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Efficient and regioselective synthesis of functionalized pyrroles by cyclocondensation of 1,3-dicarbonyl dianions with α-azidoketones

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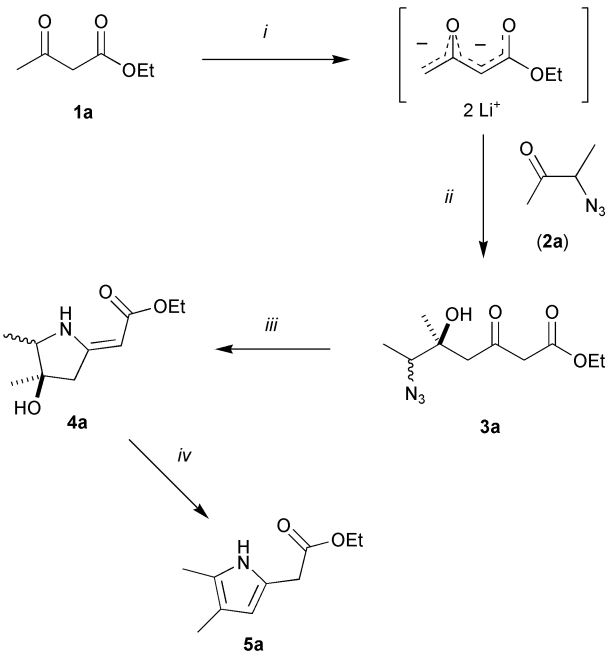
The cyclocondensation of 1,3-dicarbonyl dianions with α-azidoketones regioselectively afforded 2-alkylidenepyrrolidines which were transformed into functionalized pyrroles by treatment with acid.

Functionalized pyrroles and 2-alkylidenepyrrolidines are present in a number of pharmacologically relevant natural and unnatural products and represent useful synthetic intermediates. 2-Alkylidenepyrrolidines have been used as key intermediates during the synthesis of mitomycin antitumor antibiotics possessing antibacterial activity.[1] Functionalized pyrroles are building blocks of natural tetrapyrrole pigments,[2] such as porphobilinogen or bilirubin, and various other natural products and their analogues.[3] The pyrrole zomepirac possesses analgetic and antiphlogistic activity and has clinical applications. Substituted oligopyrroles are of interest in the field of material sciences.

Pyrroles have been prepared mainly by using the classic Knorr procedure which proceeds by initial formation of a carbon–nitrogen and subsequent formation of a carbon–carbon bond.[4] The synthesis of alkyl-substituted pyrroles by this method is problematic, since regioisomers are generally formed for non-stabilized enamine intermediates. The classic Hantzsch procedure also relies on the formation of enamines.[4d] The regioselectivity strongly depends on the substituents of the starting materials.

The proposed biosynthetic pathway of natural products such as porphobilinogen relies on the formation of a carbon–carbon rather than a carbon–nitrogen bond in the first step.[5] Only very few biomimetic pyrrole syntheses have been reported so far.[6] Herein, we wish to report what are, to the best of our knowledge, the first cyclocondensations of 1,3-dicarbonyl dianions[7] with α-azidoketones which can be considered as masked α-aminoketones.[8] These biomimetic transformations afforded functionalized 2-alkylidenepyrrolidines and pyrroles with very good regioselectivity.

Our initial attempts to induce a condensation of acetoacetate d^4 synthons with α-azidocarbonyl derivatives were unsuccessful. The Lewis acid mediated reaction of 3-azidobutan-2-one (**2a**) with 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene, an electroneutral equivalent of the dianion of ethyl acetoacetate (**1a**), resulted in formation of a complex mixture from which the desired open-chain product **3a** could be isolated, however, in only low yield (Scheme 1). Although condensations of simple silyl enol ethers with α-azido*ketals* have been reported,[6a] the reaction of 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with α-azidoketals proved unsuccessful. The problem was eventually solved by application of the free dianion of **1a** which was generated by 2.4 equiv. of LDA. The condensation of dilithiated **1a** with **2a** afforded the alcohol **3a** in good yield. The formation of the dianion allowed the functionalization of the terminal (rather than the central) carbon atom of **1a**. The reaction proceeded with excellent regio- and chemoselectivity. The diastereoselectivity (3 : 1) was only moderate, but irrelevant to pyrrole synthesis (*vide infra*). To avoid extensive side reactions, such as polymerization, deprotonation and reduction of **2a**, a number of parameters had to be optimized.† This included the reaction time, temperature, stoichiometry and concentration.



