PAPER

Synthesis of 3-Acylpyrroles, 3-(Alkoxy carbonyl)pyrroles, 1,5,6,7-Tetrahydro-4H-indol-4-ones and 3-Benzoylpyridines Based on Staudinger–Aza-Wittig Reactions of 1,3-Dicarbonyl Compounds with 2- and 3-Azido-1,1-dialkoxyalkanes

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Abstract: The Staudinger–aza-Wittig reaction of 1,3-dicarbonyl compounds with 2-azido-1,1-diethoxyethane and subsequent cyclization allowed an efficient synthesis of a variety of pyrroles, 1,5,6,7-tetrahydro-4H-indol-4-ones, and of a pyridine.

Key words: cyclization, N-heterocycles, pyrroles, azides

Pyrroles, indoles and pyridines are present in many pharmacologically active natural products. This includes, for example, the antibiotic pyrrolnitrin, the pyrroloymycins, various tetrapyrrole pigments (e.g., bilirubin), and various other natural products and their analogues.1,2 Pentasubstituted pyrroles are potent hypcholesterolemic agents which act by inhibition of HMG-CoA reductase – a key enzyme in the biosynthesis of cholesterol.3 For example, atorvastatin is used today in the clinic for the treatment of hyperlipidemias.4 Pyrroles have also found many other applications in medicinal chemistry. For example, the synthetic pyrrole zomepirac has been used in the clinic as an analgetic and antiphlogistic agent.5

Most pyrrole syntheses rely on classical condensation reactions, such as the Hantzsch reaction (condensation of α-haloketones with 1,3-dicarbonyl compounds and amines), the Paal–Knorr reaction (cyclocondensation of 1,4-diketones with amines) or the Knorr reaction (cyclocondensation of α-aminoketones with β-keto esters). In addition, various other synthetic approaches have been developed.3,4 Intramolecular aza-Wittig reactions5 provide a versatile approach to pyrroles under mild conditions.6 Recently, we have reported that functionalized pyrroles can be prepared by reaction of α-azidoketones with 1,3-dicarbonyl diazoniun and subsequent intramolecular Staudinger–aza-Wittig reaction.7 Pyrroles are also available by Lewis acid catalyzed condensation of 2-azido-1,1-dimethoxyethane with silyl enol ethers or 1,3-bis(silyloxy)-1,3-butadienes and subsequent intramolecular Staudinger–aza-Wittig reaction.8 Recently, we have reported a convenient and versatile approach to pyrroles by intermolecular Staudinger–aza-Wittig reaction of 2-azido-1,1-diethoxyethane with 1,3-dicarbonyl compounds and subsequent cyclization.9 Herein, we report full details related to the scope of this method. With regard to our preliminary communication,10 the scope was considerably extended. In addition, the strategy could be successfully applied to the synthesis of a functionalized pyridine. All reactions proceed with very good chemoselectivity under mild conditions and complement known reactions of a-aminomethylpyridines.10

2-Azido-1,1-diethoxyethane (2a) and 2-azido-1,1-dimethoxyethane (2b) were prepared by reaction of sodium azide with 2-bromo-1,1-diethoxyethane and 2-bromo-1,1-dimethoxyethane, respectively.11 The aza-Wittig reaction of 2a with methyl acetoacetate (1a) afforded enamine 3a (Scheme 1, Tables 1 and 2). Related enamines, prepared from 2-amino-1,1-dimethoxyethane, have been used for the synthesis of isoquinolines.10b

Optimal results were obtained when the reaction was carried out using a small excess of 2 (1.2 equiv) and of Ph₃P (1.3 equiv) (THF, reflux, 8 h). The transformation of 3a into the desired pyrrole 4a required a thorough optimization of the conditions (Table 1). Treatment of a CH₂Cl₂ 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 3a in CH₂Cl₂ with Me₃SiOTf at –78 to 20 °C (method B). Heating of 3a in DMSO at 150 °C for 24 h afforded 4a in 40% yield (method C); pyrrole 4a was isolated as a side-product in 19% yield (Figure 1). The use of other solvents than DMSO (e.g., THF, MeCN or 1,4-dioxane) proved to be unsuccessful.

