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A novel four component one-pot access to pyrindines and tetrahydroquinolines†

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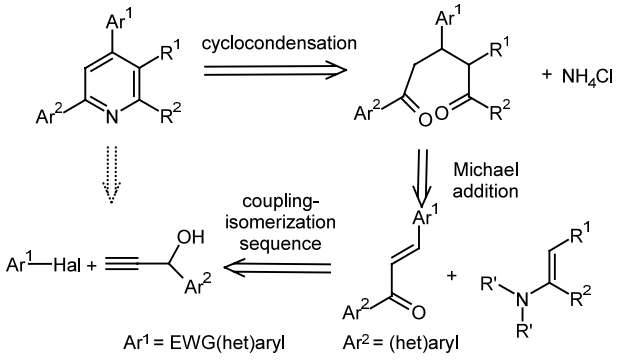
Abstract—Dihydropyrindines and tetrahydroquinolines, i.e. cyclopentyl and cyclohexyl annealed pyridines, can be synthesized in good yields in a one-pot three-step four-component process by a coupling–isomerization–Stork–enamine alkylation–cyclocondensation sequence of an electron poor (hetero)aryl halide, a terminal propargyl alcohol, a cyclic *N*-morpholino alkene and ammonium chloride. The structures of the 1,5-diketone **4d** and the tetrahydroquinoline **5c** were additionally supported by X-ray structure analyses.

Among six-membered aromatic heterocycles the pyridyl core[1] adopts a central and peculiar role. In nature, pyridine is the constituting structural unit in the coenzyme vitamin B_6 family (pyridoxal, pyridoxol, pyridoxamine) and an important subunit in numerous alkaloids.[2] However, it is also used as a versatile building block in the syntheses of natural products and as a ligand in supramolecular coordination chemistry, pyridine derivatives find broad applications. In pharmaceutical chemistry, highly substituted[3] and annealed[4] pyridines, like pyrindines and tetrahydroquinolines, have recently gained considerable interest as antiarteriosclerotics since they efficiently inhibit HMG-CoA reductase and cholesterol transport proteins. Besides, the classes of pyrindine and tetrahydroquinoline derivatives additionally display antimycobacterial,[5] fungicidal and bactericidal,[6] antiulcer[7] and anti-inflammatory activities.[8] There are numerous synthetic approaches to highly substituted pyridines; however, novel multicomponent strategies, comparable to the powerful, classical Hantzsch dihydropyridine synthesis,[9] remain particularly challenging. The facile access to unsymmetrical pyridines by the cocondensation of Michael acceptors with enols, enamines or stabilized ylids and ammonia[10] represents an intriguing starting point for the development of a novel multicomponent reaction, in particular, with respect to the generation of combinatorial libraries. Recently, we found that a palladium–coppercatalyzed domino coupling–isomerization (CI) sequence of electron-deficient halogen substituted π-systems and 1-aryl prop-2-yn-1-ols furnishing 1,3-di(hetero)aryl enones (i.e. chalcones)[11] opens a very efficient entry to three and four component one-pot syntheses of various heterocycles.[11–14] Using this new and unusual chalcone synthesis with its in situ generated Michael acceptor functionality as a pivotal point to pharmaceutically relevant heterocycles, we now communicate first synthetic studies on sequential enamine additions leading to 1,5-diketones and the development of a novel one-pot four component pyridine annellation based upon a CI–enamine addition–cyclocondensation sequence.

Our retrosynthetic analysis based upon the CI-approach (Scheme 1) suggests 1,5-diketones as key intermediates[15] on the way to highly substituted pyridines. As a consequence, we first tested the Stork enamine alkylation[16] with the in situ formed chalcones.



Scheme 1. Retrosynthetic concept for a four component pyridine synthesis.

