Tetrahedron Letters 52 (2011) 849–852

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of novel substituted 3,8,11-triazaspiro[5,6]dodecan-7-ones

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ARTICLE INFO

Article history:
Received 29 September 2010
Revised 24 November 2010
Accepted 29 November 2010
Available online 4 December 2010

Keywords:
Triazaspiro[5,6]dodecan-7-one
Solid phase

ABSTRACT

A synthesis of novel substituted 3,8,11-triazaspiro[5,6]dodecan-7-ones using a combination of solution-phase and solid-phase chemistries is described. A solution-phase approach was used to produce a key piperidine intermediate that was then incorporated into a solid-phase synthesis. The combined synthetic strategy was applied to provide a series of substituted 3,8,11-triazaspiro[5,6]dodecan-7-ones in good yield and high purity.

The triazaspirone core structure is present in molecules that exhibit a wide range of biological activities. For example, the antipsychotic agent spiperone (**1**, Fig. 1) is a potent antagonist of the dopamine D_2, serotonin 5-HT_{1A}, and serotonin 5-HT_{2A} receptors.[1] Other 1,3,8-triazaspiro[4,5]decan-4-one derivatives are reported to be selective serotonin 5-HT_{2A} receptor antagonists,[1,2] GlyT-1 inhibitors,[3] and phospholipase D inhibitors.[4] Compounds incorporating the isomeric 1,4,8,-triaza[4,5]decan-2-one scaffold are useful as cerebral function-improving agents for senile dementia and Alzheimer's disease.[5] The ring-expanded 2,4,9-triazaspiro[5,5]undecan-3-one core is present in monoamine receptor inverse agonists.[6] Further ring expansion elicits the 1,4,10-triazaspiro[5,6]dodecan-5-one motif that is incorporated into selective adrenergic α_2 receptor antagonists.[7] However, this is the only report on the synthesis and activity of molecules incorporating a [5,6]triazaspirone system. To allow the further investigation of this chemotype, additional synthetic strategies need to be developed. This Letter describes the development of a robust combined solution-phase and solid-phase synthesis of compounds incorporating a novel substituted 3,8,11-triazaspiro[5,6]dodecan-7-one system (**17**, Fig. 1).

An advantage of solid-phase synthesis over solution-phase synthesis is that extensive reaction work ups and purifications are avoided.[8] The development of optimized reaction conditions allows straightforward draining of excess reagents and subsequent washing of the solid support upon reaction completion.[9] However, not all reactions can be performed on solid phase due to reagent incompatibility with either the solid support or the linker that attaches the molecule to the solid support. Also, solid-phase reactions can generate undesirable impurities that remain covalently linked to the solid support and cannot be washed away. Solution-phase synthesis does not have these particular limitations. Reactions in solution can be performed with a wide variety of

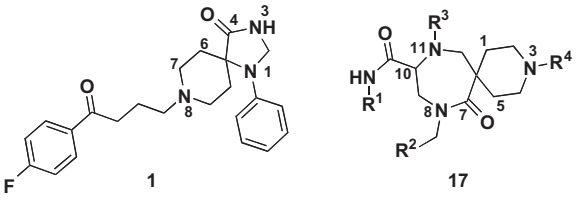
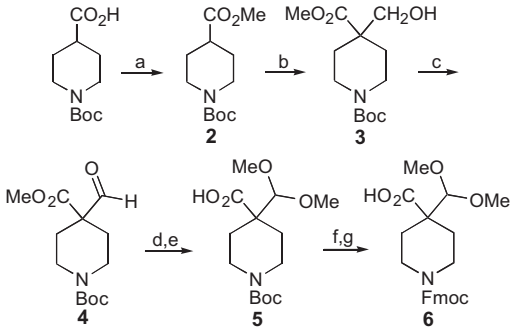


Figure 1.