Products 3a–z were prepared by reaction of 1a–w with 2-azido-1,1-diethoxyethane (2a) and 2-azido-1,1-dimethoxyethane (2b) in 50–98% yields (Table 2). Most yields were above 80%. Pyrroles 4a–t were successfully prepared from 3a–z using methods A, B, or C in 22–82% optimized yields. Methods B and C were successfully employed for the synthesis of ester-substituted pyrroles (4a–n). It is worth to be mentioned that pyrroles 4i and 4k were independently prepared from 2a and 2b. The yields of the condensation steps (to give enamines 3k,1 and 3o,p)
were quite similar. Likewise, the yields of the cyclization steps (to give pyrroles 4i and 4k) were again in the same range (method B). These experiments show that equally successful results are obtained starting with azides 2a and 2b. The reaction of 2a with acetylacetone (1s) afforded 4-(2,2-diethoxyethylamino)pent-3-en-2-one (3v) which was transformed into pyrrole 4o (68%) by method A. It is noteworthy that the Staudinger–aza-Wittig reaction of unsymmetrical 1,3-diketones 1u–w proceeded with very good regioselectivity. The cyclization generally occurred via the central carbon atom of the 1,3-dicarbonyl unit.

The application of method C gave 4o in 60% yield; besides, a small amount of pyrrole 4o¢ was isolated (5%). The cyclization of 3w, derived from heptane-3,5-dione (1t), gave 4p in good yield when method A was applied. The TFA-mediated cyclization of 3x, prepared from benzoylaceton (1u), afforded the 3-benzoylpyrrole 4r in 82% yield (method A). The use of Me₃SiOTf (0–20 °C, method B) and heating of 3m in DMSO (method C) also proved to be successful (Table 2, footnote e). However,

### Table 1. Optimization for the Synthesis of Pyrroles 4a and 4r

<table>
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*Yields of isolated products.  
*Besides, 4a was formed, see footnote in Table 2.

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### Table 2. Yields of Condensation Products (3) and Pyrroles (4)

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<td>Et</td>
<td>53</td>
<td>63</td>
<td>B</td>
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</table>

*Yields of isolated products.  
*Besides, 4a was isolated in 19% yield (Figure 1).  
*Besides, 4o was isolated in 5% yield (Figure 1).  
*Failed.  
*Conditions: method A: TFA (10 equiv), CH₂Cl₂, 0–20 °C, 12 h; method B: Me₃SiOTf (1 equiv), CH₂Cl₂, −78 to 20 °C (for β-keto esters) or 0–20 °C (for 1,3-diketones), 12 h; method C: DMSO, 150 °C, 24 h.
slightly lower yields were obtained. Pyrroles 4s and 4t were prepared in good yields starting from substituted benzophenones 1v and 1w, respectively. Method B seems to be the most general procedure to induce the cyclization step. For aliphatic 1,3-diketones (1s, t) the application of method A gave best results. For benzoylacetone derivatives (1u–w) all three methods gave satisfactory results.

Enamines 6a–d were prepared by reaction of 2a with cyclohexane-1,3-diones 5a–d (Scheme 2, Table 3). Treatment of 6a–d with TFA afforded 6,7-dihydro-1H-indol-4(5H)-ones 7a–d in very good yields (method A). Compound 7a\(^{12}\) was also successfully prepared, albeit in lower yield, by application of method C.

The Ph₃P-mediated reaction of hexane-2,5-dione (8) with 2a afforded pyrrole 9 in excellent yield by Staudinger–aza-Wittig reaction and subsequent cyclization (Scheme 3).

In conclusion, a variety of pyrroles and 1,5,6,7-tetrahydroidol-4-one-4H indol-4-ones were prepared by condensation of 1,3-dicarbonyl compounds with 2-azido-1,1-diethoxy-ethane and subsequent cyclization. The best conditions for the cyclization step (acid, Lewis acid or heating) depend on the substitution pattern of the intermediate. The strategy could be successfully applied to the synthesis of a functionalized pyridine.

All moisture-free solvents (>99.9 grade) were used as purchased and all reactions were carried out under Argon atmosphere. For \(^1\)H and \(^13\)C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (Cl, H₂O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

**CAUTION:** The handling of low-molecular weight azides is dangerous due to their potentially explosive character. Although, in our hands, neat 2a, b and 8 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 small scale. The use of a safety shield is highly recommended.

**2-Azido-1,1-diethoxyethane (2a)**

Starting with 2-bromo-1,1-diethoxyethane (31 mL, 200 mmol), sodium azide (19.50 g, 300 mmol) and potassium iodide (3.32 g, 20 mmol) in DMSO (150 mL), 2b was isolated without further purification as a colorless oil (30.629 g, 96%).
Ethyl 3-[(2,2-Diethoxyethyl)amino]but-2-enoate (3b)

Starting with ethyl acetoacetate (1b) (0.4 mL, 3.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.573 g, 3.6 mmol) and Ph₃P (1.180 g, 4.5 mmol) in THF (15 mL), 3b was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 5:1) as a colorless oil (0.656 g, 89%).

