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Synthesis of functionalized pyrroles and 6,7-dihydro-1*H*-indol-4(5*H*)-ones by reaction of 1,3-dicarbonyl compounds with 2-azido-1,1-diethoxyethane

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Abstract—The condensation of 1,3-dicarbonyl compounds with 2-azido-1,1-diethoxyethane and subsequent cyclization allowed an efficient synthesis of a variety of pyrroles and 6,7-dihydro-1*H*-indol-4(5*H*)-ones.

Pyrroles and indoles occur in numerous pharmacologically active natural and unnatural products. Functionalized pyrroles represent building blocks of natural tetrapyrrole pigments, such as porphobilinogen or bilirubin, and of various other natural products and their analogues.[1,2] The pyrrole zomepirac possesses analgetic and antiphlogistic activity and has found clinical applications.[1] Substituted oligopyrroles are of interest in the field of material sciences.[1,2] In addition, pentasubstituted pyrroles have proven to be potent hypocholesterolemic agents through the inhibition of HMG-CoA reductase—a key enzyme in the biosynthesis of cholesterol.[1i] For example, atorvastatin (Fig. 1) is used today in the clinic for the treatment of hyperlipidemias.[1i]

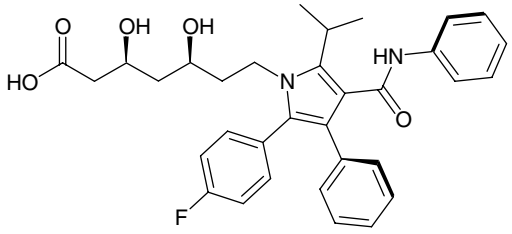

Figure 1. Hypolipidemic agent atorvastatin (Lipitor®).

Although a variety of methods for the synthesis of pyrroles are known,[3,4] the development of alternative and more selective strategies is of considerable importance. A versatile concept for the synthesis of pyrroles relies on the application of the aza-Wittig reaction.[5,6] Some years ago, we reported the synthesis of functionalized pyrroles based on reactions of α-azidoketones with 1,3-dicarbonyl dianions.[7] 2-Azido-1,1-dimethoxyethane and 2-azido-1,1-diethoxyethane represent new and interesting synthetic equivalents of aminoacetaldehyde. Recently, we have reported the synthesis of functionalized 2-alkylidenepyrrolidines and pyrroles by Lewis acid catalyzed condensation of 2-azido-1,1-dimethoxyethane with silyl enol ethers and 1,3-bis-silyl enol ethers and subsequent intramolecular Staudinger-aza-Wittig reaction.[8] These syntheses rely on the initial formation of a carbon–carbon bond and subsequent cyclization by formation of the carbon–nitrogen bond. Herein, we report the synthesis of pyrroles by application of the opposite strategy: the intermolecular Staudinger-aza-Wittig reaction of 2-azido-1,1-diethoxyethane with 1,3-dicarbonyl compounds afforded *N*-(2,2-diethoxyethyl)-3-aminoalk-2-en-1-ones, which were subsequently transformed into functionalized pyrroles and 6,7-dihydro-1*H*-indol-4(5*H*)-ones. All reactions proceeded with very good chemo- and regioselectivity under mild conditions. The reaction of 2-azido-1,1-diethoxyethane with 1,3-dicarbonyl compounds complements analogous reactions of 2-amino-1,1-dialkoxyethanes.[9] Notably, chemoselective transformations of 1,3-dicarbonyl

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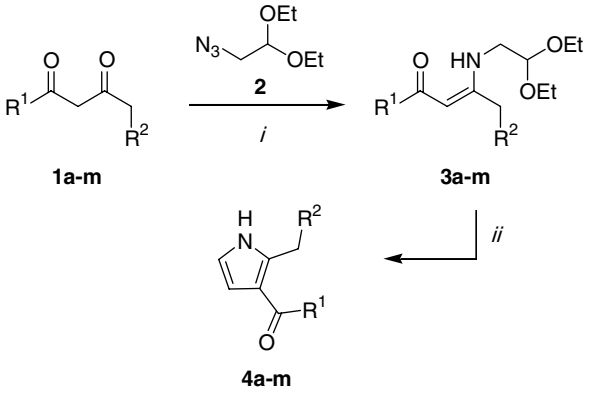
compounds containing an additional electrophilic functionality can be carried out (vide infra).

