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Synthesis of 2-Alkylidenepyrrolidines and Pyrroles by Condensation of 1,3-Dicarbonyl Dianions with α-Azidoketones and Subsequent Intramolecular Staudinger−Aza-Wittig Reaction

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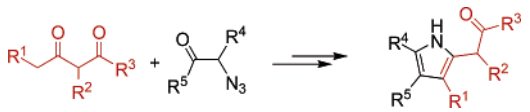

The condensation of 1,3-dicarbonyl dianions with α-azidoketones afforded open-chained condensation products that were transformed into pyrroles by Staudinger−aza-Wittig reactions and the subsequent treatment with trifluoroacetic acid.

Introduction

2-Alkylidenepyrrolidines represent versatile building blocks that have shown considerable utility in organic synthesis.[1] 2-Alkylidenepyrrolidines have been used, for example, during the synthesis of mitomycin antitumor antibiotics, microsclerodermin E, carbapenam-3-carboxylic acid, pyrrolizidines, camptothecin analogues, pyrrolidines, alkaloids (e.g., hygrine, hygroline, or cuskhygrin), and various pharmaceuticals (e.g., the vasodilator buflomedil).[2,3] We have shown earlier that 2-alkylidenepyrrolidines represent useful synthetic precursors of pyrroles. The pyrrole subunit occurs in a number of pharmacologically active natural products and synthetic drugs (e.g., zomepirac and atorvastatin).[4−6] 2-Alkylidenepyrrolidines have been prepared mainly by synthetic *modification* of suitable *N*-heterocycles.[7] Synthetic approaches, which rely on the *formation* of the *N*-heterocyclic moiety, are more rare. For example, 2-alkylidenepyrrolidines have been prepared by the reaction of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane, nucleophilic replacement of the chloride by an azido group, and subsequent Staudinger−aza-Wittig reaction.[8] In addition, 2-alkylidenepyrrolidines have been prepared by the reaction of 1,3-dicarbonyl dianions with aziridines[9] and by ring-transformation reactions of lactones.[10]

Recently, we reported the synthesis of functionalized 2-alkylidenepyrrolidines and pyrroles by the reaction of 1,3-bis-silyl enol ethers with 2-azido-1,1-dimethoxyethane and subsequent Staudinger−aza-Wittig reaction.[11] Pyrroles have been prepared also by intermolecular Staudinger−aza-Wittig reactions of 1,3-dicarbonyl compounds with 2-azido-1,1-diethoxyethane and subsequent acid-mediated cyclization.[12] However, the preparative scope of these methods is limited by the fact that, as a result of the use of 2-azido-1,1-diethoxyethane, three- and tetra-

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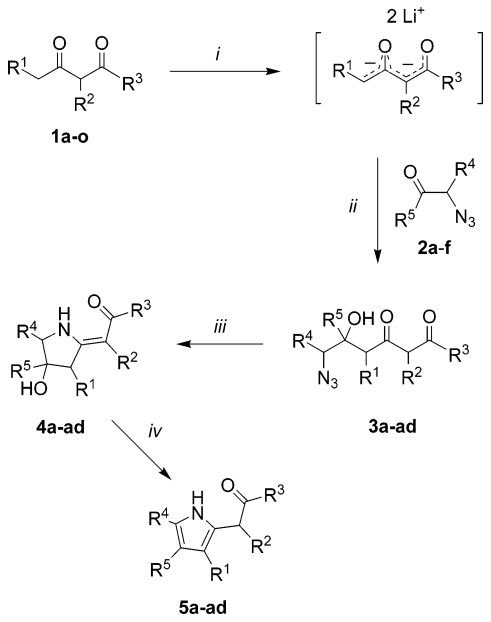
substituted pyrroles are *not* available. Some years ago, Montforts and co-workers reported[13] the synthesis of highly substituted pyrroles based on reactions of simple silyl enol ethers with azidoketals and a subsequent aza-Wittig reaction.[14] However, the application of this method to the use of 1,3-bis-silyl enol ethers failed (due to the formation of complex mixtures in their reaction with azidoketals). To overcome these limitations, we developed a new synthesis of highly substituted pyrroles based on the reaction of α-azidoketones with 1,3-dicarbonyl dianions. Herein, we report full details of this work. With regard to our preliminary communication in this field,[15] we significantly extended the preparative scope of our methodology and report, for example, the synthesis of bicyclic pyrroles and 4,5,6,7-tetrahydroindoles. All reactions proceed with excellent regioselectivity. In contrast, the preparative scope of the classic Knorr or Hantzsch procedures[4] is often limited by the formation of regioisomers. Notably, the substitution pattern of the pyrroles prepared by our methodology is not readily accessible by other methods.