Scheme 1. Reagents and conditions: (a) CH_3OCOCl, Et_3N, CH_2Cl_2, 0 °C, then anhydrous MeOH, 25 °C, 4 h; (b) LDA, Et_2O, −78 °C, then $(CH_2O)_n$, THF, −78 °C, 4 h; (c) $(COCl)_2$, DMSO, iPr_2NEt, CH_2Cl_2, −78 °C, 45 min; (d) *p*-toluenesufonic acid monohydrate, MeOH, $HC(OMe)_3$, 60 °C, 4 h; (e) KOH, H_2O, MeOH, reflux, 4 h; (f) trifluoroacetic acid, CH_2Cl_2, 25 °C, 30 min; (g) Fmoc-Cl, Na_2CO_3, THF, H_2O, 25 °C, 20 h.

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† In 2008, Pharmacopeia, Inc. was acquired by Ligand Pharmaceuticals, Inc.

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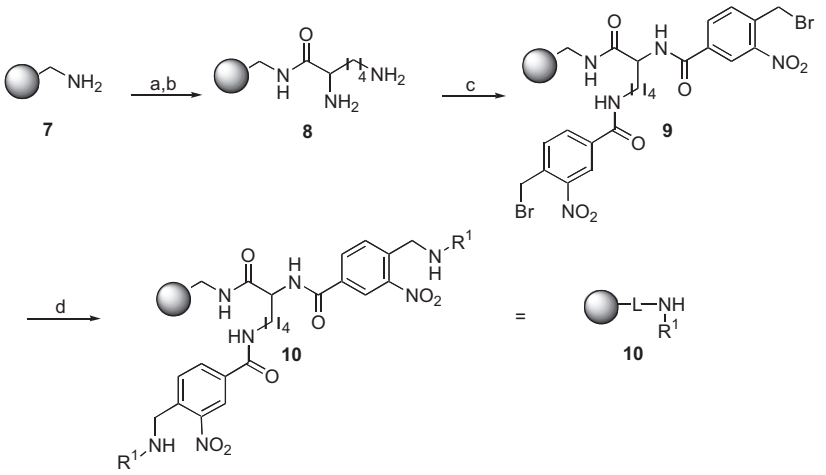
doi:10.1016/j.tetlet.2010.11.150

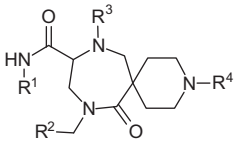


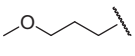
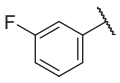
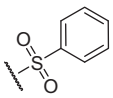
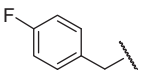
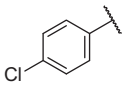
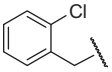
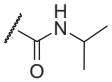
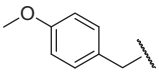
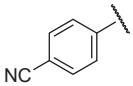
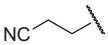
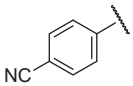
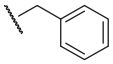
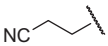
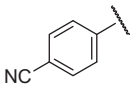
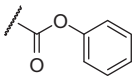
Scheme 2. Reagents and conditions: (a) *N*-α-*N*-ε-bis-Fmoc-Lys, HOBt monohydrate, DIC, CH_2Cl_2, DMF, 25 °C, 20 h; (b) piperidine, DMF, 25 °C, 1 h; (c) 4-carboxy-2-nitrobenzyl bromide, HOBt monohydrate, DIC, CH_2Cl_2, DMF, 25 °C, 20 h; (d) R^1-NH_2, THF, 25 °C, 20 h.

reagents with subsequent purification to remove any undesirable by-products. The combination of solution-phase and solid-phase reactions in a synthetic strategy can be a powerful tool to both utilize the respective advantages and circumvent the respective weaknesses of each technique. The synthesis of novel 3,8,11-triazaspiro[5,6]dodecan-7-ones detailed here employs such a combined solution-phase and solid-phase approach.

