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Tetrahydropyridine (THP) ring expansion under the action of activated terminal alkynes. The first synthesis and X-ray crystal structure of tetrahydropyrimido[4,5-*d*]azocines

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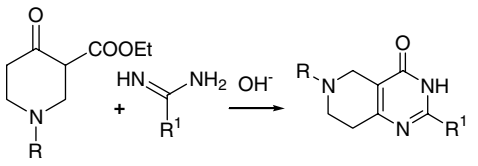
Abstract—Tetrahydropyridopyrimidines (THPPm) **1**–**3** underwent tandem cleavage–cyclization piperidine ring enlargement under the action of terminal activated alkynes to produce tetrahydropyrimido[4,5-*d*]azocines **4**–**7** in good preparative yields. The latter compounds are representatives of a new heterocyclic system.

Medium-sized N-containing heterocycles, in particular eight-membered rings, are key structures of various structurally remarkable natural products.[1–3] They are also frequently used as precursors in syntheses of biologically active compounds. Annulated azocines have recently been demonstrated to possess substantial bioactivity as preventatives of urinary disturbance,[4] AChE inhibitors[5] and 17-β-hydroxysteroid dehydrogenase inhibitors.[6] As the direct formation of these ring sizes from acyclic precursors is entropically and enthalpically disfavored, the efficient construction of medium-sized cycles is a challenge and has therefore attracted considerable attention during the past years. We have recently reported THP ring enlargement in tetrahydropyrrolopyridines and tetrahydrocarbolines[7] and unusual Stevens rearrangement in benzo[*b*]naphthyridines under the action of dimethyl acetylenedicarboxylate (DMAD).[8] Fused pyrimidines are common sources for the development of new therapeutic agents and due to the fact that only a few examples of pyrimidoazocines are known,[9,10] we were interested in developing an efficient synthetic procedure for the synthesis of pyrimidoazocine derivatives. We now report a new one-pot procedure for the synthesis of previously unknown tetrahydropyrimido[4,5-*d*]azocines starting from readily available tetrahydropyridopyrimidines (THPPm) derivatives.

Tetrahydropyrido[4,3-*d*]pyrimidines **1**–**3** were synthesized according to the procedure previously described[11] (Scheme 1).

Compounds **1**–**3** were treated[12] with ethyl propiolate or methyl propiolate in dry methanol at 25 °C. In all cases the reaction proceeded smoothly, giving azocines **4**–**6**[13–15] as the only products (Scheme 2).

The structure of compound **5** was investigated by X-ray diffraction.[16] Suitable crystals were obtained by recrystallization from methanol by slow evaporation at room temperature. The refined X-ray crystal structure of **5** is shown in Figure 1. The conformation of the eight-membered ring is a twisted bath, in which the C(1), C(4), N(1), and C(7) atoms are almost coplanar, whilst the C(2), C(3), C(8), and C(9) atoms are located in the same



1 R=Me, R^1=Ph (59%)
2 R=Bn, R^1=Ph (79%)
3 R=Bn, R^1=Me (62%)

Scheme 1.

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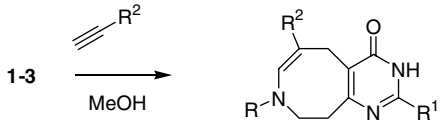


4 R=Me, R^1=Ph, R^2=CO_2Et (57%)
5 R=Bn, R^1=Ph, R^2=CO_2Me (81%)
6 R=Bn, R^1=Me, R^2=CO_2Et (67%)

Scheme 2.