2-Azido-1,1-diethoxyethane (**2**) was prepared according to the procedure reported for the synthesis of 2-azido-1,1-dimethoxyethane.[8,10] The aza-Wittig reaction of **2** with methyl acetoacetate (**1a**) afforded the enamine **3a** (Scheme 1 and Table 2). Related enamines, prepared from 2-amino-1,1-dimethoxyethane, have been used for the synthesis of isoquinolines.[9b] Optimal results were obtained when the reaction was carried out using a small excess of **2** (1.2 equiv) and of PPh_3 (1.3 equiv) (THF, reflux, 8 h).[11–13] The transformation of **3a** into the desired pyrroles **4a** required a thorough optimization of the conditions (Table 1).[14] Treatment of a CH_2Cl_2 solution of **3a**, prepared from methyl acetoacetate (**1a**), with TFA at 0 → 20 °C afforded **4a** in 22% yield (*method A*). The yield was increased to 35% by treatment of a CH_2Cl_2 solution of **3a** with Me_3SiOTf at −78 → 20 °C (*method B*). Heating of a DMSO solution of **3a** at 150 °C for 24 h afforded **4a** in 40% yield (*method C*); the pyrrole **4a′** was isolated as a side-product in 19% yield. *Methods C* and *B* were successfully employed for the synthesis of the ester substituted pyrroles **4b–c** and **4d–k**, respectively (Table 2).

The reaction of **2** with acetylacetone (**1l**) afforded 4-(2,2-diethoxyethylamino)pent-3-en-2-one (**3l**), which was transformed into the pyrrole **4l** (68%) by *method A*.



Scheme 1. Synthesis of **3a–m** and **4a–m**. Reagents and conditions: (i) PPh_3, THF, reflux, 8 h; (ii) see Tables 1 and 2. *Method A*: TFA (10 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; *method B*: Me_3SiOTf (1 equiv), CH_2Cl_2, −78 → 20 °C (for β-ketoesters) or 0 → 20 °C (for 1,3-diketones), 12 h; *method C*: DMSO, 150 °C, 24 h.

The application of *method C* gave **4l** in 60% yield; besides, a small amount of pyrrole **4l′** was isolated (5%). The TFA-mediated cyclization of **3m**, prepared from benzoylacetone (**1m**), afforded the 3-benzoylpyrrole **4m** in 82% yield (*method A*).[14] The use of Me_3SiOTf (0 → 20 °C, *method B*) and heating of a DMSO solution of **3m** (*method C*) also proved to be successful (Table 1). Reflux of neither **3a** nor **3m** in other solvents such as, THF, CH_3CN, or 1,4-dioxane afforded the corresponding pyrroles.

The enamines **6a–d** were prepared by reaction of **2** with cyclohexane-1,3-diones **5a–d** (Scheme 2 and Table 3). Treatment of **6a–d** with TFA afforded the 6,7-dihydro-1*H*-indol-4(5*H*)-ones **7a–d** in very good yields (*method A*). Indole **7a** was also prepared by application of *method C*.[15]

In summary, we have reported a new and efficient approach to a variety of pyrroles and 6,7-dihydro-1*H*-indol-4(5*H*)-ones based on aza-Wittig reactions of 2-azido-1,1-diethoxyethane and subsequent cyclizations.

