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A novel one-pot four-component access to tetrahydro-β-carbolines by a coupling-amination-aza-annulation-Pictet–Spengler sequence (CAAPS)†

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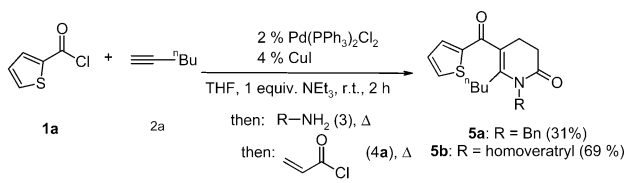
The four-component coupling-amination-aza-annulation-Pictet–Spengler (CAAPS) sequence of acid chlorides 1, terminal alkynes 2, tryptamine derivatives 6, and acryloyl chloride derivatives 4 represents a facile and rapid one-pot access to tetrahydro-β-carbolines 7 in moderate to good yields.

Multicomponent and sequential one-pot processes address very fundamental principles of synthetic efficiency and reaction design[1] and they are steadily gaining a considerable and increasing academic, economic and ecological interest. Additionally, the aspect of a modular chemistry of one-pot reactions can be readily expanded into combinatorial and solid phase syntheses[1,2] promising manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts and even novel molecule based materials. Therefore, we are designing novel multicomponent syntheses by alkyne activation[3] initiated by transition metal catalyzed CC-bond forming processes[4] like the Sonogashira coupling.[5]

Just recently, we could show that the Sonogashira coupling of acid chlorides and alkynes generating alkynones, that now open a new mode of consecutive reactions, gives rise to the formation of enaminones and pyrimidines in sequential three-component transformations.[6,7] In particular, the newly generated enaminone functionality[6,7] is electronically amphoteric and can be addressed in Michael additions, at its enamine reactivity, or even in their combination. Here, we communicate the design of the first four-component aza-annulations and a novel rapid coupling-amination-aza-annulation-Pictet–Spengler (CAAPS) sequence as a new modular entry to tetrahydro-β-carboline frameworks.

(Hetero)aryl acid chlorides **1**, terminal alkynes **2** and primary amines react in the sense of a one-pot coupling-amination (CA) sequence to furnish *Z*-configured enaminones in excellent yields.[7] Encouraged by this facile access to enaminones which are key intermediates in heterocyclic syntheses[8] we set out to probe the compatibility of a subsequent aza-annulation reaction[9] with the conditions of the CA sequence. Hence, after performing the CA reaction with thienoyl chloride (**1a**), 1-hexyne (**2a**), and benzyl amine (**3a**) or homoveratryl amine (**3b**), acryloyl chloride (**4a**) was added and after gentle heating the intermediate enaminones were smoothly converted into 5-acyl dihydropyrid-2-ones **5** that were isolated in moderate to good yield as colorless oils (Scheme 1).

The structure of the lactams **5** is unambiguously supported by the expected appearance of the characteristic proton and carbon resonances and multiplicities in the NMR spectra. Additionally, the mass spectrometric, IR spectroscopic, and combustion analytical data corroborate the suggested molecular structure of these aza-annulation products.



Scheme 1 One-pot four-component coupling-amination-aza-annulation (CAA) sequence.

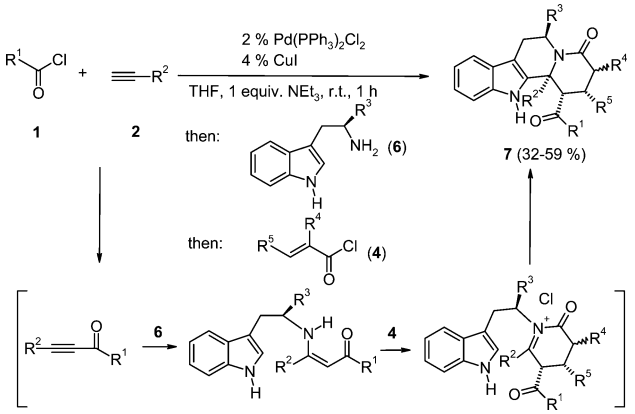
However, upon applying tryptamine (**6a**) or (*S*)-(−)-tryptophane methylester (**6b**) as primary amines in the CAA sequence the lactams **5** were not the final reaction products, but as a result of a subsequent Pictet–Spengler reaction,[10] only the indolo[2,3-a]quinolizin-4-ones **7** were isolated in moderate to good yields as colorless crystals (Scheme 2, Table 1).[11] Thus, a *N*-acyliminium cyclization[12] terminates the CAA reaction by a Pictet–Spengler cyclization[13] in the sense of a four-component coupling-aza-annulation-Pictet–Spengler sequence (CAAPS) and generates a maximum of structural complexity and diversity in a one-pot fashion.