SCHEME 1. Synthesis of 5a−5ad[a]



[a] (*i*) 2.4 equiv of LDA, THF, 0 °C; (*ii*) −78 °C → 20 °C; (*iii*) PPh_3, CH_2Cl_2, 24 h, THF, 45 °C; (*iv*) TFA, CH_2Cl_2, 1 h, 20 °C.

Results and Discussion

The reaction of the dianions of 1,3-dicarbonyl compounds **1a**−**o** with α-azidoketones **2a**−**f** afforded the 6-azido-5-hydroxy-3-oxoalkanoates **3a**−**ad**. The intramolecular Staudinger−aza-Wittig reaction of the latter gave the 2-alkylidenepyrrolidines **4a**−**ad**, which were transformed into the pyrroles **5a**−**ad** by treatment with trifluoroacetic acid (TFA; Scheme 1, Table 1).

The reaction of dilithiated ethyl and *tert*-butyl acetoacetate (**1a**,**b**) with 3-azidobutan-2-one (**2a**) and 1-azidopropan-2-one (**2b**) afforded the open-chained products **3a**−**d**, which were transformed into the 2-alkylidenepyrrolidines **4a**−**d**. The reaction of the ethyl esters **4a**,**b** with TFA gave the desired pyrroles **5a**,**b**. Treatment of the *tert*-butyl esters **4c**,**d** with TFA resulted in decomposition. The reaction of dilithiated methyl 4-methoxyacetoacetate (**1c**) with **2a** and **2b** and subsequent cyclization afforded the 2-alkylidenepyrrolidines **4e**,**f**. Treatment of the latter with TFA resulted in decomposition. The reaction of dilithiated methyl 3-oxopentanoate (**1d**) with **2a** and subsequent cyclization afforded the 2-alkylidenepyrrolidine **4g**, which was transformed into the 3,4,5-trimethylpyrrole **5g**. Likewise, 3-ethyl-4-methylpyrrole **5h** was prepared from ethyl 6-oxohexanoate (**1e**) and **2b**. The cyclocondensation of dilithiated ethyl 2-methylacetoacetate (**1f**) with **2b** gave **4i**, which was transformed into the pyrrole **5i** by treatment with TFA. The pyrroles **5j** and **5l** were prepared based on reactions of dilithiated ethyl 2-benzylacetoacetate (**1g**) and 2-acetyl-γ-butyrolactone (**1h**) with **2b**.

The cyclocondensation of the dianions of ethyl cycloalkanone-2-carboxylates **1i**−**k** with **2a**,**b** afforded **4m**−**p**, which were

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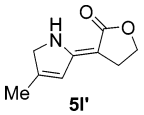
TABLE 1. Products and Yields