Table 2. Yields of condensation products (**3**) and pyrroles (**4**)

3, 4	R^1	R^2	% (**3**)[a]	% (**4**)[a]	Method[d]
a	OMe	H	86	40[b]	C
b	OEt	H	89	58	C
c	$O(CH_2)_2OMe$	H	89	51	C
d	$OCH_2CH{=}CH_2$	H	90	37	B
e	OMe	Me	82	39	B
f	OEt	Et	75	55	B
g	OEt	*n*Hex	84	58	B
h	OEt	*n*Oct	86	57	B
i	OEt	*n*Non	91	54	B
j	OEt	*n*Dec	91	56	B
k	OEt	$(CH_2)_6Cl$	83	47	B
l	Me	H	98	68	A
				60[c]	C
m	Ph	H	97	82	A

[a] Yields of isolated products.
[b] Besides, **4a′** was isolated in 19% yield.
[c] Besides, **4l′** was isolated in 5% yield.
[d] *Method A*: TFA, CH_2Cl_2; *method B*: Me_3SiOTf (1.0 equiv), CH_2Cl_2; *method C*: DMSO, 150 °C.

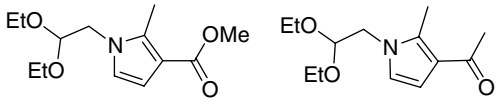
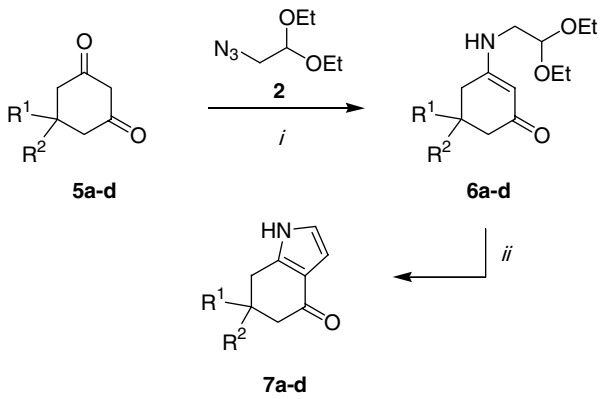


Table 1. Optimization for the synthesis of pyrroles **4a** and **4m**

Substrate	Solvent	*t* (h)	Conditions	Conversion[a] (%)
3a	CH_2Cl_2	12	TFA, 20 °C	Decomposition
3a	CH_2Cl_2	12	TFA, 0 → 20 °C	22
3a	CH_2Cl_2	12	Me_3SiOTf, −78 → 20 °C	35
3a	DMSO	24	150 °C	40[b]
3m	CH_2Cl_2	12	TFA, 0 → 20 °C	82
3m	CH_2Cl_2	12	Me_3SiOTf, 0 → 20 °C	79
3m	DMSO	24	150 °C	72

[a] Yields of isolated products.
[b] Besides, **4a′** was formed, see Table 2 footnote.



Scheme 2. Synthesis of 6,7-dihydro-1*H*-indol-4(5*H*)-ones **7a**–**d**. Reagents and conditions: (i) PPh_3, THF, reflux, 8 h; (ii) *method A*: TFA (10 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; *method C*: DMSO, 150 °C, 24 h.

Table 3. Yields of enamines **6** and 6,7-dihydro-1*H*-indol-4(5*H*)-ones **7**

6, **7**	R^1	R^2	% (**6**)[a]	% (**7**)[a]	Method
a	H	H	97	95	A
				71	C
b	Me	Me	92	60	A
c	Me	H	94	75	A
d	Ph	H	91	73	A

[a] Yields of isolated products.

The reactions of 2-azido-1,1-diethoxyethane with 1,3-dicarbonyl compounds can be carried out under mild conditions and complement analogous reactions of 2-amino-1,1-dialkoxyethanes.

