ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c5cc06855j

Received 14th August 2015,
Accepted 26th August 2015

DOI: 10.1039/c5cc06855j

www.rsc.org/chemcomm

Synthesis of functionalized tryptamines by Brønsted acid catalysed cascade reactions†

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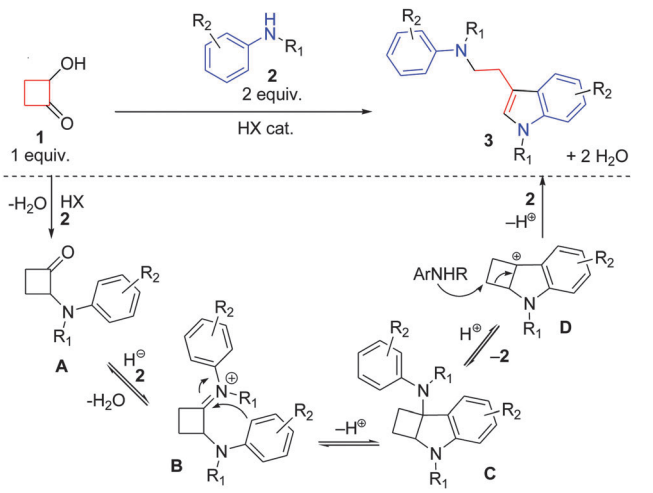
An original synthetic protocol has been developed for the preparation of highly functionalized tryptamines from 2-hydroxycyclobutanone and secondary arylamines *via* a solvent-free Brønsted acid catalysed two-step reaction sequence.

Given the ease of its preparation[1] and the chemical reactivity bestowed by the presence of two adjacent functional groups on a strained four-membered-ring,[2] 2-hydroxycyclobutanone **1** has considerable potential as a building block for organic synthesis. Some notable applications include ring cleavage and methylation to furnish an ester–aldehyde,[3] one-pot Wittig reaction-acetalization leading to an oxabicyclo[3.2.0]heptane,[4] preparation of methylenecyclobutane nucleoside analogues[5] and stereoselective organocatalysed aldol condensation reactions in the presence of L-amino acids.[6]

Recently, we discovered that 2-hydroxycyclobutanone **1** was a choice substrate for organocatalysed condensation reactions with amines, providing access to optically active 2-aminocyclobutanones.[7] Previous studies had shown us that in the presence of a Brønsted acid catalyst the cyclobutanone motif can behave as an electrophilic acceptor for intramolecular nucleophilic addition in a ring closure-ring fission process.[8] This propensity should be enhanced for a cyclobutyliminium species,[9] which led us to speculate that the reaction of 2-hydroxycyclobutanone **1** with two equivalents of a secondary arylamine **2** might deliver a one-pot cascade-reaction[10] assembly of the tryptamine molecular scaffold. According to our hypothesis (Scheme 1), a Brønsted acid catalyst[11] should promote the formation of the corresponding 2-aminocyclobutanone **A** from **1** and one equivalent of **2**. Subsequent acid-mediated condensation with a second equivalent of **2** should furnish the corresponding 2-cyclobutyliminium **B** which undergoes intramolecular ring closure to **C**. Rearrangement by an acid-induced "depart-and-return" process[8b] *via* **D** should lead to a tryptamine **3**.

To test our hypothesis we first examined the reaction between 2-hydroxycyclobutanone **1** and *N*-methyl aniline **2a**, conducted under reflux in toluene using 20 mol% of PTSA as the catalyst. We were delighted to find that the desired tryptamine product **3a** could be isolated from the reaction mixture in 55% yield (Table 1, entry 1). Changing the solvent from toluene to 1,4-dioxane, EtOH or EtOAc did not bring any appreciable improvement in the chemical yields (entries 2–4). However, a higher conversion was observed in solvent-free conditions at room temperature (entry 5), providing **3a** in 67% yield. Other Brønsted acid catalysts were evaluated in solvent-free conditions: HI (entry 6) gave a comparable result to that obtained using PTSA, whereas HBr, HCl, MsOH and TFA performed less well (entries 7–10). Further evaluation of the solvent-free reaction conditions using a higher or lower catalyst loading (entries 11 and 12) indicated that the optimum yield of **3a** was obtained in the presence of 20 mol% of PTSA.



Scheme 1 Rational design for the synthesis of tryptamines *via* a Brønsted acid-catalysed cascade reaction.