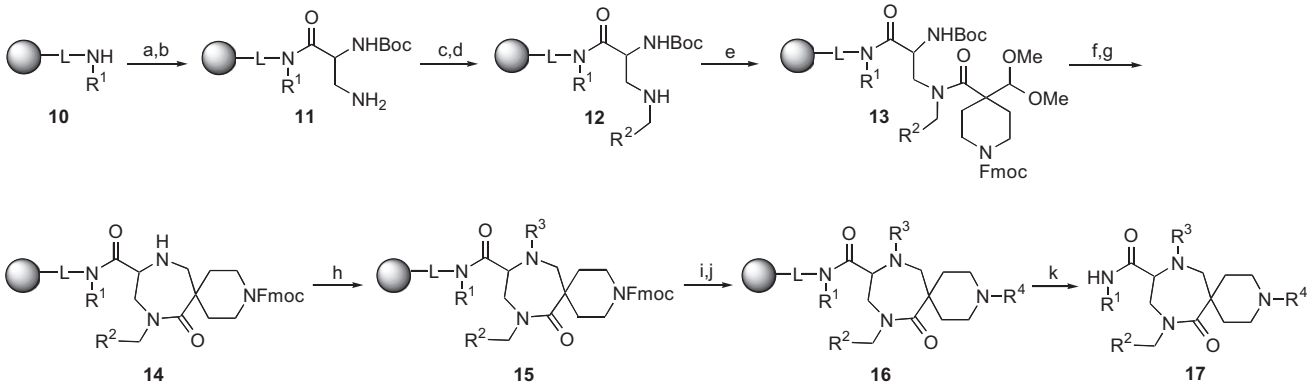
The synthetic strategy to access the 3,8,11-triazaspiro[5,6]dodecan-7-ones was initiated by the construction of 1-Fmoc-4-(dimethoxymethyl)piperidine-4-carboxylic acid (**6**) in solution (Scheme 1). Boc-protected isonipecotic acid was esterified to give the methyl ester **2**. Deprotonation of **2** with lithium diisopropylamide (LDA) at −78 °C was followed by hydroxymethylation with paraformaldehyde to generate alcohol **3**. The use of a strong base such as LDA would be incompatible with the photo-labile linker subsequently used in the solid-phase part of this synthetic strategy (vide infra). Swern oxidation of alcohol **3** provided aldehyde **4**. Protection of the aldehyde functionality in **4** as a dimethyl acetal followed by hydrolysis of the ester gave **5**. The Boc protecting group in **5** was then removed and replaced with an Fmoc

Table 1
Substituted 3,8,11-triazaspiro[5,6]dodecan-7-ones



Compound	R^1	R^2	R^3	R^4	pmol per bead[a]	Yield[b] (%)	Purity[c] (%)
17a					543	35	85
17b					618	40	85
17c					1157	75	91
17d					337	22	83
17e					313	20	87
17f					295	19	71

[a] Based on comparison with an analytical reference.
[b] Based on average loading per bead.
[c] Based on HPLC analysis at 215 nm.



Scheme 3. Reagents and conditions: (a) *N*-α-Boc-*N*-β-Fmoc-diaminopropionic acid, HOBt monohydrate, DIC, CH_2Cl_2, DMF, 25 °C, 20 h; (b) piperidine, DMF, 25 °C, 1 h; (c) R^2-CHO, THF, 25 °C, 20 h; (d) $NaCNBH_3$, MeOH, CH_3COOH, 25 °C, 20 h; (e) 1-Fmoc-4-(dimethoxymethyl)piperidine-4-carboxylic acid (**6**), BOPCl, *i*Pr_2NEt, CH_2Cl_2, 25 °C, 3 d; (f) TFA, CH_2Cl_2, H_2O, 25 °C, 30 min; (g) $NaCNBH_3$, CH_3 COOH, DMF, 25 °C, 20 h; (h) benzenesulfonyl chloride, methyl chloroformate, acetic anhydride, or allyl chloroformate, *i*Pr_2NEt, CH_2Cl_2, 25 °C, 20 h; or paraformaldehyde, or benzaldehyde, $NaCNBH_3$, MeOH, CH_3COOH, 25 °C, 20 h; (i) piperidine, DMF, 25 °C, 1 h; (j) isopropyl isocyanate, acetic anhydride, or phenyl chloroformate, *i*Pr_2NEt, CH_2Cl_2, 25 °C, 20 h; or paraformaldehyde, $NaCNBH_3$, MeOH, CH_3COOH, 25 °C, 20 h; (k) isopropanol/H_2O/TFA (80:20:3), *hv* (330 nm), 50 °C, 1 h.

protecting group to give **6** in order to be compatible with the subsequent solid-phase synthesis.