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11. **CAUTION:** The handling of low-molecular weight azides is dangerous, due to their potentially explosive character. Although, in our hands, neat **2** did not appear to be shock sensitive, the compound 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.
12. *Synthesis of 2-azido-1,1-diethoxyethane* (**2**): Sodium azide (19.5 g, 300.0 mmol) and potassium iodide (3.32 g, 20.0 mmol) were added to a solution of 2-bromo-1,1-diethoxyethane (31 mL, 200.0 mmol) in DMSO (150 mL) at 20 °C. The reaction mixture was heated to 90 °C and stirred for 5 days at 90 °C. After cooling to 20 °C, water (200 mL) and diethylether (200 mL) were added, the organic layer was separated, and the aqueous layer was repeatedly extracted with diethylether (4 × 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The azidoacetal **2** was isolated without further purification as a colorless oil (30.63 g, 96%). For safety reasons, it is recommended to carry out the reaction on a small scale (no decrement of the yield was observed) and to use a safety shield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.25$ (t, $J = 7.2$ Hz, 6H, 2 × CH_3), 3.25 (d, $J = 5.4$ Hz, 2H, CH_2–N_3), 3.54–3.64 (m, 2H, OCH_2), 3.68–3.78 (m, 2H, OCH_2), 4.61 (t, $J = 5.4$ Hz, 1H, OCH). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 15.0$ (2 × CH_3), 52.2 (CH_2–N_3), 62.7 (2 × OCH_2), 101.21 (OCH). IR (neat, cm^{-1}): $\tilde{\nu} = 2980$ (s), 2932 (m), 2884 (m), 2104 (s, N_3), 1479 (w), 1446 (w), 1376 (w), 1348 (w), 1273 (s), 1233 (w), 1130 (s), 1067 (s), 946 (w), 921 (w), 844 (w). MS (EI, 70 eV): *m*/*z* (%) = 160 (M^+, 100), 145 (31), 114 (17), 91 (24).
13. *Typical procedure for the synthesis of enamines* (**3**): *Synthesis of 3-(2,2-diethoxyethylamino)-1-phenylbut-2-en-1-one* (**3m**): To a THF solution (10 mL) of benzoylacetone (0.200 g, 1.2 mmol) and 2-azido-1,1-diethoxyethane (**2**) (0.236 g, 1.5 mmol) was added triphenylphosphine (0.656 g, 2.5 mmol) at 20 °C. The reaction mixture was heated and stirred for 8 h at reflux. After cooling to 20 °C, the solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → 1:1) to give **3m** as a yellowish oil (0.322 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.25$ (t, $J = 7.1$ Hz, 6H, 2 × CH_3), 2.10 (s, 3H, CH_3), 3.46 (dd, $J = 6.4$, 5.6 Hz, 2H, NCH_2), 3.59 (dq, $J = 9.3$, 7.1 Hz, 2H, OCH_2), 3.76 (dq, $J = 9.3$, 7.1 Hz, 2H, OCH_2), 4.59 (t, $J = 5.6$ Hz, 1H, OCH), 5.68 (s, 1H, CH═C), 7.40 (m, 3H, 3 × CH of Ph), 7.86 (m, 2H, 2 × CH of Ph), 11.42 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 15.2$ (2C), 19.5 (CH_3), 46.3 (NCH_2), 63.3 (2 × OCH_2), 92.5 (*C*H═C), 101.1 (OCH), 126.7 (2C), 127.9 (2C), 130.2 (CH of Ph), 140.3 (C of Ph), 164.7 (N–*C*═CH), 187.8 (C═O). IR (neat, cm^{-1}): $\tilde{\nu} = 3060$ (w), 2977 (m), 2930 (w), 2830 (w), 2883 (w), 1606 (s), 1550 (s), 1525 (m), 1483 (w), 1444 (m), 1378 (m), 1327 (s), 1294 (s), 1245 (m), 1172 (w), 1127 (s), 1065 (s), 1031 (m), 818 (w), 793 (w), 740 (m), 714 (w), 684 (w). MS (EI, 70 eV): *m*/*z* (%) = 277 (M^+, 7), 232 (6), 199 (7), 174 (7), 160 (2), 158 (6), 144 (1), 117 (1), 103 (100), 91 (14), 77 (17). HRMS (ESI): calcd for $C_{16}H_{23}NO_3$ [M^+]: 277.16779; found: 277.16803. Anal. Calcd for $C_{16}H_{23}NO_3$ (277.363): C 69.29, H 8.36, N 5.05. Found: C 69.61, H 8.37, N 5.22.
