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Synthetic methods for γ-lactam and pyrrole derivatives exploiting a three-component coupling strategy

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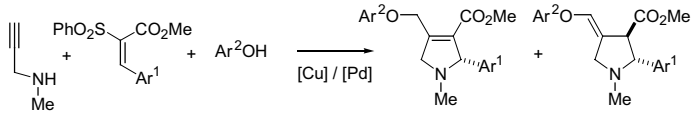
Dedicated to the memory of Odile Miani

Abstract—4-Aryloxymethyl-3-pyrrolines and their isomeric pyrrolidines—assembled via a one-pot, three-component coupling of propargylic amines, vinyl sulfones, and phenols—may be elaborated further to provide an easy access to 2,4-disubstituted pyrrole-3-carboxylates and 3,4-disubstituted pyrrolidin-2-ones. The latter were prepared by means of an unprecedented rearrangement process involving hydrogenolysis of 2-aryl pyrrolidine-3-carboxylates, whereas the pyrrole carboxylates arose from aromatization of the corresponding pyrrolines.

Nitrogen heterocycles are of considerable pharmacological relevance and the development of new methods to synthesize them efficiently is an important field in organic chemistry.[1,2] Multicomponent strategies are of particular interest as they offer the possibility of rapidly producing libraries of small molecules without tedious and time-consuming purification. They are therefore valuable tools in the search for new drug candidates.[3] Recently, we described a new one-pot, three-component coupling strategy based on two consecutive metal-catalyzed reactions, which provides a straightforward entry into elaborate 4-aryloxymethyl-3-pyrrolines **1** and their isomeric pyrrolidines **2** through the assembly of three flexible readily available starting materials: propargylic amines, vinyl sulfones, and phenols (Scheme 1).[4] We envisioned that these heterocycles would represent useful scaffolds for derivatization chemistry. Further synthetic manipulations may indeed offer new opportunities to access other interesting nitrogen heterocyclic structures and thereby widen the synthetic potential of our multicomponent process.

To this end we reasoned that upon subjection to catalytic hydrogenation, heterocycles **1** and **2** would rearrange to afford a novel series of γ-lactam derivatives **3** through consecutive hydrogenation of the double bond,



a: $Ar^1 = Ar^2 = Ph$
b: $Ar^1 = Ph$; Ar^2 = (3,4-methylenedioxy)phenyl
c: $Ar^1 = Ar^2$ = (3,4-methylenedioxy)phenyl
d: $Ar^1 = Ph$; Ar^2 = *p*MeO-phenyl
e: Ar^1 = (3,4-methylenedioxy)phenyl; Ar^2 = *p*MeO-phenyl

Scheme 1.

Keywords: Lactams; Pyrroles; Hydrogenation; Rearrangement; Aromatization.
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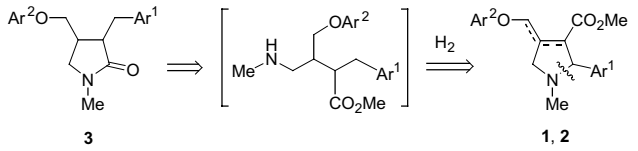


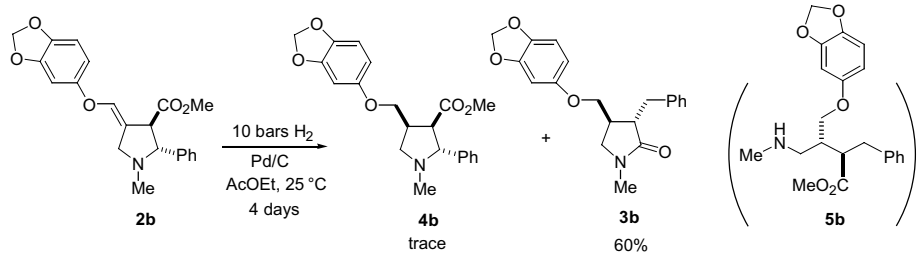
Scheme 2.

ring opening by cleavage of the *N*-benzyl bond, and ring closure taking advantage of the ester group (Scheme 2). To the best of our knowledge this synthetic approach toward γ-lactams had not been previously explored.