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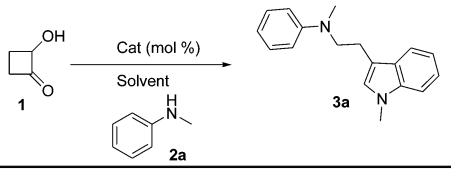
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. See DOI: 10.1039/c5cc06855j

Table 1 Initial screening studies[a]

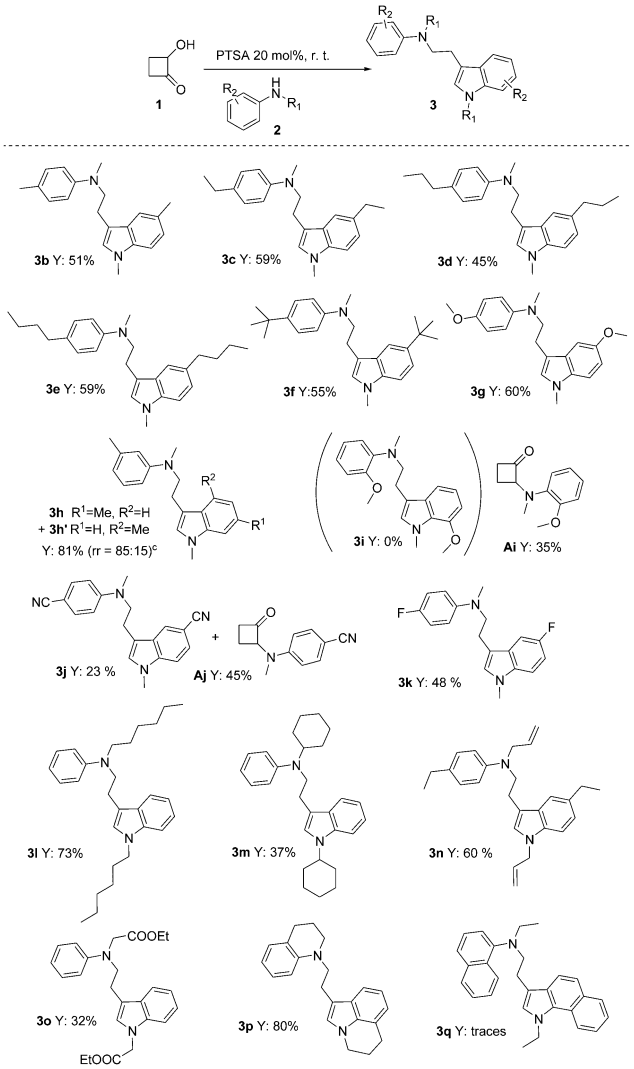


Entry	Cat. (mol%)	Solvent	Temp.	Yield **3a**[b] (%)
1[c]	PTSA (20)	Toluene	Reflux	55
2	PTSA (20)	1,4-Dioxane	Reflux	38
3	PTSA (20)	EtOH	Reflux	30
4	PTSA (20)	EtOAc	Reflux	48
5	**PTSA (20)**	**Neat**	**r.t.**	**67**
6	HI (20)	Neat	r.t.	65
7	HBr (20)	Neat	r.t.	50
8	HCl (20)	Neat	r.t.	42
9	MsOH (20)	Neat	r.t.	36
10	TFA (20)	Neat	r.t.	61
11	PTSA (10)	Neat	r.t.	53
12	PTSA (35)	Neat	r.t.	62

[a] Reactions were performed with 0.465 mmol of **1**, 0.930 mmol of **2a**, 0.093 mmol of catalyst, 0.5 mL solvent, 4 days. [b] Isolated yield after flash chromatography. [c] The reaction conducted at room temperature after 7 days gave **3a** in 52% yield associated with a significant amount of the corresponding aminocyclobutanone **Aa** (25% yield).