14. *Representative procedures for the synthesis of pyrroles* (**4**): *Synthesis of (2-methyl-1H-pyrrol-3-yl)phenylmethanone* (**4m**): *Method A*: To a CH_2Cl_2-solution (3 mL) of **3m** (0.050 g, 0.18 mmol) was added TFA (0.14 mL, 1.8 mmol) at 0 °C. The reaction mixture was allowed to warm to 20 °C during 12 h and was stirred for 4 h at 20 °C. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 50:1 → 3:1) to give **4m** as a yellowish solid (0.027 g, 82%). *Method B*: To a CH_2Cl_2-solution (3 mL) of **3m** (0.050 g, 0.18 mmol) was added Me_3SiOTf (0.050 g, 0.18 mmol) at 0 °C. The reaction mixture was allowed to warm to 20 °C during 12 h and was stirred for 4 h at 20 °C. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 50:1 → 1:1) to give **4m** as a yellowish solid (0.026 g, 79%). *Method C:* A DMSO solution (5 mL) of **3m** (0.100 g, 0.36 mmol) was stirred at 150 °C for 24 h. After cooling to 20 °C, water (10 mL) was added and the mixture was extracted with diethylether (4 × 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 50:1 → 1:1) to give **4m** as a yellowish solid (0.048 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.54$ (s, 3H, CH_3), 6.40 (dd, $J = 3.0$, 2.7 Hz, 1H, CH), 6.55 (dd, $J = 3.0$, 2.4 Hz, 1H, CH), 7.41–7.51 (m, 3H, 3 × CH of Ph), 7.78–7.81 (m, 2H, 2 × CH of Ph), 9.06 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 13.7$ (CH_3), 112.5, 115.6 (CH), 119.6 (C), 128.0 (2C), 129.0 (2C), 131.1 (CH of Ph), 136.7 (C of Ph), 140.6 (C), 192.8 (C═O). In the NOESY spectrum cross peaks were found for the protons NH with CH_3, NH with H-5, CH_3 with H–*ortho*-C_6H_5 and H-4 with H–*ortho*-C_6H_5, which confirm the given structure. ^{1}H NMR ($CDCl_3$, 500.13 MHz): $\delta = 8.94$ (br s, 1H, NH), 7.78 (m, 2H, *o*-Ph), 7.49 (m, 1H, *p*-Ph), 7.42 (m, 2H, *m*-Ph), 6.54 (t, 1H, $^3J_{4,5} \sim {}^3J_{5,NH} \sim 3.0$ Hz, H-5), 6.39 (t, 1H, $^3J_{4,5} \sim {}^4J_{4,NH} \sim 3.0$ Hz, H-4),2.53 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 192.7$ (CO), 140.6 (*i*-Ph), 136.7 (C–2), 131.1 (*p*-Ph), 129.0 (*o*-Ph), 128.0 (*m*-Ph), 119.6 (C–3), 112.5 (C–4), 115.6 (C–5), 13.7 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu} = 3232$ (w), 2924 (w), 1608 (s), 1561 (m), 1446 (s), 1367 (m), 1340 (w), 1277 (m), 1212 (w), 1180 (w), 1148 (w), 1101 (w), 1075 (w), 1032 (w), 880 (m), 792 (m), 743 (w), 712 (s), 702 (s), 672 (w), 612 (w). MS (EI, 70 eV): *m*/*z* (%) = 185 (M^+, 73), 170 (3), 107 (100), 80 (13), 77 (24). HRMS (ESI): calcd for $C_{12}H_{11}NO$ [M^+]: 185.08406; found: 185.08483.
15. Bobbitt, J. M.; Kulkarni, C. L.; Dutta, C. P.; Kofod, H.; Chiong, K. N. *J. Org. Chem.* **1978**, *43*, 3541.