To test the feasibility of this process, the respective reactivities of **1** and **2** toward hydrogenation were investigated separately. To this end a range of five pyrrolines **1a**–**e** and pyrrolidines **2a**–**e** were prepared according to procedures reported previously[4] and separated by conventional chromatographical techniques. First attempts conducted on **2b** using Pd/C under 1 atm H_2 in various solvents (EtOAc, MeOH, benzene) gave poor results, the reactions proceeding very slowly. However, aside from non-negligible amounts of recovered starting material, the desired lactam **3b** was always isolated from the reaction mixtures along with pyrrolidine **4b**, both products being formed as single diastereomers. These could be easily separated by chromatography and their respective stereochemistries were elucidated by extensive NMR experiments (^{1}H, ^{13}C NMR, COSY 2D, HMBC or HSQC–TOCSY, NOESY 2D). On subjecting pyrrolidine **4b** to hydrogenation, it was also confirmed that this was the first intermediate species to be generated in the process, which subsequently undergoes ring rearrangement to furnish **3b**.[5] It should be noted, however, that no traces of the putative amino ester intermediate **5b** were detected in the reaction mixtures within the limits of ^{1}H NMR sensitivity. Finally, the best results were obtained by increasing the pressure to 10 bars of H_2 in EtOAc. Under these conditions **2b** was totally consumed and furnished the desired lactam **3b** almost exclusively in 60% isolated yield, albeit in 4 days reaction time (Scheme 3).[6]

Unfortunately, when **1b** was subjected to the same reaction conditions an intractable mixture of products was obtained aside from a large quantity of (3,4-methylenedioxy)phenol (85% recovery based on **1b**) indicating that, as would be expected, competitive reductive cleavage of the benzyloxy group was occurring. The generality of the process was thus investigated with pyrrolidines **2**, all of which gave the corresponding pyrrolidin-2-ones in comparable yields (50–72%) but with quite different reaction times. It was indeed observed that reaction rates decreased with increasing functionalization of the aryl moieties (Fig. 1).[7]

We next investigated the reactivity of the isomeric pyrrolines **1a**–**e** toward aromatization as an opportunity to access pyrrole derivatives of type **6**. We found that the pyrroles could indeed be obtained in high yields upon treatment of the pyrrolines with 1.1 equiv of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in toluene at room temperature (Fig. 2).[8,9]



Scheme 3.

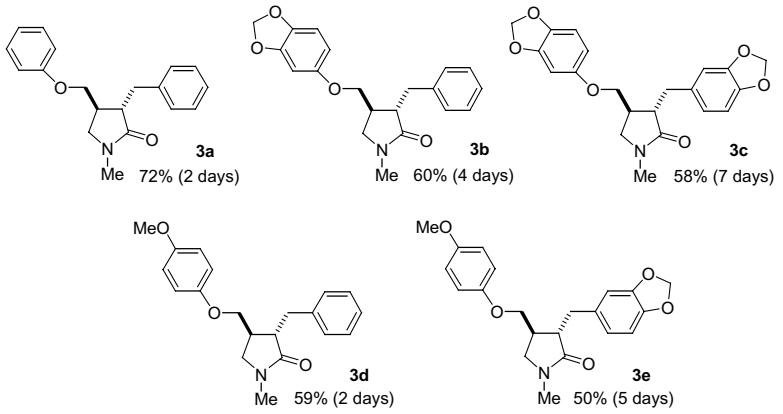


Figure 1.

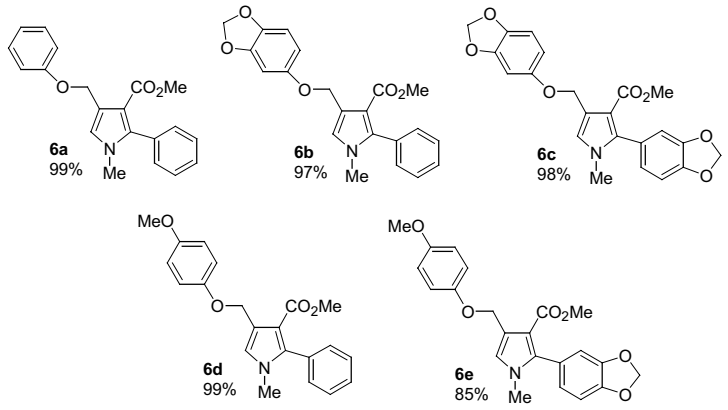


Figure 2.

In summary, we have shown that a variety of five-membered nitrogen heterocycles—pyrrolidines, pyrrolines, pyrroles, and γ-lactams—may be easily prepared by exploiting a three-component combination of propargylic amines, vinyl sulfones, and phenols. Of particular interest is the new entry to the γ-lactam derivatives based on the unprecedented rearrangement of 2-aryl pyrrolidine-3-carboxylates under classical catalytic hydrogenation conditions.