1	2	3,4,5	R^1	R^2	R^3	R^4	R^5	3[a] (%)	4[a] (%)	5[a] (%)
a	**a**	**a**	H	H	OEt	Me	Me	50	59	41[b]
a	**b**	**b**	H	H	OEt	H	Me	57	61[c]	41[b]
b	**a**	**c**	H	H	O(*t*-Bu)	Me	Me	69	66	0
b	**b**	**d**	H	H	O(*t*-Bu)	H	Me	59	55	0
c	**a**	**e**	OMe	H	OMe	Me	Me	49	66	0
c	**b**	**f**	OMe	H	OMe	H	Me	53	71	0
d	**a**	**g**	Me	H	OMe	Me	Me	52	75[c]	87
e	**b**	**h**	Et	H	OEt	H	Me	56	78	75
f	**b**	**i**	H	Me	OEt	H	Me	70	68[b]	81
g	**b**	**j**	H	$PhCH_2$	OEt	H	Me	51	0	32
g	**a**	**k**	H	$PhCH_2$	OEt	Me	Me	48	0	0
h	**b**	**l**	H	$-(CH_2)_2O-$		H	Me	61	0	33[d]
i	**a**	**m**	$-(CH_2)_3-$		OEt	Me	Me	73	62	91
i	**b**	**n**	$-(CH_2)_3-$		OEt	H	Me	71	71	88
j	**b**	**o**	$-(CH_2)_4-$		OEt	H	Me	32	43[c,e]	83[c]
k	**b**	**p**	$-(CH_2)_5-$		OEt	H	Me	28	28	93[c]
l	**b**	**q**	$-(CH_2)_2-$		OEt	H	Me	55	0	43
a	**c**	**r**	H	H	OEt	H	Ph	54	73	94
d	**c**	**s**	Me	H	OMe	H	Ph	51	93	77
i	**c**	**t**	$-(CH_2)_3-$		OEt	H	Ph	81	57	73
a	**d**	**u**	H	H	OEt	Me	Ph	72	93	77
d	**d**	**v**	Me	H	OMe	Me	Ph	32	75	0
f	**d**	**w**	H	Me	OEt	Me	Ph	32	58	66
m	**c**	**x**	H	H	Me	H	Ph	21	0	33
n	**b**	**y**	$-(CH_3)_3-$		Ph	H	Me	50	0	15[b]
a	**e**	**z**	H	H	OEt	$-(CH_2)_4-$		97	27	69
f	**e**	**aa**	H	Me	OEt	$-(CH_2)_4-$		41	0	0
o	**f**	**ab**	H	H	$N(Et)_2$	$-(CH_2)_3-$		34	0	15
h	**f**	**ac**	H	$-(CH_2)_2O-$		$-(CH_2)_3-$		63	0	23
o	**e**	**ad**	H	H	$N(Et)_2$	$-(CH_2)_4-$		36	0	76[b]

[a] Isolated yields. All pyrrolidines **4** (except for **4b**,**d**,**s**,**z**) were obtained as diastereomeric mixtures (ds = 5:1−1.5:1, assignment arbitrary). [b] Unstable compound; a small amount of the decomposition products could not be separated. [c] A small amount of triphenylphosphane oxide could not be separated. [d] Unseparable mixture with isomer **5l′**. [e] Together with **5o**.



5l′

transformed into the 5,6-, 5,7-, and 5,8-bicyclic pyrroles **5m**−**p**. The condensation of ethyl cyclopentanone-2-carboxylate (**1l**) with **2b** gave **4q**. The Staudinger−aza-Wittig reaction of the latter directly furnished the 5,5-bicyclic pyrrole **5q**. The condensation of the dianions of **1a**, **1d**, and **1i** with α-azidoacetophenone (**2c**) gave the condensation products **3r**−**t**, which were transformed into the pyrroles **5r**−**t** via **4r**−**t**. The reaction of dilithiated **1a**, **1d**, and **1f** afforded **3u**−**w**, which were transformed into the corresponding 2-alkylidenepyrrolidines **4u**−**w**. Treatment of **4u** and **4w** with TFA afforded the pyrroles **5u** and **5w**. The addition of TFA to **4v** resulted in decomposition. The condensation of dilithiated acetylacetone with **2c** afforded **3x** in low yield. The Staudinger−aza-Wittig reaction of the latter directly furnished the **5x**. The 5,6-bicyclic pyrrole **5y** was prepared, albeit in low yield, from 2-benzoylcyclohexanone (**1n**) and **2b**. The reaction of dilithiated **1a** with 2-azidocyclohexanone (**2e**) and the subsequent aza-Wittig reaction afforded **4z**. Treatment of the latter with TFA furnished the 5,6-bicyclic pyrrole **5z**. The reaction of the dianion of *N*,*N*-diethyl-acetylacetamide (**1o**) with **2e** gave **3ad**, which was directly transformed into **5ad** by the aza-Wittig reaction. The condensation of dilithiated **1o** and **1h** with 2-azidocyclopentanone afforded **3ab** and **3ac**, which were directly transformed, albeit in low yield, into the corresponding 5,5-bicyclic pyrroles **3ab** and **3ac**. Pyrrolidines **4** were isolated as diastereomeric mixtures (ds = 5:1−1.5:1, assignment arbitrary). Due to the formation of an intramolecular hydrogen bond N−H···O, all pyrrolidines contain a *Z*-configured exocyclic double bond. However, the configuration of the exocyclic double bond and the formation of diastereomeric mixtures is irrelevant for the synthesis of pyrroles **5**.