IR (neat): 3289 (w), 2980 (s), 2932 (m), 2808 (m), 1741 (m), 1725 (m), 1656 (s), 1609 (s), 1502 (m), 1447 (s), 1381 (m), 1288 (s), 1240 (m), 1176 (s), 1146 (s), 975 (w), 935 (w), 849 (w), 791 (m), 706 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 1.23 (t, J = 7.2 Hz, 6 H, 2 × CH₃), 1.52 (t, J = 7.2 Hz, 6 H, 2 × CH₃), 1.93 (s, 3 H, CH₃), 3.33 (dd, J = 6.3, 5.7 Hz, 2 H, NCH₂), 3.51–3.61 (m, 2 H, OCH₂), 3.62 (s, 3 H, OCH₃), 3.68–3.76 (m, 2 H, OCH₂), 4.48 (d, J = 2.7 Hz, 1 H, CH=C), 4.51 (d, J = 5.4 Hz, 1 H, OCH), 8.61 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 15.2 (2 C), 19.6 (CH₃), 46.0 (NCH₂), 49.8 (OCH₃), 63.1 (2 C, OCH₂), 82.6 (CHO=CH), 102.0 (OCH), 161.6 (N=CH₂), 170.6 (O=CH=O).
Starting with allyl acetoacetate (1e) (0.33 mL, 2.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.382 g, 2.4 mmol) and Ph3P (0.787 g, 3.0 mmol) in THF (10 mL), 3e was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 5:1) as a colorless oil (0.341 g, 62%).

IR (neat): 3292 (w), 2978 (s), 2932 (s), 2885 (s), 1744 (s), 1503 (m), 1449 (m), 1383 (m), 1292 (m), 1244 (s), 1169 (s), 849 (m), 787 (s), 705 cm−1 (w).

HRMS (ESI): m/z calcd for C14H27NO4 [M•]: 273.19401; found: 273.19401; identified: 273.19401.

tert-Butyl 3-(2,2-Diethoxyethyl)amino)but-2-enoate (3g)

Starting with tert-butyl acetoacetate (1e) (0.33 mL, 2.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.382 g, 2.4 mmol) and Ph3P (0.787 g, 3.0 mmol) in THF (10 mL), 3e was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 5:1) as a colorless oil (0.341 g, 62%).

IR (neat): 3292 (w), 2978 (s), 2932 (s), 2885 (s), 1744 (s), 1503 (m), 1449 (m), 1383 (m), 1292 (m), 1244 (s), 1169 (s), 849 (m), 787 (s), 705 cm−1 (w).

HRMS (ESI): m/z calcd for C14H27NO4 [M•]: 273.19401; found: 273.19401; identified: 273.19401.

**Methyl 3-(2,2-Diethoxyethyl)amino)pent-2-enoate (3h)**

Starting with methyl propionylacetate (1f) (0.495 g, 3.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.573 g, 3.6 mmol) and Ph3P (1.180 g, 4.5 mmol) in THF (15 mL), 3f was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 3:1) as a slightly light yellow oil (0.604 g, 82%).

IR (neat): 3288 (w), 2978 (w), 2932 (w), 1658 (s), 1606 (s), 1501 (m), 1444 (s), 1383 (m), 1234 (w), 1280 (m), 1236 (s), 1177 (s), 1136 (s), 1083 (s), 792 cm−1 (m).

HRMS (ESI): m/z calcd for C14H27NO4 [M•]: 275.16271; found: 275.16255.

**Ethyl 3-(2,2-Diethoxyethyl)amino)hex-2-enoate (3i)**

Starting with ethyl acetoacetate (1g) (0.41 mL, 3.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.573 g, 3.6 mmol) and Ph3P (1.180 g, 4.5 mmol) in THF (15 mL), 3g was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 3:1) as a colorless oil (0.341 g, 62%).

IR (neat): 3291 (w), 2978 (s), 2931 (m), 2884 (m), 1665 (s), 1606 (s), 1503 (m), 1446 (m), 1381 (m), 1359 (m), 1286 (s), 1238 (s), 1169 (s), 1130 (s), 1058 (s), 1000 (m), 931 (m), 787 (m), 705 cm−1 (w).