With the optimized reaction conditions in hand, we next examined the reaction scope using a series of secondary arylamines; results are summarized in Scheme 2. A reasonable substituent tolerance in arylamines **2** emerged, allowing access to a variety of highly functionalized tryptamines **3** with diverse ring-substituent patterns. *N*-Methyl arylamines **2b–g** bearing electron-donating groups at the *para*-position furnished the corresponding tryptamines **3b–g** in 45–60% yield. Similarly, *meta*-substituted aniline **2h** gave a good yield (81%) of the corresponding tryptamine as an inseparable mixture of the two regioisomers **3h** + **3h′**. In contrast, aniline **2i** bearing a methoxy substituent at the *ortho*-position failed to produce a tryptamine; the only compound isolated from the reaction was the intermediate 2-aminocyclobutanone **Ai** with 35% yield. *N*-Methyl arylamines **2j** and **2k** bearing electron-withdrawing groups at the *para*-position also underwent the tandem reaction to give tryptamines **3j** (23%) and **3k** (48%). In the former case, the major product was the intermediate 2-aminocyclobutanone **Aj** (45%). Other *N*-alkyl anilines were examined using the optimized reaction conditions: yields of tryptamines were good (60 and 73%) for anilines **2l** and **2n** with primary alkyl and allylic substituents respectively, while an aniline **2m** with a secondary alkyl substituent gave the corresponding tryptamine **3m** with a more moderate yield (37%). The *N*-carboethoxymethyl aniline **2o** gave tryptamine **3o** in 32% yield, showing tolerance of the ester functional group. Interestingly, the best result was obtained using tetrahydroquinoline **2p** which provided the corresponding tryptamine **3p** in 80% yield. *N*-Ethyl-1-naphthylamine **2q** was also examined but tryptamine **3q** was isolated in only trace amounts.

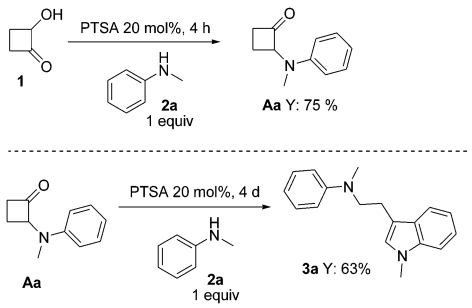
Some control experiments were carried out in order to probe the reaction mechanism (Scheme 3). Treatment of 2-hydroxycyclobutanone **1** with one equivalent of *N*-methyl aniline **2a** and 20 mol% of PTSA gave 2-aminocyclobutanone **Aa**, isolated with 75% yield after 4 h reaction time. Subsequently, **Aa** was treated



Scheme 2 Exploration of the substrate scope.[a,b] [a] Reactions were performed with 0.465 mmol of **1**, 0.930 mmol of **2**, 0.093 mmol of PTSA, room temperature, 6 days. [b] Isolated yields after flash chromatography are given. [c] The ratio of the inseparable regioisomers was determined by ^{1}H NMR analysis; regioisomers could not be unambiguously assigned.

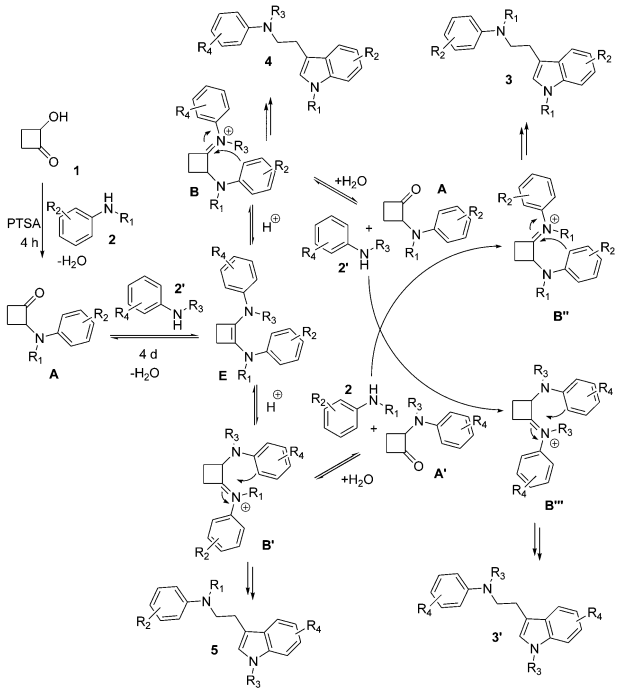
one equivalent of **2a** in the presence of PTSA (20 mol%), which led smoothly to the expected tryptamine **3a** within 4 days, in 63% isolated yield. These observations support the working mechanistic hypothesis proposed in Scheme 1: it can be reasoned that the first step of the sequence involves the formation of the 2-aminocyclobutanone intermediate **A** which subsequently undergoes in a tandem ring closure-ring fission process to form **3**. The observed formation of **Ai** and **Aj** during the respective reactions involving **2i** and **2j** is consistent with this proposal.

