm^{-1}$) was observed. **Release of compounds 7a–c**: The resin **6** (150 mg) was stirred in trifluoroacetic acid (TFA, 10 mL) at room temperature overnight. The resin was removed by filtration and washed with $CH_2Cl_2$ and MeOH. The organic solution was evaporated under vacuum to give the crude product which was purified by rapid chromatography on silica gel. **Preparation of 1 (X=CO-O, *n*=2, $NR_1R_2$=N-Me piperazine)**: Resin **6** (X=O-$(CH_2)_2$Br) (100 mg) in $CH_2Cl_2$ (3.5 mL) was stirred for 40 h at room temperature in the presence of N-Me piperazine (1 mL) and DIEA (0.5 mL). The resin was filtered, washed several times with DMF, $CH_2Cl_2$ and MeOH and dried under high vacuum. This was stirred for 1 h with TFA (5 mL) at room temperature. The solution was evaporated, diluted with water, treated with $Na_2CO_3$ and extracted with diethyl ether to give 17 mg (48%) of pure compound **1** identical to the authentical sample.