**1H NMR (CDCl 3, 300 MHz):** δ = 1.24 (t, J = 7.2 Hz, 3 H, CH3), 1.55 (sext, J = 7.2 Hz, 2 H, CH2), 1.93 (s, 1 H, CH), 2.17 (t, J = 5.7 Hz, 1 H, OCH), 4.52 (t, J = 7.5 Hz, 2 H, OCH2), 8.61 (br s, 1 H, NH).

HRMS (ESI): m/z calcd for C14H27NO4 [M•]: 273.19401; identified: 273.19401.

**Allyl 3-(2,2-Diethoxyethyl)amino)but-2-enoate (3g)**

Starting with allyl acetoacetate (1g) (0.41 mL, 3.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.573 g, 3.6 mmol) and Ph3P (1.180 g, 4.5 mmol) in THF (15 mL), 3g was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 3:1) as a colorless oil (0.341 g, 62%).

IR (neat): 3291 (w), 2978 (s), 2931 (m), 2884 (m), 1665 (s), 1606 (s), 1503 (m), 1446 (m), 1381 (m), 1359 (m), 1286 (s), 1238 (s), 1169 (s), 1130 (s), 1058 (s), 1000 (m), 931 (m), 787 (m), 705 cm−1 (w).
**tert-Butyl 3-[(2,2-Diethoxyethoxy)amino]hept-2-en-3-olate (3j)**

Starting with tert-butyl 3-oxopropanoate (1j) (0.401 g, 2.0 mmol), 2-azido-1,1-diethylenethane (2a) (0.382 g, 2.4 mmol), and Ph₃P (0.787 g, 3.0 mmol) in THF (10 mL), 3j was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 5:1) as a colorless oil (0.490 g, 78%).

IR (neat): 2970 (s), 2934 (s), 2874 (m), 1736 (s), 1719 (s), 1649 (s), 1608 (s), 1459 (m), 1370 (m), 1314 (m), 1285 (m), 1247 (s), 1147 (s), 1068 (m), 1014 (w), 844 (w), 793 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 0.91 (t, J = 7.2 Hz, 3 H, CH₃), 1.23 (t, J = 7.2 Hz, 6 H, 2 × CH₃), 1.29–1.36 (m, 2 H, CH₂), 1.47 (s, 9 H, i-Pr), 1.58 (quint, J = 7.2 Hz, 2 H, CH₂), 2.18 (t, J = 7.2 Hz, 2 H, CH₂), 2.36 (dd, J = 6.1, 5.4 Hz, 2 H, NCH₂), 3.32–3.61 (m, 2 H, OCH₂), 3.68–3.78 (m, 2 H, OCH₂), 4.41 (s, 1 H, CH), 4.51 (t, J = 5.4 Hz, 1 H, OCH), 8.61 (br s, 1 H, NH).

MS (EI, 70 eV): m/z (%) = 329 (M⁺, 4), 284 (8), 226 (5), 143 (6), 130 (25), 103 (100), 75 (45).


**Ethyl 3-[(2,2-Diethoxyethoxy)amino]dec-2-enoate (3m)**

Starting with ethyl 3-oxodecanoate (1l) (0.485 g, 2.0 mmol), 2-azido-1,1-diethylenethane (2a) (0.382 g, 2.4 mmol) and Ph₃P (0.787 g, 3.0 mmol) in THF (10 mL), 3m was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 10:1) as a slightly light yellow oil (0.612 g, 86%).

IR (neat): 3280 (w), 2970 (s), 2927 (s), 2860 (s), 1654 (s), 1607 (s), 1501 (m), 1458 (m), 1376 (m), 1284 (s), 1234 (s), 1173 (s), 1134 (s), 1060 (s), 790 (m), 713 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H, CH₃), 1.15–1.33 (m, 21 H, 3 × CH₃, 6 × CH₂), 1.50 (quint, J = 7.5 Hz, 2 H, CH₂), 2.18 (t, J = 7.5 Hz, 2 H, CH₂), 3.26 (dd, J = 6.0, 5.7 Hz, 2 H, NCH₂), 3.52–3.62 (m, 2 H, OCH₂), 3.68–3.78 (m, 2 H, OCH₂), 4.09 (q, J = 7.2 Hz, 2 H, OCH₂), 4.47 (s, 1 H, CH), 4.51 (t, J = 5.7 Hz, 1 H, OCH), 8.62 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 13.9, 14.4, 15.1 (2 C, CH₂), 22.5, 27.8, 29.1, 29.2, 29.3, 29.4, 31.7, 32.4 (CH₂), 45.5 (NCH₂), 58.1, 62.9 (2 C, OCH₂), 82.0 (CH=CH), 101.8 (OCH), 165.2 (N=C=CH), 170.4 (O=C=O).

