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The cyclocondensation of 1,3-dicarbonyl dianions with  $\alpha$ 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.<sup>1</sup> Functionalized pyrroles are building blocks of natural tetrapyrrole pigments,<sup>2</sup> such as porphobilinogen or bilirubin, and various other natural products and their analogues.<sup>3</sup> 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.<sup>4</sup> 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.<sup>4d</sup> 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.<sup>5</sup> Only very few biomimetic pyrrole syntheses have been reported so far.<sup>6</sup> Herein, we wish to report what are, to the best of our knowledge, the first cyclocondensations of 1,3-dicarbonyl dianions<sup>7</sup> with  $\alpha$ -azidoketones which can be considered as masked  $\alpha$ -aminoketones.<sup>8</sup> 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  $\alpha$ -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 silvl enol ethers with  $\alpha$ -azidoketals have been reported,<sup>6a</sup> the reaction of 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with  $\alpha$ -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.<sup>†</sup> This



**Scheme 1** Synthesis of **4a** and **5a**: *i*, 2.4 equiv. LDA, THF, 0 °C; *ii*,  $-78 \rightarrow 20$  °C; *iii*, PPh<sub>3</sub>, 24 h, 45 °C; *iv*, TFA, CH<sub>2</sub>Cl<sub>2</sub>, 1 h, 20 °C.

included the reaction time, temperature, stoichiometry and concentration.

Hydrogenation of **3a** (H<sub>2</sub>, Pd/C) directly afforded the desired 2-alkylidenepyrrolidine **4a** by deprotection and subsequent nucleophilic attack of the amino onto the carbonyl group (15% yield).<sup>†</sup> The yield could be greatly improved by use of PPh<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub> solution of **4a** with TFA gave the desired alkyl-substituted pyrrole **5a** by elimination of water and migration of the exocyclic double bond.



Table 1 Products and yields

Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	R <sup>3</sup>	R <sup>4</sup>	<b>3</b> [%] <sup>a</sup>	<b>4</b> [%] <sup>a</sup>	<b>5</b> [%] <sup>a</sup>
a	Н	Н	OEt	Me	55	70	46
b	Н	Н	OEt	Н	57	68	71
с	Н	Н	OtBu	Me	69	76	0
d	Н	Н	OtBu	Н	60	65	0
e	OMe	Н	OMe	Me	51	81	0
f	OMe	Н	OMe	Н	53	78	0
g	Me	Н	OMe	Me	50	76	70
ĥ	Et	Н	OEt	Н	51	72	75
i	Н	Н	NEt <sub>2</sub>	Me	71	_	79
j	Н	Me	OEt	Н	70	78	81
k	Н	Bn	OEt	Н	51	_	32
1	Н	H –CH <sub>2</sub>		Н	60		$42^{b}$
m	-(CH	-(CH <sub>2</sub> ) <sub>3</sub> -		Me	73	65	91
n	-(CH <sub>2</sub> ) <sub>3</sub> -		OEt	Н	71	72	88

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

To study the preparative scope of the new methodology the substituents of the 1,3-dicarbonyl compound and of the  $\alpha$ azidoketone were systematically varied (Table 1). The reaction of the dianion of 1a with  $\alpha$ -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-methoxvacetoacetate (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<sub>3</sub>. 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- $\gamma$ -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

<sup>†</sup> 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<sub>4</sub>Cl (50 ml) was added, the organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (2 × 70 ml) and with CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 ml). The combined organic layers were extracted with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by chromatography (silica gel, etherpetroleum ether (bp 40–70 °C) = 1:4 → 1:3) to give **3a** as a yellow oil (471 mg, 55%, 3:1 mixture of diastereomers). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>,

major isomer):  $\delta$  = 1.14–1.32 (m, 9 H, 3 × CH<sub>3</sub>), 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*<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta$  = 13.35, 14.05, 23.77 (CH<sub>3</sub>), 49.34, 50.79, 61.56 (CH<sub>2</sub>), 64.21 (CH), 74.31 (C), 166.79, 203.91 (C=O). MS (DCI, 70 eV): 261 ([M + NH<sub>4</sub>]<sup>+</sup>, 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<sub>3</sub> (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  $\times$ 50 ml). The combined organic layers were extracted with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), 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). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.04–1.38 (m, 9 H, 3 × CH<sub>3</sub>), 2.64 (m, 2 H, ring-CH<sub>2</sub>), 3.60, 3.70 (2 × q, J = 6 Hz, 1 H, CHCH<sub>3</sub>, 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). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta = 13.18, 14.64, 17.27, 21.85, 23.26$  (CH<sub>3</sub>), 45.98, 47.38, 58.54, 58.57 (CH<sub>2</sub>), 62.75, 64.36, 78.25, 78.41 (CH), 110.42, 110.43 (C), 162.43 (C=CO2Et), 170.43 (C=O). MS (EI, 70 eV): 199 (M+, 100), 184 (26), 156 (84), 154 (64), 110 (47); the exact molecular mass for  $C_{10}H_{17}O_3N m/z =$  $199.1208 \pm 2 \text{ mD} (M^+)$  was confirmed by HRMS (EI, 70 eV).

*Ethyl* (4,5-dimethyl-pyrrol-2-yl)acetate (**5a**): to a CH<sub>2</sub>Cl<sub>2</sub> 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%). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.31 (t, J = 7 Hz, 3 H, CH<sub>2</sub>CH<sub>3</sub>), 1.99 (s, 3 H, CH<sub>3</sub>), 2.26 (s, 3 H, CH<sub>3</sub>), 3.58 (s, 2 H, CH<sub>2</sub>CO<sub>2</sub>Et), 4.18 (q, J = 7 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 5.78 (s, 1 H, CH), 8.17 (br, 1 H, NH). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta$  = 10.71, 10.89, 14.14 (CH<sub>3</sub>), 33.29, 60.99 (CH<sub>2</sub>), 109.03 (CH), 114.00, 120.39, 123.61, 171.41 (C). MS (EI, 70 eV): 181 (M<sup>+</sup>, 23), 108 (100); the exact molecular mass for C<sub>10</sub>H<sub>15</sub>O<sub>2</sub>N *m*/z = 181.1103 ± 2 mD (M<sup>+</sup>) 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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