The successful formation of the indolo[2,3-a]quinolizin-4-one core is unambiguously supported by ^{1}H NMR, ^{13}C NMR, 2D NOESY experiments, IR spectroscopy, MS spectrometry, combustion analytical data and, additionally, it is corroborated by numerous X-ray structure analyses (for **7h** see Fig. 1).‡

Interestingly, however, is the excellent diastereoselectivity of the CAAPS sequence where the R^2, acyl-R^1, and R^5 substituents are exclusively placed in a *syn–syn* arrangement (Table 1, entries 1–5, 7, 8), whereas with an R^4 substituent other than hydrogen, epimers are formed at that position with moderate selectivity (entry 6, d.r. = 4.5 : 1). Most surprisingly, with (*S*)-(−)-tryptophan methyl ester (**6b**) as tryptamine derivative the only cyclization product isolated in 45% yield is the tetrahydro-*β*-carboline **7h** (entry 8, Fig. 1) that is formed as a single diastereomer.

Tetrahydro-β-carbolines not only constitute subunits in numerous alkaloids[14] but they are also templates for drug discovery and have been used as scaffolds for combinatorial libraries. They display a pronounced antitumor and antiviral activity[15] and some of them have been shown to efficiently inhibit monoamine oxidase A[16] and bind with nanomolar affinity to serotonin receptors in the central nervous system.

In conclusion, the four-component CAAPS sequence where five bonds are formed in a one-pot reaction proceeds with reasonable yields and delivers, starting from electronically diverse acid chlorides and aliphatic, aromatic alkynes as well as (TMS)acetylene, a broad variety of tetrahydro-β-carbolines **7**. Studies scouting the scope and limitation of this novel tetrahydro-β-carboline



Scheme 2 One-pot four-component coupling-aza-annulation-Pictet–Spengler sequence (CAAPS).

† Electronic supplementary information (ESI) available: Experimental details and X-ray structure data for **7h**. See http://www.rsc.org/suppdata/cc/b4/b404559a/

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Table 1 Coupling-amination-aza-annulation-Pictet–Spengler (CAAPS) sequence to indolo[2,3-a]quinolizin-4-ones **7**

Entry	Acid chloride **1**	Alkyne **2**	Tryptamine **6**	α,β-Unsaturated acid chloride **4**	Tetrahydro-β-carboline **7** (yield)
1[a]	R^1 = 2-thienyl (**1a**)	R^2 = ^{n}Bu (**2a**)	R^3 = H (**6a**)	R^4 = R^5 = H (**4a**)	**7a** (R^1 = 2-thienyl, R^2 = ^{n}Bu , R^3 = R^4 = R^5 = H, 52%)
2[a]	R^1 = *p*-$O_2NC_6H_4$ (**1b**)	**2a**	**6a**	**4a**	**7b** (R^1 = *p*-$O_2NC_6H_4$, R^2 = ^{n}Bu , R^3 = R^4 = R^5 = H, 43%)
3[a]	R^1 = *p*-$MeOC_6H_4$ (**1c**)	**2a**	**6a**	**4a**	**7c** (R^1 = *p*-$MeOC_6H_4$, R^2 = ^{n}Bu, R^3 = R^4 = R^5 = H, 59%)
4[a]	**1a**	R^2 = Ph (**2b**)	**6a**	**4a**	**7d** (R^1 = 2-thienyl, R^2 = Ph, R^3 = R^4 = R^5 = H, 41%)
5[a]	**1a**	**2a**	**6a**	R^4 = H, R^5 = CH_3 (**4b**)	**7e** (R^1 = 2-thienyl, R^2 = ^{n}Bu, R^3 = R^4 = H, R^5 = CH_3, 50%)
6[a]	**1a**	**2a**	**6a**	R^4 = CH_3, R^5 = H (**4c**)	**7f** (R^1 = 2-thienyl, R^2 = ^{n}Bu, R^3 = R^5 = H, R^4 = CH_3, 54%, *syn–syn*/*syn–anti* = 4.5 : 1)[b]
7[a]	**1a**	R^2 = TMS (**2c**)	**6a**[c]	**4a**	**7g** (R^1 = 2-thienyl, R^2 = R^3 = R^4 = R^5 = H, 32%)
8[d]	**1a**	**2a**	R^3 = CO_2CH_3 (**6b**)[e]	**4a**	**7h** (R^1 = 2-thienyl, R^2 = ^{n}Bu, R^3 = CO_2Me, R^4 = R^5 = H, 45%)