The first step of the synthesis, the condensation of the dianion with the azidoketone, was generally accomplished with moderate to very good yields (except for the reactions of the dianion of acetylacetone). The intramolecular Staudinger−aza-Wittig reaction was successful for most of the substrates; the formation of 2-alkylidenepyrrolidines from **3j**−**l**, **3y**, and **3aa**−**ad** proved to be unsuccessful. Either pyrroles were directly formed, albeit in low yield, or decomposition was observed. The TFA-mediated aromatization proved to be unsuccessful for substrates **4c**−**f**, as a result of decomposition. Unexpectedly, pyrrole **5v** could *not* be isolated. Tetrahydropyrrole **5z** was obtained from **4z** in good yield. The bicyclic products **4aa**−**ad**, required for the synthesis of the corresponding tetrahydropyrroles, could *not* be prepared. The desired tetrahydropyrroles were isolated in low yields during the intramolecular Staudinger−aza-Wittig reaction of **3aa**−**ad**. Notably, some pyrrolidines **4** and pyrroles **5** tend to be unstable, and decomposition products could not be completely removed. For some products, a small amount of triphenylphosphane oxide could not be removed, despite much synthetic efforts. Notably, the handling of azides is dangerous, due to their potentially explosive character. In fact, all reactions should be carried out on a small scale, and the use of a safety shield is highly recommended.

Experimental Section

General. All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric (MS) data were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60−200 mesh) was used. Melting points are uncorrected. The α-azidoketones **2a**−**f** were prepared according to literature procedure. 3-Azidobutan-2-one (**2a**) was prepared by reaction of 3-chlorobutan-2-one with NaN_3.[16] 1-Azidopropan-2-one (**2b**) was prepared from 3-chlorobutan-2-one and NaN_3.[17] α-Azidoacetophenone (**2c**) was prepared from α-chloroacetophenone.[18] α-Azidopropiophenone (**2d**) was prepared from α-chloropropiophenone.[19] 2-Azidocyclohexanone (**2e**)[19] and 2-azidocyclopentanone (**2f**)[20] were prepared from 2-chlorocyclohexanone and 2-chlorocyclopentanone, respectively.

CAUTION: The handling of azides is dangerous due to their potentially explosive character. Although, in our hands, azides **2** did not appear to be shock sensitive, the compounds should be handled with great care. Neat azides must not be heated or distilled, and all reactions should be carried out on a small scale. The use of a safety shield is highly recommended.

General Procedure for the Reaction of 1,3-Dicarbonyl Compounds 1a−**o with α-Azidoketones 2a**−**f.** To a solution of diisopropylamine (2.6 equiv) in anhydrous THF (35 mL) was added *n*-BuLi (2.6 equiv, 23 or 15% solution in hexane) at 0 °C. After stirring for 15 min, the dicarbonyl compound **1** (1.1 equiv) was added, and the solution was stirred for 1 h at 0 °C. A THF solution (5 mL) of azidoketone **2** (1.0 equiv) was added at −78 °C, and the

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reaction mixture was warmed to ambient temperature over a period of 12 h. After stirring for an additional 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), and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:4 → 1:3) to give the azido alcohol **3** as a diastereomeric mixture. Due to its instability, the product should be used for further transformations within 24 h.