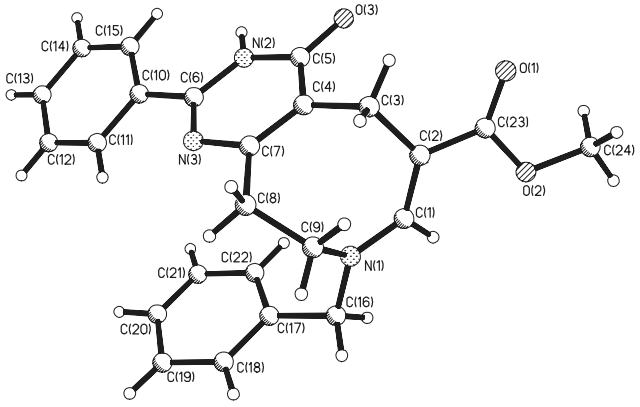
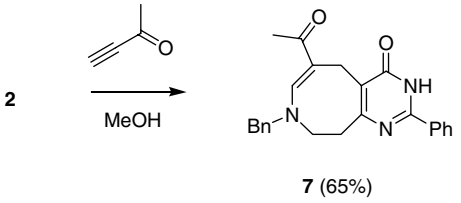


Figure 1.

direction from this plane within 1.11, 1.25, 1.27, and 1.26 Å, respectively.

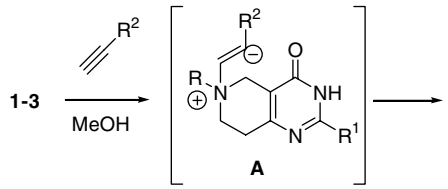
In order to determine the scope and limitations of this reaction, we examined the reactivity of three other terminal alkynes (phenylacetylene, propiolaldehyde diethyl acetal, and 3-butyn-2-one) toward compound **2**. While the first two alkynes were unreactive (only tar-like products and unreacted **2** were isolated even after 24 h of refluxing in methanol), the reaction with 3-butyn-2-one proceeded smoothly, providing azocine **7**[17] in 65% yield (Scheme 3).

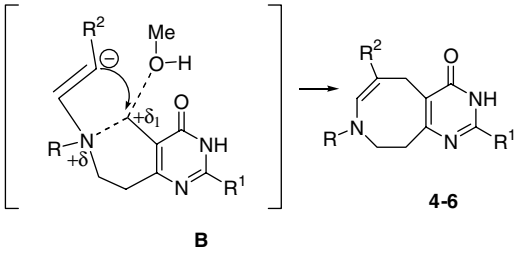
Our attempts to use other solvents (MeCN, THF, and DMF) in this reaction failed, in all cases multicomponent unseparable reaction mixtures were formed. We presume, that the reaction proceeds via the intermediate zwitterion **A**, resulting from Michael addition of the tertiary nitrogen to the alkyne. Cleavage of the C(1)–N bond occurs via the formation of six-membered transition state **B** in which a molecule of alcohol facilitates the S_N reaction (Scheme 4).



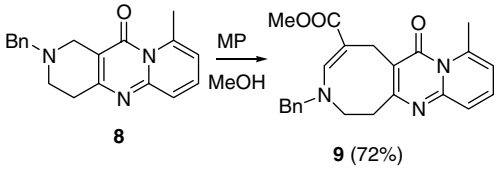
7 (65%)

Scheme 3.





Scheme 4.



Scheme 5.

To see whether this piperidine ring enlargement is general for the THPPm family, we carried out the reaction of a trycyclic derivative **8**[18] with methyl propiolate (MP) in methanol (Scheme 5).

Analogous to the above results, azocine **9**[17] was isolated in 72% yield.

In conclusion, using a new, alkyne-induced piperidine ring enlargement reaction, we have elaborated an effective synthetic pathway toward the previously unknown tetrahydropyrimido[4,5-*d*]azocine system.