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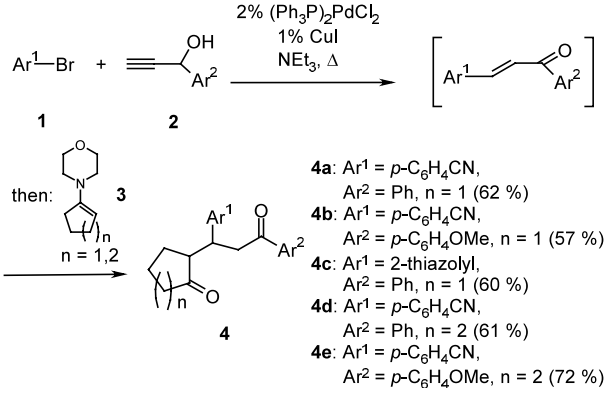
Thus, we submitted *p*-bromo benzonitrile (**1a**), or 2-bromo thiazole (**1b**), aryl propynols **2**,[17] and after some reaction time cyclic enamines **3** like 1-morpholino cyclopentene or hexene, respectively, to the reaction conditions of the Sonogashira coupling in boiling triethylamine. After aqueous workup of an initially formed enamine species, in all cases the light yellow 1,5-diketones **4** were obtained in 57–72% yield as crystalline solids (Scheme 2).[18,19]

The NMR spectroscopic data support the formation of the 1,5-diketones, in particular, in the ^{13}C NMR spectra of **4** by the indicative appearance of the two significant carbonyl resonances at δ 195 for the arylalkyl ketone and at δ 219 for the cycloalkanone. Interestingly, the formation of diastereomeric 1,5-diketones with a diastereomeric ratio ranging from 2:1 to 4:1 can be observed only in the case of the cyclopentenone derivatives **4a**–**c**. Furthermore, the structure of **4** was unambiguously supported by an X-ray crystal structure analysis (Fig. 1) of compound **4d**.[20]

Finally, we have combined the one-pot CI–Stork–enamine–alkylation reaction with the amine cyclization for designing a novel four-component pyridine synthesis. Thus, applying *p*-bromo benzonitrile (**1a**) and aryl propynols **2** to the conditions of the chalcone formation, and after some reaction time adding cyclic enamines **3** to the reaction mixture and, finally, adding benzyl amine or ammonium chloride in the presence of acetic acid the annealed pyridines **5**, i.e. pyrindines and tetrahydroquinolines were formed in moderate to good yields as colorless crystals (Scheme 3).[18,21]



Scheme 2. Three-component 1,5-diketone synthesis based upon a coupling–isomerization–enamine addition sequence.

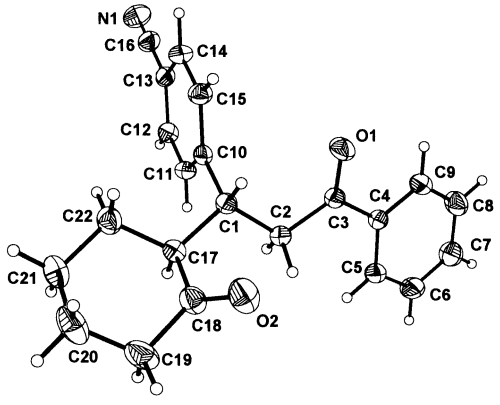
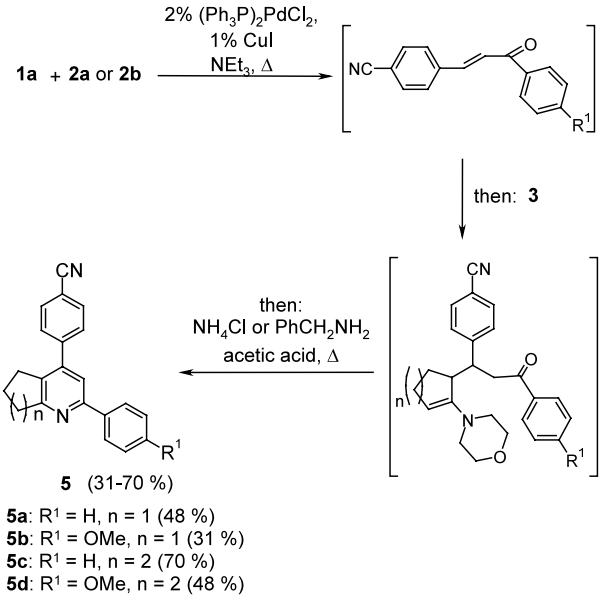


Figure 1. ORTEP plot of compound **4d**.