Ethyl 6-Azido-5-hydroxy-5-methyl-3-oxoheptanoate (3a). The starting materials diisopropylamine (0.92 g, 9.2 mmol), *n*-BuLi (3.9 mL, 9.2 mmol, 23% solution in hexane), ethyl acetoacetate (**1a**; 0.51 g, 3.9 mmol), and 3-azidobutan-2-one (**2a**; 0.40 g, 3.54 mmol) yielded **3a** as a yellow oil (0.43 g, 50%). ^{1}H NMR (250 MHz, $CDCl_3$, major isomer): δ 1.14−1.32 (m, 9H, 3 × CH_3), 2.78 (m, 2H, 4-H), 3.39−3.65 (m, 1H, 6-H), 3.54 (s, 2H, 2-H), 4.20 (q, J = 7 Hz, 2H, CH_2CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$, major isomer): δ 13.3, 14.0, 23.7, 49.3, 50.7, 61.5, 64.2, 74.3, 166.8, 203.9. IR (neat) $\tilde{\nu}$: 3587 (br, w), 2984 (w), 2112 (s), 2008 (s), 1730 (s), 1728 (s), 1709 (s), 1655 (w), 1648 (w), 1449 (w), 1384 (m), 1371 (m), 1319 (m), 1259 (m), 1208 (w), 1180 (m), 1113 (w), 1095 (w), 1056 (w), 1030 (w) cm^{-1}. MS (DCI, 70 eV): *m*/*z* (%) 261 ([M + NH_4]$^+$, 40), 216 (24), 200 (40), 190 (100), 147 (40).

General Procedure for the Synthesis of 2-Alkylidenepyrrolidines 4a−ad. To a THF solution (10 mL) of **3** was added PPh_3 (1.2 equiv) at 20 °C, and the reaction mixture was stirred for 24 h at 45 °C. The solution was cooled to ambient temperature, and water (50 mL) was added. The organic and the aqueous layers 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), and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:2 or ether/petroleum ether = 1:5 → 1:2) to give pyrrolidine **4**.

Ethyl (*Z*)-(4-Hydroxy-4,5-dimethylpyrrolidin-2-ylidene)acetate (4a). Treatment of **3a** (0.20 g, 0.82 mmol) with PPh_3 yielded **4a** as a yellow oil (0.09 g, 59%, a small amount of the *E*-isomers was present). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.04−1.38 (m, 9H, 3 × CH_3), 2.64 (m, 2H, =CCH_2), 3.60, 3.70 (2 × q, ^3J = 6 Hz, 1H, CHCH$_3$), 4.13 (q, ^3J = 7 Hz, 2H, CH_2CH$_3$), 4.52, 4.54 (2 × s, 1H, CH=C, *Z*-isomer), 4.83, 4.92 (2 × s, 1H, CH=C, *E*-isomer), 7.74, 7.81 (2 × br, 1H, NH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.2, 14.6, 17.3, 21.8, 23.2, 46.0, 47.4, 58.5, 58.6, 62.7, 64.4, 78.2, 78.4, 110.4, 162.4, 170.4. MS (EI, 70 eV): *m*/z (%) 199 (M$^+$, 100), 184 (26), 156 (84), 154 (64), 110 (47). The exact molecular mass *m*/*z* = 199.1208 ± 2 ppm [M$^+$] for $C_{10}H_{17}NO_3$ was confirmed by HRMS (EI, 70 eV).

General Procedure for the Synthesis of the Pyrroles 5a−ad. To an anhydrous CH_2Cl_2 solution (10 mL) of the pyrrolidine **4** 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 the pyrrole **5**.

Methyl (3,4,5-Trimethylpyrrol-2-yl)acetate (5g). Starting with **4g** (0.95 g, 4.77 mmol), pyrrole **5g** was isolated as a brownish oil (0.75 g, 87%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.92 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 7.94 (br, 1H, NH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 9.0, 9.0, 11.0, 31.2, 52.0, 113.8, 115.6, 116.4, 122.6, 171.9. IR (neat) $\tilde{\nu}$: 3394 (m), 2951 (m), 2921 (m), 2860 (w), 1731 (s), 1715 (s), 1600 (m), 1436 (m), 1383 (w), 1345 (w), 1316 (w), 1238 (s), 1208 (s), 1193 (s), 1166 (s), 1119 (w), 1019 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) 181 (M$^+$, 25), 122 (100), 107 (6), 77 (4), 53 (2). The exact molecular mass *m*/*z* = 181.1103 ± 2 ppm [M$^+$] for $C_{10}H_{15}NO_2$ was confirmed by HRMS (EI, 70 eV).

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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