Acknowledgements

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12. General experimental procedure: To a stirred solution of pyridopyrimidine **1**–**3** (1 mmol) in 15 mL of methanol at 25 °C, 1.2 mmol of ethyl propiolate was added and stirring was continued for an additional 3 h (TLC monitoring). Methanol was evaporated under reduced pressure and the resulting residues were recrystallized from ethanol to give compounds **4**–**6**.
13. **Ethyl 8-methyl-4-oxo-2-phenyl-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6-carboxylate 4**: Pale yellow crystals, mp 133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 8.30 (d, $J = 7.2$ Hz, 2H), 7.68 (m, 2H), 7.54 (m, 1H), 7.43 (s, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.06 (s, 2H), 3.80 (t, $J = 6.4$ Hz, 2H), 3.40 (t, $J = 6.4$ Hz, 2H), 3.00 (s, 3H), 1.16 (t, $J = 7.2$ Hz, 3H). EIMS: *m*/*z* (%): 339 (M^+, 5), 309 (20), 295 (100), 267 (25), 142 (45), 114 (30), 104 (45), 84 (22), 70 (25), 59 (20), 42 (60), 29 (50). Anal. Calcd For $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.94; H, 6.12; N, 12.27.
14. **Methyl 8-benzyl-4-oxo-2-phenyl-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6-carboxylate 5**: Yellow crystals, mp 245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.26 (d, $J = 7.8$ Hz, 2H), 7.68 (m, 2H), 7.66 (s, 1H), 7.56 (m, 1H), 7.21–7.15 (m, 5H), 4.35 (s, 2H), 4.08 (s, 2H), 3.81 (t, $J = 7.1$ Hz, 2H), 3.66 (s, 3H), 3.20 (t, $J = 7.1$ Hz, 2H). EIMS: *m*/*z* (%): 401 (M^+, 15), 341 (15), 310 (15), 91 (100), 65 (25). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2, 162.2, 152.8, 151.8, 148.2, 137.2, 132.1, 131.5, 129.1 (2CH), 128.8, 127.9 (2CH), 127.7 (2CH), 127.5 (2CH), 103.1, 95.6, 61.0, 51.1, 48.4, 39.4, 20.2. IR (KBr) 1632 and 1575 cm^{-1}. Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.75; H, 5.78; N, 10.40.
15. **Ethyl 8-benzyl-2-methyl-4-oxo-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6-carboxylate 6**: White crystals, mp 209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 7.62 (s, 1H), 7.30–7.10 (m, 5H), 4.32 (s, 2H), 4.17 (q, $J = 7.0$ Hz, 2H), 3.96 (s, 2H), 3.75 (t, $J = 6.4$ Hz, 2H), 3.07 (t, $J = 6.4$ Hz, 2H), 2.36 (s, 3H), 1.27 (t, $J = 7.0$ Hz, 3H). EIMS: *m*/*z* (%): 353 (M^+, 10), 279 (25), 216 (12), 188 (12), 161 (15), 91 (100). IR (KBr) 1692, 1655 and 1608 cm^{-1}. Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.83; H, 6.48; N, 11.75.
16. Crystal structure analysis for **5**: $C_{24}H_{23}N_3O_3$, $M_r = 401.45$ g mol^{-1}, triclinic, space group *P*-1, $a = 8.5060(17)$, $b = 11.060(2)$, $c = 11.261(2)$ Å, $\alpha = 89.41(3)°$, $\beta = 79.27(3)°$, $\gamma = 86.66(3)°$, $V = 1039.1(4)$ Å^3, $Z = 2$, $\rho = 1.283$ g cm^3, $\mu = 0.086$ cm^{-1}, $F(000) = 424$, crystal size: $0.43 \times 0.27 \times 0.14$ mm. Crystal data was collected on a Cad-4 diffractometer (λMoK_α radiation, graphite monochromator; ω scanning, $2\theta_{max} = 50°$). A total of 3649 reflections ($1.84° < \theta < 25.17°$) were collected of which 3627 were unique ($R(int) = 0.0958$). The structure was solved with the program SHELXS-97[19] and refined using SHELXL-97[20] to $R_1 = 0.0520$ and $wR(F^2) = 0.1284$ for 1740 reflections with $I > 2\sigma(I)$; max\min residual electron density 0.279 and -0.221 e Å^{-3}. Crystallographic data (excluding structure factors) for compound **5** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 287968.
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