Solid-Phase Synthesis of 2,3,5,6-Tetrahydro-1*H*-imidazo[1,2-*a*]benzo[*d*]-[1,3]diazepines via $Pd(OAc)_2$/$Cu(OAc)_2$-Cocatalyzed Cyclization

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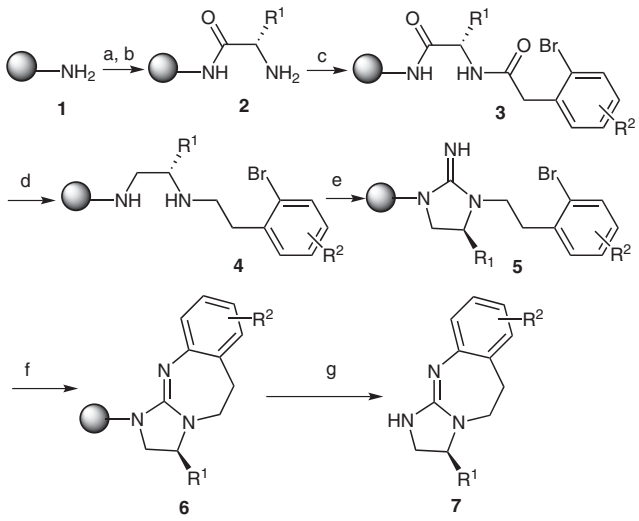
Abstract: An efficient approach for the solid-phase synthesis of 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]benzo[*d*][1,3]diazepines has been developed. It was realized by $Pd(OAc)_2$/$Cu(OAc)_2$-cocatalyzed intramolecular aryl guanidinylation.

Key words: solid-phase synthesis, 1,3-benzodiazepines, $Pd(OAc)_2$/$Cu(OAc)_2$, cyclization, guanidinylation

Combinatorial chemistry is a powerful tool for the preparation of large organic compound collections utilized in the drug discovery process.[1] Heterocyclic compounds are well known for their broad range of biological activities.[2] Thus, an ever increasing number of pharmaceutically useful heterocyclic compounds have been prepared using solid-phase approaches.[3] 1,3-Benzodiazepine derivatives possess broad pharmacological properties, such as antidepressant,[4] antihypertensive,[5] antitumor activities,[6] and dopamine antagonists.[7] In addition, guanidine-containing moieties are found in many biologically active compounds and are known to have useful therapeutic implications.[8] To this extent, it is plausible that a tricyclic fused scaffold incorporating the 1,3-benzodiazepine and guanidine moiety would possess biologically relevant properties. As part of our ongoing efforts directed toward the solid-phase synthesis of small molecules and heterocyclic compounds for discovering biologically relevant compounds,[9] herein, we report an efficient solid-phase synthetic approach for the 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]benzo[*d*][1,3]diazepines.

As outlined in Scheme 1, the parallel solid-phase synthesis of 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*] benzo[*d*]-[1,3]diazepines was carried out using the 'tea-bag' methodology.[10] Starting from (*p*-methylbenzhydrylamine) MBHA resin **1**, a variety of Boc-protected amino acids were coupled to the resin using standard coupling procedures. The Boc group was removed using 55% TFA in CH_2Cl_2. The resulting primary amine **2** was coupled with 2-bromophenyl acetic acid derivatives to provide the resin-bound compound **3**. Exhaustive reduction of the two amide bonds by treatment with BH_3–THF generated diamine **4** which possessed two secondary amines. Then the resin-bound compound **5** was obtained by cyclization with cyanogen bromide. It was reported that the arylation of guanidines can be realized by palladium- or copper-catalyzed intramolecular and intermolecular coupling of aryl halides with guanidines.[11] Following optimization of the reaction conditions, we found the resin-bound compound **6** could be obtained by treatment of **5** with $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (1 equiv), and Cs_2CO_3 (5 equiv) in DMF at 100 °C for 48 hours in good yield and purity. The reaction did not need any ligands or additives and was performed under air. The desired product was obtained following cleavage from the resin using HF for 1.5 hours at 0 °C. The results are summarized in Table 1. Eight Boc-protected amino acids and three 2-bromophenyl acetic acid derivatives were employed to illustrate the versatility of this approach. It was observed that two Boc-protected amino acids (R^1 = 2-naphthyl-CH_2, cyclohexyl-CH_2; entries 11 and 12) gave comparably low yield. In addition, 2-bromophenyl acetic acid derivatives possessed 5-Cl group at R^2 position (entry 2) provided higher yield when compared to other compounds [R^2 = H, 4,5-$(MeO)_2$; entries 1 and 3].



Scheme 1 Solid-phase synthesis of 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]benzo[*d*][1,3]diazepines **7**. *Reagents and conditions*: (a) Boc-L-AA(R^1)-OH (6 equiv, 0.1 M), HOBt (6 equiv, 0.1 M), DIC (6 equiv, 0.1 M) in DMF, r.t., 2 h; (b) 55% TFA–CH_2Cl_2, 0.5 h; (c) R^2ArCH_2COOH (10 equiv, 0.1 M), HOBt (10 equiv, 0.1 M), DIC (10 equiv, 0.1 M) in DMF, r.t., overnight; (d) BH_3–THF, 65 °C, 4 d; (ii) piperidine, 65 °C, 20 h; (e) CNBr (10 equiv, 0.1 M) in CH_2Cl_2, r.t., overnight; (f) $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (1 equiv), Cs_2CO_3 (5 equiv), DMF, 100 °C, 48 h; (g) HF, 0 °C, 1.5 h.