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References and notes

1. *Comprehensive Heterocyclic Chemistry II*; Katritsky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996.
2. Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *17*, 2862–2892, and previous annual reports.
3. For recent reviews, see: Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111; Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80; Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499; Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144; Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329; Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
4. Clique, B.; Vassiliou, S.; Monteiro, N.; Balme, G. *Eur. J. Org. Chem.* **2002**, 1493–1499.
5. Pyrrolidine **4b** could be obtained exclusively upon subjection of **2b** to hydrogenation (1 atm H_2, EtOAc, room temperature) in the presence of PtO_2 (10 mol%) as catalyst. However, three successive operations with new loadings of catalyst were needed in order to achieve a total conversion (73% yield).
6. Typical procedure. A stainless steel bomb equipped with a magnetic stirbar was charged with pyrroline **2b** (60 mg, 0.163 mmol) and 10% Pd/C (20 mg) in EtOAc (2 mL). The bomb was purged with argon, pressurized to 10 bars of H_2, and maintained at that pressure for 4 days. The pressure was released and the reaction mixture was filtered through a short pad of silica gel using ethyl acetate as eluant and concentrated in vacuo. The residue was purified by column chromatography (silica gel; ethyl acetate/petroleum ether 4/1) to afford **3b** (33 mg, 60%) as an oil. IR (neat): 3020, 1680, 1490, 1260, 1180, 1035, 730, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 2.45–2.55 (1H, m), 2.60–2.70 (1H, m), 2.77–2.82 (1H, m), 2.84 (3H, s), 3.12–3.30 (3H, m), 3.46–3.62 (2H, m), 5.90 (2H, s), 6.11 (1H, dd, $J = 8.4$ and 2.5 Hz), 6.30 (1H, d, $J = 2.5$ Hz), 6.63 (1H, d, $J = 8.4$ Hz), 7.15–7.35 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): 30.2, 36.7, 37.0, 46.4, 51.1, 70.4, 98.4, 101.6, 105.9, 108.3, 127.0, 128.8, 129.1, 139.2, 142.3, 148.6, 154.3, 175.3. HRMS (CI): calcd for $C_{20}H_{22}NO_4$ (MH^+) 340.1549, found 340.1548. Data for **4b**: Mp 68–70 °C. IR (neat): 3050, 2950, 2780, 1735, 1505, 1495, 750, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 2.17 (3H, s), 2.34 (1H, t, $J = 9.0$ Hz), 3.05–3.18 (2H, m), 3.40–3.50 (1H, m), 3.50 (3H, s), 3.58 (1H, d, $J = 8.8$ Hz), 3.88 (1H, dd, $J = 9.1$ and 5.2 Hz), 3.98 (1H, dd, $J = 9.1$ and 6.7 Hz), 5.91 (2H, s), 6.29 (1H, dd, $J = 8.5$ and 2.6 Hz), 6.45 (1H, d, $J = 2.6$ Hz), 6.69 (1H, d, $J = 8.5$ Hz), 7.28–7.40 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): 39.1, 54.6, 40.5, 52.1, 59.9, 68.4, 74.0, 98.4, 101.6, 106.0, 108.3, 128.2, 129.0, 140.8, 142.2, 148.6, 154.5, 173.1. HRMS (CI): calcd for $C_{21}H_{24}NO_5$ (MH^+) 370.1655, found 370.1660.
7. We had already observed the same phenomenon during the hydrogenation of analogous furan derivatives: Garçon, S.; Cavicchioli, M.; Vassiliou, S.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 4069–4073.
8. Typical procedure. A solution of DDQ (34 mg, 0.15 mmol) in toluene (1 mL) was added to a solution of pyrroline **1b** (50 mg, 0.136 mmol) in toluene (1.5 mL) and the reaction mixture was stirred at room temperature for 15 min. The mixture was diluted with diethyl ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by column chromatography (silica gel; ethyl acetate/petroleum ether 9/1) to afford **6b** (47 mg, 97%) as an oil. IR (neat): 3050, 2920, 2850, 1700, 1500, 1490, 740, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 3.40 (3H, s), 3.58 (3H, s), 5.20 (2H, s), 5.91 (2H, s), 6.48 (1H, dd, $J = 8.5$ and 2.6 Hz), 6.63 (1H, d, $J = 2.6$ Hz), 6.73 (1H, d, $J = 8.5$ Hz), 6.77 (1H, s), 7.37–7.50 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): 35.1, 51.1, 65.5, 98.8, 101.5, 106.6, 108.4, 111.2, 121.6, 122.3, 128.4, 128.8, 131.0, 132.3, 140.1, 141.9, 148.6, 155.1, 165.6. HRMS (CI): calcd for $C_{21}H_{20}NO_5$ (MH^+) 366.1341, found 366.1347.
9. It should be noted that pyrroles **6** could not be obtained from pyrrolidines **2** using the same oxidation conditions.