The NMR spectroscopic and combustion analytical data as well as an X-ray structure analysis[20] of the tetrahydroquinoline **5c** (Fig. 2) strongly support the successful four-component one-pot synthesis of pyrido cyclopentanes and cyclohexanes **5**.

Presumably, the enamine formed in the Stork enamine alkylation step is protonated by acetic acid to give a reactive electrophilic iminium ion that now participates in the concluding cyclocondensation step. However, it is still remarkable and a subject of current investigations why in the formation of the pyrindine **5b**, under these reaction conditions, the application of benzyl amine as a source of nitrogen leads to a debenzylation



Scheme 3. Four-component synthesis of pyrindines and tetrahydroquinolines based upon a CI–enamine addition–cyclocondensation sequence.

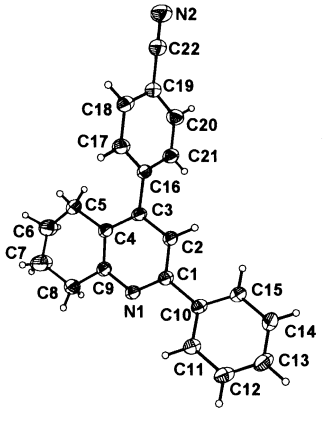


Figure 2. ORTEP plot of compound **5c**.

with concomitant aromatization rather than to the formation of the dihydropyridines. As a working hypothesis the presence of palladium and copper species as dehydrogenation catalysts will be examined in stepwise model reactions and reported in due course.

In conclusion, this preliminary study shows that the mild reaction conditions of the CI sequence of electron poor (hetero)aryl halides with 1-aryl propargyl alcohols giving rise to chalcones can be extended to a one-pot three-component synthesis of 1,5-diketones applying a Stork enamine alkylation with morpholino cyclopentenes and cyclohexenes and, even further, to a one-pot four-component synthesis of the pharmaceutically important classes of pyrindines and tetrahydroquinolines. This methodology not only combines modern catalytic cross-coupling reactions with classical cyclocondensations, but rather opens one-pot synthetic strategies as a consequence of mild reaction conditions and functional group compatibility. Further studies directed to exploit and extend this novel one-pot heterocycle synthesis to pyridines in general and their pharmaceutical evaluation are currently underway.

Supplementary material

Tables of data collection parameters, bond lengths and angles, positional and thermal parameter, and least-squares planes for **4f** and **6b**.

Acknowledgements

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18. All new compounds have been fully characterized spectroscopically and by correct elemental analysis.
19. **Typical procedure (4e)**: A mixture of 364 mg (2.00 mmol) of **1a**, 340 mg (2.10 mmol) of 1-(*p*-methoxy)phenyl