Scheme 1 Synthesis of **4a** and **5a**: *i*, 2.4 equiv. LDA, THF, 0 °C; *ii*, −78 → 20 °C; *iii*, PPh_3, 24 h, 45 °C; *iv*, TFA, CH_2Cl_2, 1 h, 20 °C.

Hydrogenation of **3a** (H_2, Pd/C) directly afforded the desired 2-alkylidenepyrrolidine **4a** by deprotection and subsequent nucleophilic attack of the amino onto the carbonyl group (15% yield).† The yield could be greatly improved by use of PPh_3 (70%). The cyclocondensation proceeded by a domino Staudinger-aza-Wittig reaction with subsequent migration of the double bond. The product was formed with good *Z*-selectivity, due to formation of an intramolecular hydrogen bond N–H···O. Treatment of a CH_2Cl_2 solution of **4a** with TFA gave the desired alkyl-substituted pyrrole **5a** by elimination of water and migration of the exocyclic double bond.

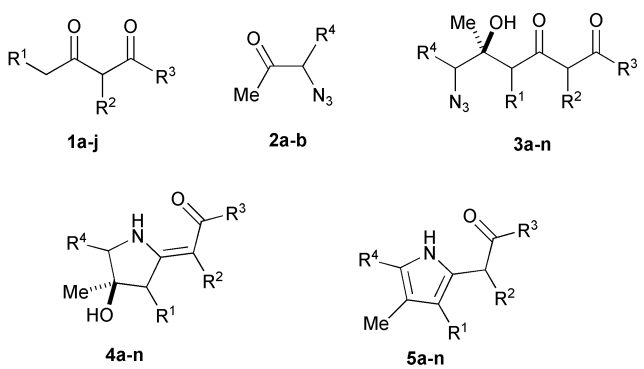


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Table 1 Products and yields

Entry	R^1	R^2	R^3	R^4	**3** [%][a]	**4** [%][a]	**5** [%][a]
a	H	H	OEt	Me	55	70	46
b	H	H	OEt	H	57	68	71
c	H	H	O*t*Bu	Me	69	76	0
d	H	H	O*t*Bu	H	60	65	0
e	OMe	H	OMe	Me	51	81	0
f	OMe	H	OMe	H	53	78	0
g	Me	H	OMe	Me	50	76	70
h	Et	H	OEt	H	51	72	75
i	H	H	NEt_2	Me	71	—	79
j	H	Me	OEt	H	70	78	81
k	H	Bn	OEt	H	51	—	32
l	H	$-CH_2CH_2O-$		H	60	—	42[b]
m	$-(CH_2)_3-$		OEt	Me	73	65	91
n	$-(CH_2)_3-$		OEt	H	71	72	88

[a] Isolated yields. All pyrrolidines **4** (except for **4b**,**d**) were obtained as diastereomeric mixtures (ds = 5:1–1.5:1, assignment arbitrary). [b] A small amount of a prototropic isomer is contained in **5l**.

To study the preparative scope of the new methodology the substituents of the 1,3-dicarbonyl compound and of the α-azidoketone were systematically varied (Table 1). The reaction of the dianion of **1a** with α-azidoacetone (**2b**) gave **3b** which was transformed into pyrrolidine **4b** and pyrrole **5b**. Starting with *t*-butyl acetoacetate (**1b**), pyrrolidines **4c**–**d** were prepared. Treatment of **4c**–**d** with TFA resulted in decomposition. The cyclocondensation of **2a**,**b** with dilithiated methyl 4-methoxyacetoacetate (**1c**) afforded the *Z*-configured pyrrolidines **4e**–**f** in good yields and as diastereomeric mixtures. The corresponding pyrroles were again not available, due to destruction of the substrate. Starting with methyl 3-oxopentanoate (**1d**) and ethyl 3-oxohexanoate (**1e**), pyrrolidines **4g**–**h** and pyrroles **5g**–**h** (containing additional ring substituents) were prepared. The reaction of **2a** with dilithiated *N*,*N*-diethylacetylacetic amide (**1f**) gave **3i** which directly afforded pyrrole **5i** upon treatment with PPh_3. The cyclocondensation of ethyl 2-methylacetoacetate (**1g**) with **2b** afforded pyrrolidine **4j** and pyrrole **5j** (containing an additional substituent at the side-chain). Similarly, pyrrole **5k** was prepared from ethyl 2-benzylacetoacetate (**1h**). The use of cyclic substrates was next studied. Starting with 2-acetyl-γ-butyrolactone (**1i**), pyrrolidine **4l** and pyrrole **5l** were prepared. The cyclocondensation of **2a**,**b** with dilithiated ethyl cyclohexanone-2-carboxylate (**1j**) gave pyrrolidines **4m**–**n** which were transformed into the bicyclic pyrroles **5m**–**n**.