[a] In THF. [b] The mixture of diastereomers was separated by column chromatography. [c] After the coupling step 1.00 mmol of an aqueous TBAF solution was added prior to the addition of **6a**. [d] In toluene. [e] Additionally, together with 2.00 mmol of **6b** (as a hydrochloride), 0.28 mL (2.00 mmol) of triethylamine were added.

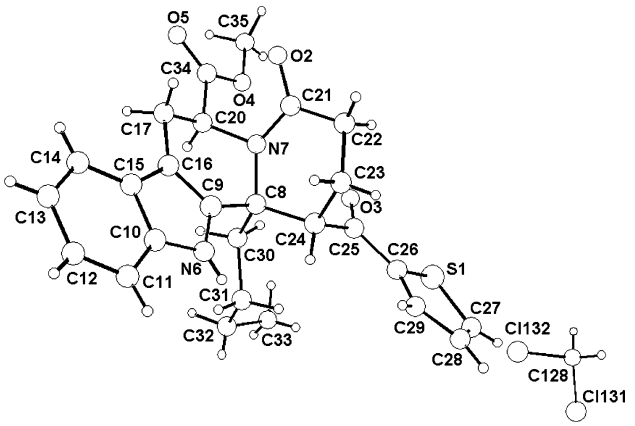

Fig. 1 Molecular structure of **7h** (R^1 = 2-thienyl, R^2 = nBu, R^3 = CO_2CH_3, R^4 = R^5 = H). For a better overview only one of both independent host molecules is shown.

synthesis and the concomitant enhancement of molecular diversity in pharmaceutically interesting targets are currently underway.

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Notes and references

‡ Crystal data **7h**: $C_{26}H_{28}N_2O_4S{\cdot}CH_2Cl_2$, M = 549.5, monoclinic, space group $P2_1$, a = 12.022(1), b = 14.950(1), c = 14.663(1) Å, α = 90.0, β = 94.869(2), γ = 90.0°, V = 2625.9(4) Å^3, T = 100(2) K, Z = 4, ρ = 1.390 g cm^{-3}, crystal dimensions 0.21 × 0.15 × 0.12 mm^3, Mo K_α radiation, μ = 0.364 mm^{-1}, λ = 0.71073 Å. Data were collected on a Bruker Smart APEX diffractometer and a total of 10561 of the 23151 reflections were unique [R(int) = 0.0423]. Refinement on F^2, $wR2$ = 0.107 (observed reflections), $R1$ = 0.050 for [$I > 2\sigma(I)$]. CCDC 235421. See http://www.rsc.org/suppdata/cc/b4/b404559a/ for crystallographic data in .cif or other electronic format.

1 For recent reviews, see *e.g.*: I. Ugi, A. Dömling and B. Werner, *J. Heterocycl. Chem.*, 2000, **37**, 647; L. Weber, K. Illgen and M. Almstetter, *Synlett*, 1999, 366.

2 S. Kobayashi, *Chem. Soc. Rev.*, 1999, **28**, 1.

3 See *e.g.*: A. S. Karpov, F. Rominger and T. J. J. Müller, *J. Org. Chem.*, 2003, **68**, 1503; T. J. J. Müller, J. P. Robert, E. Schmälzlin, C. Bräuchle and K. Meerholz, *Org. Lett.*, 2000, **2**, 2419; T. J. J. Müller, M. Ansorge and D. Aktah, *Angew. Chem., Int. Ed.*, 2000, **39**, 1253.

4 For recent reviews on transition metal assisted sequential transformations, see *e.g.*: G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem.*, 2003, 4101; G. Battistuzzi, S. Cacchi and G. Fabrizi, *Eur. J. Org. Chem.*, 2002, 2671.