Solid-phase synthesis was initiated by acylating aminomethyl-terminated Argogel® resin **7** with *N*-α-*N*-ε-bis-Fmoc-lysine followed by Fmoc deprotection to generate **8** (Scheme 2). This increases the loading capacity of the resin by doubling the number of amino groups for further derivatization. The double-loaded resin **8** was subsequently acylated with the photo-labile linker precursor 4-carboxy-2-nitrobenzyl bromide to give **9**. This linker allows cleavage of intermediates and product from solid phase via photolysis at 330 nm, and is compatible with all the chemistry utilized in the solid-phase part of this synthetic strategy.[10] Reaction of the benzyl bromide **9** with a primary amine provides the resin-bound secondary amine **10**. A large excess of amine was utilized in order to minimize undesired cross-linking between unreacted benzylic bromide functionality and the secondary amine formed during this reaction. A range of primary amines were successfully utilized (Table 1). The secondary amine **10** was then acylated with *N*-α-Boc-*N*-β-Fmoc-diaminopropionic acid, followed by Fmoc deprotection to give **11** (Scheme 3). Both enantiomers of *N*-α-Boc-*N*-β-Fmoc-diaminopropionic acid were successfully utilized. The resin-bound primary amine **11** was further derivatized through reductive alkylation with an aldehyde (R^2-CHO) to give **12**. To insure mono-alkylation of the primary amine, a two-step reductive

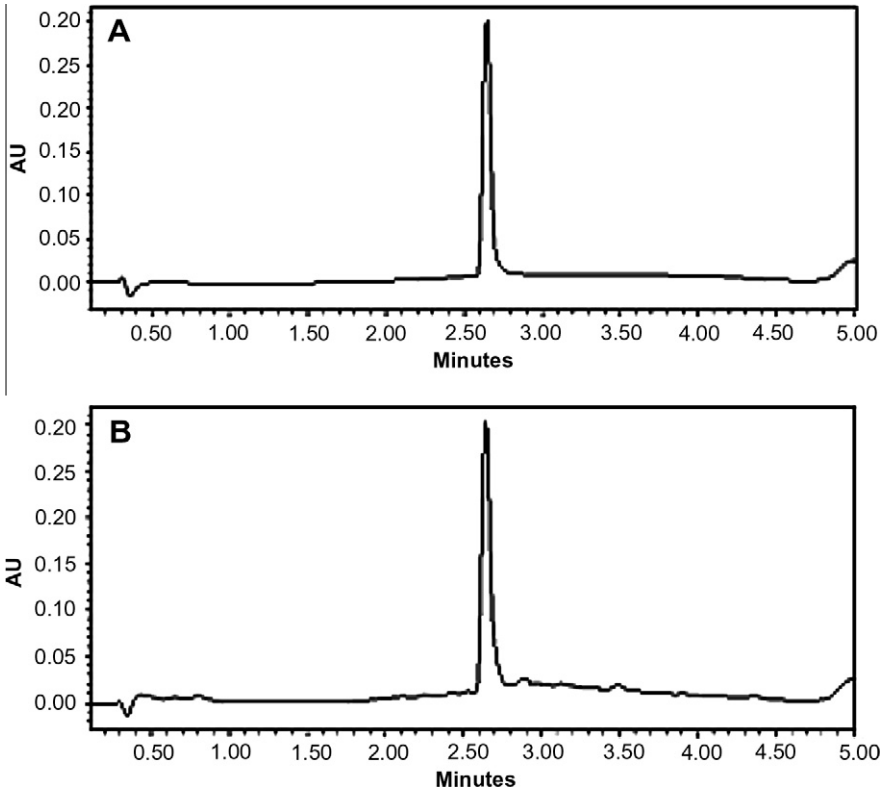


Figure 2. (A) HPLC profile of the standard of **17b** at 215 nm. (B) HPLC profile of the crude bead eluent of **17b** at 215 nm.

alkylation was performed. This involved imine formation, removal of excess aldehyde, and subsequent imine reduction with sodium cyanoborohydride.