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Notes and references

† Typical experimental procedures: *Ethyl 3-oxo-5-methyl-5-hydroxy-6-azidoheptanoate* (**3a**): To a THF solution (35 ml) of diisopropylamine (0.92 g, 9.2 mmol) was added *n*BuLi (3.9 ml, 9.2 mmol, 23% solution in hexane) at 0 °C. After stirring for 15 min **1a** (0.51 g, 3.9 mmol) was added and the solution was stirred for 1 h at 0 °C. A THF solution (5 ml) of **2a** (400 mg, 3.54 mmol) was added at −78 °C and the reaction mixture was warmed to ambient temperature over 12 h. After stirring for 3 h at 20 °C a saturated aqueous solution of NH_4Cl (50 ml) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 70 ml) and with CH_2Cl_2 (2 × 50 ml). The combined organic layers were extracted with brine, dried (Na_2SO_4), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by chromatography (silica gel, ether–petroleum ether (bp 40–70 °C) = 1:4 → 1:3) to give **3a** as a yellow oil (471 mg, 55%, 3:1 mixture of diastereomers). ^{1}H NMR (250 MHz, $CDCl_3$, major isomer): δ = 1.14–1.32 (m, 9 H, 3 × CH_3), 2.78 (m, 2 H, 4-H), 3.39–3.65 (m, 1 H, 6-H), 3.54 (s, 2 H, 2-H), 4.20 (q, J = 7 Hz, 2 H, CH_2CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.35, 14.05, 23.77 (CH_3), 49.34, 50.79, 61.56 (CH_2), 64.21 (CH), 74.31 (C), 166.79, 203.91 (C=O). MS (DCI, 70 eV): 261 ($[M + NH_4]^+$, 40), 216 (24), 200 (40), 190 (100), 147 (40).

Ethyl (4,5-dimethyl-pyrrolidin-2-ylidene)acetate (**4a**): to a THF solution (10 ml) of **3a** (0.2 g, 0.82 mmol) was added PPh_3 (0.258 g, 0.98 mmol) at 20 °C and the reaction mixture was stirred for 24 h at 45 °C. The solution was cooled to ambient and water (50 ml) was added. The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were extracted with brine, dried (Na_2SO_4), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by chromatography (silica gel, ether–petroleum ether = 1:2) to give **4a** as a yellow oil (114 mg, 70%, mixture of diastereomers). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04–1.38 (m, 9 H, 3 × CH_3), 2.64 (m, 2 H, ring-CH_2), 3.60, 3.70 (2 × q, J = 6 Hz, 1 H, $CHCH_3$, diastereomers), 4.13 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.52, 4.54 (2 × s, 1 H, C=CH, diastereomers), 7.74, 7.81 (2 × br, 1 H, NH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.18, 14.64, 17.27, 21.85, 23.26 (CH_3), 45.98, 47.38, 58.54, 58.57 (CH_2), 62.75, 64.36, 78.25, 78.41 (CH), 110.42, 110.43 (C), 162.43 (C=CO_2Et), 170.43 (C=O). MS (EI, 70 eV): 199 (M^+, 100), 184 (26), 156 (84), 154 (64), 110 (47); the exact molecular mass for $C_{10}H_{17}O_3N$ m/z = 199.1208 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV).

Ethyl (4,5-dimethyl-pyrrol-2-yl)acetate (**5a**): to a CH_2Cl_2 solution (10 ml) of **4a** (0.095 g, 0.52 mmol) was slowly added TFA (0.5 ml) and the solution was stirred at 20 °C for 1 h. The solvent and the acid were removed *in vacuo* and the residue was purified by chromatography (silica gel, ether–petroleum ether = 1:10) to give **5a** as a red oil (40 mg, 46%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.99 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 3.58 (s, 2 H, CH_2CO_2Et), 4.18 (q, J = 7 Hz, 2 H, CH_2CH_3), 5.78 (s, 1 H, CH), 8.17 (br, 1 H, NH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 10.71, 10.89, 14.14 (CH_3), 33.29, 60.99 (CH_2), 109.03 (CH), 114.00, 120.39, 123.61, 171.41 (C). MS (EI, 70 eV): 181 (M^+, 23), 108 (100); the exact molecular mass for $C_{10}H_{15}O_2N$ $m\backslash z$ = 181.1103 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV). All new compounds were characterized spectroscopically and gave correct elemental analyses and/or high resolution mass data.

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