propargyl alcohol (**2b**), 28 mg (0.04 mmol) of $Pd(PPh_3)_2Cl_2$ and 4 mg (0.02 mmol) of CuI in 4 mL of degassed triethylamine/THF (3:1) or 4 mL of degassed triethylamine under nitrogen was heated to reflux temperature for 12 h. After cooling to room temperature, 380 mg (2.3 mmol) of *N*-morpholino cyclohexene (**3b**) in 1 mL of triethylamine was added to the reaction mixture and heating to reflux temperature for 46 h, work up, chromatography on silica gel (cyclohexane/ethylacetate 2:1) and recrystallization from ethanol gave 519 mg (72%) of **4e** isolated as light yellow crystals. Mp 154–155°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16–1.28 (m, 1H), 1.56–1.82 (m, 4H), 2.02 (d, $J=7.4$ Hz, 1H), 2.24–2.51 (m, 2H), 2.74 (td, $J=9.8$ Hz, $J=4.9$ Hz, 1H), 3.21 (dd, $J=9.8$ Hz, $J=9.8$ Hz, 1H), 3.50 (dd, $J=4.0$ Hz, $J=4.0$ Hz, 1H), 3.75–3.84 (m, 1H), 3.84 (s, OCH_3, 3H), 6.89 (d, $J=8.7$ Hz, 2H), 7.33 (d, $J=8.2$ Hz, 2H), 7.54 (d, $J=8.0$ Hz, 2H), 7.89 (d, $J=8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.43 (CH_2), 28.29 (CH_2), 32.48 (CH_2), 41.19 (CH), 42.43 (CH_2), 42.89 (CH_2), 55.05 (CH), 55.34 (OCH_3), 110.24 ($C_{quat.}$), 113.61 (CH), 118.74 ($C_{quat.}$), 129.26 (CH), 129.60 ($C_{quat.}$), 130.27 (CH), 132.06 (CH), 148.02 ($C_{quat.}$), 163.42 ($C_{quat.}$), 196.40 ($C_{quat.}$), 212.31 ($C_{quat.}$). EI MS (70 eV, m/z (%)): 361 (M^+, 1), 263 ($M^+-C_6H_8O$, 37), 211 ($M^+-C_9H_{10}O_2$, 20), 150 ($C_9H_{10}O_2^+$, 59), 135 ($C_8H_7O_2^+$, 100), 77 ($C_6H_5^+$, 19). Anal. calcd for $C_{23}H_{23}NO_3$ (361.44): C, 76.43; H, 6.41; N, 3.88. Found: C, 76.10; H, 6.37; N, 3.86%.

20. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC no. 187789 (**4f**) and CCDC no. 187790 (**6b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).
21. **Typical procedure (5c)**: A mixture of 364 mg (2.00 mmol) of **1a**, 280 mg (2.10 mmol) of 1-phenyl propargyl alcohol (**2a**), 28 mg (0.04 mmol) of $Pd(PPh_3)_2Cl_2$ and 4 mg (0.02 mmol) of CuI in 4 mL of degassed triethylamine/THF (3:1) or 4 mL of degassed triethylamine under nitrogen was heated to reflux temperature for 12 h. After cooling to room temperature, 460 mg (2.75 mmol) of *N*-morpholino cyclohexene (**3b**) in 1 mL of triethylamine was added to the reaction mixture and heating to reflux temperature was continued for 16 h. Then, after cooling to room temperature, 428 mg (8 mmol) of ammonium chloride and 5 mL of acetic acid were added and the mixture was heated to reflux temperature for 14 h to furnish after workup, chromatography and recrystallization from ethanol, 432 mg (70%) of analytically pure **5c** as colorless crystals. Mp 194–195°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.77 (m, $J=7.0$ Hz, 2H, CH_2), 1.95 (m, $J=6.0$ Hz, 2H, CH_2), 2.59 (t, $J=6.4$ Hz, 2H, CH_2), 3.10 (t, $J=6.6$ Hz, 2H, CH_2), 7.26 (s, 1H), 7.34–7.50 (m, 5H), 7.75 (dd, $J=8.6$ Hz, $J=2.0$ Hz, 2H), 7.96 (dd, $J=8.0$ Hz, $J=1.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.84 (CH_2), 22.91 (CH_2), 27.14 (CH_2), 33.26 (CH_2), 111.72 ($C_{quat.}$), 118.33 (CH_2), 118.54 ($C_{quat.}$), 126.77 (CH_2), 127.83 ($C_{quat.}$), 128.66 (CH), 128.70 (CH), 129.37 (CH), 132.16 (CH_2), 139.22 ($C_{quat.}$), 144.45 ($C_{quat.}$), 148.24 ($C_{quat.}$), 154.56 ($C_{quat.}$), 158.10 ($C_{quat.}$). EI MS (70 eV, m/z (%)): 310 (M^+, 92), 309 (M^+-H, 100). Anal. calcd for $C_{22}H_{18}N_2$ (310.40): C, 85.13; H, 5.85; N: 9.02. Found: C, 84.80; H, 5.87; N, 8.94%.