5 For a recent review, see *e.g.*: K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46.

6 A. S. Karpov and T. J. J. Müller, *Org. Lett.*, 2003, **5**, 3451.

7 A. S. Karpov and T. J. J. Müller, *Synthesis*, 2003, 2815.

8 For recent reviews on the synthetic potential of enaminones in heterocycle syntheses, see *e.g.*: Y. V. Smirnova and Z. A. Krasnaya, *Russ. Chem. Rev.*, 2000, **69**, 1021; J. P. Michael, C. B. De Koning, D. Gravestock, G. D. Hosken, A. S. Howard, C. M. Jungmann, R. W. M. Krause, A. S. Parsons, S. C. Pelly and T. V. Stanbury, *Pure Appl. Chem.*, 1999, **71**, 979; P. Lue and J. V. Greenhill, *Adv. Heterocycl. Chem.*, 1997, **67**, 207.

9 For recent examples of aza-annulations, see *e.g.*: K. Paulvannan and T. Chen, *J. Org. Chem.*, 2000, **65**, 6160; P. Benovsky, G. A. Stephenson and J. R. Stille, *J. Am. Chem. Soc.*, 1998, **120**, 2493.

10 For a recent review, see *e.g.*: E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797.

11 Typical procedure (Compound **7c**): in a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed THF or toluene. Then 0.14 mL (1.00 mmol) of triethylamine, as well as 171 mg (1.00 mmol) of **1c** and 0.12 mL (1.05 mmol) of **2a** were successively added to the solution. The reaction mixture was stirred at room temperature for 1 h. Then, 320 mg (2.00 mmol) of tryptamine (**6a**) were added and the reaction mixture was heated to 70 °C and maintained at this temperature over 10 h. Then, 0.41 mL (5.00 mmol) of acryloyl chloride (**4a**) was added and the reaction mixture was heated to 70 °C and maintained at this temperature over 3 h. The reaction mixture was diluted with methanol and stirred for 10 min. Then, after workup and chromatography (silica gel, diethyl ether) 254 mg (59%) of the analytically pure tetrahydro-β-carboline **7c** was obtained as colorless crystals, mp. 201–202 °C, $[\alpha]_D^{24}$ +178° (c = 2.0, CH_2Cl_2). R_f = 0.25 (diethylether). ^{1}H NMR ($CDCl_3$, 300 MHz): δ, 0.85 (t, J, = 7.0 Hz, 3 H), 1.05–1.40 (m, 4 H), 1.96–2.12 (m, 1 H), 2.20–2.40 (m, 2 H), 2.75–3.07 (m, 6 H), 3.74 (s, 3 H), 3.93 (dd, J, = 13.2 Hz, J, = 4.9 Hz, 1 H), 5.23–5.31 (m, 1 H), 6.74 (d, J, = 9.0 Hz, 2 H), 7.04–7.17 (m, 3 H), 7.46–7.52 (m, 1 H), 7.66 (d, J, = 9.0 Hz, 2 H), 8.27 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ, 13.9 (CH_3), 20.9 (CH_2), 21.5 (CH_2), 23.2 (CH_2), 27.2 (CH_2), 29.6 (CH_2), 35.7 (CH_2), 39.8 (CH_2), 52.6 (CH), 55.3 (CH_3), 62.0 (C_{quat}), 110.7 (C_{quat}), 111.0 (CH), 113.7 (CH), 118.0 (CH), 119.3 (CH), 121.8 (CH), 125.9 (C_{quat}), 129.4 (C_{quat}), 130.3 (CH), 134.3 (C_{quat}), 135.7 (C_{quat}), 163.7 (C_{quat}), 169.6 (C_{quat}), 201.5 (C_{quat}). Anal. calcd. for $C_{27}H_{30}N_2O_3$ (430.6): C 75.32, H 7.02, N 6.51. Found: C 74.93, H 7.01, N 6.46%.

12 For a recent review on cyclization of *N*-acyliminium ions, see *e.g.*: B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431.

13 The aza-annulation-Pictet–Spengler reaction was reported last year independently from our group: M. M. Abelman, J. K. Curtis and D. R. James, *Tetrahedron Lett.*, 2003, **44**, 6527.

14 For overviews, see *e.g.*: E. Breitmaier, *Alkaloide*, Teubner Studienbücher, Stuttgart, 1997, p. 52; K. Stuart and R. Woo-Ming, *Heterocycles*, 1975, **3**, 223.

15 For reviews, see *e.g.*: S. Urban, S. J. H. Hickford, J. W. Blunt and M. H. G. Munro, *Curr. Org. Chem.*, 2000, **4**, 765; J. B. Hudson, *Antiviral Res.*, 1989, **12**, 55; D. J. McKenna and G. H. Towers, *J. Psychoact. Drugs*, 1984, **16**, 347.

16 B. T. Ho, *J. Pharm. Sci.*, 1972, **61**, 821.