On the basis of the proposed mechanism, we considered that the reaction process should be tested for the synthesis of tryptamines derived from two different *N*-alkyl anilines **2** and **2′**, by employing one equivalent of each of these reagents sequentially in the one-pot procedure. Thus, in the presence of PTSA (20 mol%), 2-hydroxycyclobutanone **1** was treated with one equivalent of an *N*-methyl aniline **2** then, after 4 hours, one



Scheme 3 Control experiments.

equivalent of a different *N*-methyl aniline **2′** was added and the reaction left to proceed for 4 days. Three such **2**/**2′** aniline combinations were examined, and in each case both of the possible sequential order roles was considered; results are summarized in Scheme 4. In every case, the anticipated ''hetero-assembly'' tryptamine product **4**, with the first-added aniline incorporated as the indole core, was indeed obtained (5–44% yield). However, the isomeric tryptamine **5**, with the second-added aniline incorporated as the indole core, was also obtained (2–18%). Furthermore, a significant amount of the ''homo-assembly'' tryptamines **3** and **3′** were formed (12–39%).



2	2′	Tryptamine products (%)[b]	Unreacted **2**(%)/**2′**(%)
2a	**2b**	**3a** (23) / **3b** (39) / **4ab** (10) / **5ab** (10)	6/12
2b	**2a**	**3a** (19) / **3b** (30) / **4ab** (14) / **5ab** (6)	9/22
2a	**2l**	**3a** (19) / **3l** (22) / **4al** (5) / **5al** (12)	7/35
2l	**2a**	**3a** (19) / **3l** (24) / **4al** (17) / **5al** (5)	31/4
2a	**2p**	**3a** (20) / **3p** (13) / **4ap** (8) / **5ap** (18)[c]	11/30
2p	**2a**	**3a** (12) / **3p** (12) / **4ap** (44) / **5ap** (2)	17/13

Scheme 4 Synthesis of tryptamines derived from two different anilines using a sequential one pot procedure.[a] [a] Reaction conditions: **1** (0.465 mmol), **2** (0.465 mmol) and PTSA (0.093 mmol) were made to react for 4 h at room temperature and then, after addition of **2′** (0.465 mmol) the mixture was stirred for 4 d. [b] Reaction products were inseparable using standard chromatographic methods; conversions were calculated from analytical GC-MS data. [c] The reaction between **Aa** (0.465 mmol; pure, isolated) and **2p** (0.465 mmol), carried out over 4 d in the presence of PTSA (0.093 mmol), exhibits a similar trend: **3a** (19%) / **3p** (17%) / **4ap** (5%) / **5ap** (50%) / **2a** (6%) / **2p** (3%).

A plausible explanation is that the condensation of the initially-formed 2-aminocyclobutanone **A** with the second aniline **2′** might generate cyclobutenediamine **E**, which is the common intermediate in an acid-catalysed equilibration of two 2-aminocyclobutyliminium species **B** and **B′**. Since these cations are in equilibrium with the corresponding cyclobutanones (**A** and **A′**) and free anilines (**2** and **2′**) respectively, any combination of **A** or **A′** with an aniline **2′** or **2** now becomes possible, so that four different intramolecular ring closure-ring fission processes (*via* **B**, **B′**, **B″** or **B‴**) can be envisaged, leading to tryptamines **4**, **5**, **3** and **3′** respectively.[12]

In summary, a new solvent-free Brønsted acid catalysed cascade reaction has been established, allowing access to highly substituted tryptamines from simple starting materials in a one-pot metal-free and solvent-free process under mild conditions. To the best of our knowledge, there are no literature reports of the construction of an indole skeleton using the present strategy;[13] the use of a 4-carbon synthon to provide the indole C2, C3 and the two exocyclic centres in a tryptamine synthesis is highly original,[14] since most synthetic methods involve modifications of other indole derivatives.[15] It is noteworthy that indoles react with cyclobutanone derivatives in the presence of a Lewis acid in a quite different fashion, to give hydrocarbazoles.[16] Tryptamines are of great importance due to their wide-ranging biological activities leading to applications in medicinal chemistry and recreational use,[17] as well as serving as intermediates for the preparation of more complex heterocyclic structures. This concise approach for the assembly of tryptamine derivatives should lend itself to the creation of natural product-inspired molecular-complexity compound collections.[18]

Financial support from the MIUR, Rome, and by the University of Cagliari, Fondazione Banco di Sardegna and Sardinia Regional Government is acknowledged (P.O.R. Sardegna F.S.E. Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2007–2013-Axis IV Human Resources, Objective l.3, Line of Activity l.3.1). We are grateful to E. Kolodziej and D. Gori for timely assistance with sample analysis.

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