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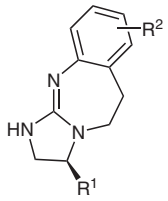
Table 1 Individual 2,3,5,6-Tetrahydro-1*H*-imidazo[1,2-*a*]benzo[*d*][1,3]diazepines



Entry	Product[12]	R^1	R^2	Yield (%)[a]	Purity (%)[b]	MW (found)[c]
1	**7a**	Me	H	77	99	202.0 $[M + 1]^+$
2	**7b**	Me	5-Cl	85	98	236.0 $[M + 1]^+$
3	**7c**	Me	4,5-$(MeO)_2$	77	90	261.9 $[M + 1]^+$
4	**7d**	H	H	76	95	188.0 $[M + 1]^+$
5	**7e**	H	5-Cl	84	98	222.0 $[M + 1]^+$
6	**7f**	Bn	5-Cl	81	98	312.0 $[M + 1]^+$
7	**7g**	*i*-Pr	4,5-$(MeO)_2$	68	92	290.1 $[M + 1]^+$
8	**7h**	*s*-Bu	H	72	98	244.0 $[M + 1]^+$
9	**7i**	*s*-Bu	5-Cl	73	97	278.0 $[M + 1]^+$
10	**7j**	*i*-Bu	H	80	96	244.0 $[M + 1]^+$
11	**7k**	2-naphthyl-CH_2	H	50	96	328.1 $[M + 1]^+$
12	**7l**	cyclohexyl-CH_2	H	58	99	284.1 $[M + 1]^+$

[a] Yields (%) are based on the weight of crude material and are relative to the initial loading of the resin.
[b] The purity of the crude material was estimated by the peak area from analytical HPLC traces at λ = 254 nm.
[c] Confirmed by mass spectra (ESI).

In summary, we have devoloped an efficient approach for the synthesis of 2,3,5,6-tetrahydro-1*H*-imidazo [1,2-*a*]-benzo[*d*][1,3]diazepines on solid phase via $Pd(OAc)_2$/$Cu(OAc)_2$-cocatalyzed intramolecular aryl guanidinylation. The screening of these potentially bioactive compounds will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Typical Procedure for the Synthesis of 7**
MBHA resin (100 mg, loading: 1.1 mmol/g) was contained in a polypropylene mesh packet. The resin was washed with

CH_2Cl_2 (2 × 5 mL) followed by neutralization with 5% DIEA in CH_2Cl_2 (3 × 5 mL) and washed with CH_2Cl_2 (2 × 5 mL). The first Boc-L-amino acid (6 equiv, 0.1 M in DMF) was coupled to MBHA resin using DIC (6 equiv) and HOBt (6 equiv) for 2 h at r.t., then the resin was washed with DMF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL). After that, the Boc group was removed with 55% TFA in CH_2Cl_2 (5 mL) for 30 min at r.t. Then the packet was washed with CH_2Cl_2 (2 × 5 mL), neutralized with 5% DIEA in CH_2Cl_2 (3 × 5 mL) and washed with CH_2Cl_2 (2 × 5 mL). The resin-bound amine was then acylated with a 2-bromo phenyl acetic acid derivative (10 equiv, 0.1 M in DMF) using DIC (10 equiv) and HOBt (10 equiv) as coupling reagents overnight. The resin was washed with DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and MeOH (5 mL × 2) and lyophilized. The afforded resin was reduced with BH_3–THF (40 equiv) at 65 °C for 4 d followed by decantation of the reaction solution and quenching with MeOH. After washing with DMF (5 mL) and MeOH (4 × 5 mL), the resin was treated with piperidine at 65 °C overnight to disproportionate the borane complex. Following decantation of the piperidine–borane solution, the resin packet was washed with DMF (4 × 5 mL), CH_2Cl_2 (4 × 5 mL), and MeOH (2 × 5 mL) and dried. The resulting resin-bound diamine was cyclized with cyanogen bromide (10 equiv, 0.1 M in CH_2Cl_2) at r.t. overnight. The resin was then washed with CH_2Cl_2 (3 × 5 mL), IPA (2 × 5 mL),CH_2Cl_2 (3 × 5 mL) and dried. To each tube was added the resin packet, $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (1 equiv), and Cs_2CO_3 (5 equiv), followed by anhyd DMF (10 mL). The tube was sealed, and the mixture was heated at 100 °C for 48 h. Following washing with DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and MeOH (2 × 5 mL), the resin was cleaved with HF at 0 °C for 1.5 h. The desired product was extracted with AcOH–H_2O (95:5) and lyophilized. The product was characterized by electrospray LC-MS under ESI conditions, ^1H and ^{13}C NMR.

Compound **7a**: ESI-MS (*m*/*z*): 202.0 [M + H^+]. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.44 (s, 1 H), 7.23–7.18 (m, 2 H), 7.13–7.12 (m, 1 H), 7.02–7.00 (m, 1 H), 4.07–4.03 (m, 1 H), 3.76–3.72 (m, 1 H), 3.55–3.47 (m, 2 H), 3.17 (dd, *J* = 9.5, 6.5 Hz, 1 H), 3.07 (ddd, *J* = 15.0, 8.5, 3.0 Hz, 1 H), 2.99 (ddd, *J* = 15.0, 6.0, 2.5 Hz, 1 H), 1.25 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.8, 137.8, 130.2, 130.1, 127.6, 123.4, 120.3, 58.9, 47.5, 46.3, 32.5, 17.9.