A number of aromatic aldehydes were used (Table 1). The next step involving acylation of the resin-bound secondary amine **12** with **6** is the point at which the solution-phase and solid-phase methods converged. This reaction proved challenging due to the sterically-hindered carboxylic acid functionality in **6**. Typical acylation conditions including carboxylic acid activation with *N*,*N*′-diisopropylcarbodiimide (DIC)/hydroxybenzotriazole (HOBt), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), and bromo-tri-pyrrolidinophosphonium hexafluorophosphate (PyBrOP) did not achieve a complete reaction. The use of bis(2-oxo-oxazolidinyl)phosphinic chloride (BOPCl) in the presence of $i\mathrm{Pr}_2\mathrm{NEt}$ at room temperature for 3 days gave complete conversion to amide **13** as evidenced by a negative bromophenol blue test. Subsequent concomitant acid-mediated removal of the Boc and the acetal protecting groups from **13** was followed by the spontaneous formation of a seven-membered cyclic imine. Reduction of this imine with sodium cyanoborohydride gave the triazaspiro[5,6]dodecan-7-one ring system **14**. The secondary amine in **14** was derivatized (R^3) with a set of electrophilic reagents including benzenesulfonyl chloride, methyl chloroformate, acetic anhydride, paraformaldehyde, benzaldehyde, and allyl chloroformate to give **15** (Table 1). The allyl carbamate formed here was later removed just prior to photolysis ultimately producing the secondary amine **17f**.[11] Fmoc deprotection of **15** was followed by an additional *N*-derivatization (R^4) utilizing isopropyl isocyanate, phenyl chloroformate, paraformaldehyde, and acetic anhydride to give 3,8,11-triazaspiro[5,6]dodecan-7-ones **16**. The secondary amine was also left underivatized. Cleavage of the desired substituted 3,8,11-triazaspiro[5,6]dodecan-7-ones **17** from the solid support was accomplished via photolysis of **16** at 330 nm. Substituted 3,8,11-triazaspiro[5,6]dodecan-7-ones **17a–f** were successfully produced using a range of combinations of R^1, R^2, R^3, and R^4 groups (Table 1).

To determine the yields and purities of **17a–f** following the photolysis, the combined eluent from 20 beads of each compound was quantitatively analyzed versus an analytically pure sample of the corresponding 3,8,11-triazaspiro[5,6]dodecan-7-one.[12] Released compound yields ranged from 19% to 75% (Table 1). The purity levels of crude **17a–f** were high, which is exemplified by the HPLC chromatogram in Figure 2.

In conclusion, a robust and general combined solution-phase and solid-phase method exploiting the advantages of each technique for the synthesis of 3,8,11-triazaspiro[5,6]dodecan-7-ones has been developed. The synthesis performed well with a range of R^1, R^2, R^3, and R^4 components and provided a high level of purity. This synthetic strategy can be readily applied to additional analogs and also the construction of both parallel and combinatorial 3,8,11-triazaspiro[5,6]dodecan-7-one libraries.

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9. A typical washing protocol after a solid-phase reaction involves sequentially washing two times each with the reaction solvent, MeOH, DMF, and CH_2Cl_2. Prior to the initiation of a solid-phase reaction the resin is typically washed two times with the reaction solvent.
10. (a) Rich, D. A.; Gurwara, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 1575–1579; (b) Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, *107*, 4936–4942.
11. The Alloc protecting group was removed under the following conditions: a THF solution of 1,3-dimethylbarbituric acid (5.0 equiv) was degassed with argon prior to the addition to the resin. Tetrakis(triphenylphosphine)palladium(0) (0.25 equiv) was then added as a solid and the resulting resin suspension shaken for 18 h at 25 °C.
12. Analytical standards of **17a–f** were synthesized using the combined solution-phase and solid-phase approach described in this Letter, and purified by semi-preparative HPLC. Analytical HPLC analysis was conducted using a PDA-linked Waters Millenium 2690 and Phenomenex Luna 3um 50 × 3 mm C8 column.