MS (EI, 70 eV): m/z (%) = 357 (M⁺, 1), 312 (2), 254 (2), 212 (5), 200 (4), 154 (5), 126 (3), 103 (100), 96 (12), 75 (55).


**tert-Butyl 3-[(2,2-Diethoxyethoxy)amino]dec-2-en-3-olate (3n)**

Starting with tert-butyl 3-oxodecanoate (1m) (0.200 g, 0.7 mmol), 2-azido-1,1-diethylenethane (2a) (0.142 g, 0.9 mmol) and Ph₃P (0.291 g, 1.1 mmol) in THF (10 mL), 3n was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 5:1) as a slightly light yellow oil (0.250 g, 88%).

IR (neat): 3278 (w), 2970 (s), 2927 (s), 2859 (s), 1650 (s), 1607 (s), 1496 (m), 1458 (m), 1370 (m), 1288 (s), 1241 (s), 1140 (s), 1068 (s), 1013 (m), 949 (w), 848 (w), 791 (m), 714 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H, CH₃), 1.23 (t, J = 7.2 Hz, 6 H, 2 × CH₃), 1.27–1.39 (m, 3 H, 7 × CH₂), 1.46 (s, 9 H, 3 × CH₃), 2.15 (t, J = 7.8 Hz, 2 H, CH₂), 3.30 (dd, J = 6.0, 5.7 Hz, 2 H, NCH₂), 3.50–3.60 (m, 2 H, OCH₂), 3.68–3.78 (m, 2 H, OCH₂), 4.40 (s, 1 H, CH), 4.50 (t, J = 5.7 Hz, 1 H, OCH), 8.61 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 13.9, 14.5, 15.1 (2 C, CH₂), 22.5, 27.8, 29.1, 29.2, 29.3, 29.4, 31.7, 32.4 (CH₂), 45.5 (NCH₂), 58.1, 62.9 (2 C, OCH₂), 82.0 (CH=CH), 101.8 (OCH), 165.2 (N=C=CH), 170.4 (O=C=O).

MS (EI, 70 eV): m/z (%) = 385 (M⁺, 4), 312 (1), 282 (2), 226 (8), 214 (31), 197 (27), 155 (60), 114 (12), 103 (100), 75 (31).

HRMS (ESI): m/z calc for C₁₂H₁ₐN₃O₃ [M⁺]: 385.3178; found: 385.3178.

**Ethyl 3-[(2,2-Diethoxyethoxy)amino]tridec-2-enoate (3o)**

Starting with ethyl 3-oxotridecanoate (1n) (0.141 g, 0.6 mmol), 2-azido-1,1-diethylenethane (2b) (0.087 g, 0.7 mmol) and Ph₃P (0.787 g, 3.0 mmol) in THF (10 mL), 3o was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 10:1) as a slightly light yellow oil (0.555 g, 84%).
(0.216 g, 0.8 mmol) in THF (5 mL), 3o was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 3:1) as a light yellow oil (0.163 g, 86%).

IR (neat): 3282 (w), 2928 (s), 2857 (s), 1655 (s), 1608 (s), 1501 (m), 1458 (m), 1372 (m), 1287 (m), 1242 (s), 1179 (s), 1135 (s), 1080 (s), 1056 (s), 981 (w), 790 (m), 713 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H, CH₃), 1.25 (t, J = 7.2 Hz, 3 H, CH₂), 1.26–1.33 (m, 14 H, 7 × CH₂), 1.51 (quint, J = 7.5 Hz, 2 H, CH₂), 2.17 (t, J = 7.8 Hz, 2 H, CH), 3.32 (dd, J = 6.0, 5.7 Hz, 2 H, NCH₂), 3.42 (s, 6 H, 2 × OCH₃), 4.09 (q, J = 7.2 Hz, 2 H, OCH₂), 4.41 (t, J = 5.7 Hz, 1 H, OCH), 4.48 (s, 1 H, CH), 8.60 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 14.0, 14.5 (CH₂), 22.6, 23.4, 27.9, 28.9, 29.2, 29.3, 29.4, 29.5, 31.8, 32.5 (CH₃), 44.6 (NCH₃), 54.3 (2 C, OCH₃), 58.2 (OCH₂), 82.2 (CH=CH), 103.4 (OCH), 165.3 (N– CH=CH), 170.6 (O=C–O).

MS (EL, 70 eV): m/z (%) = 357 (M⁺, 3), 343 (4), 326 (1), 312 (6), 282 (13), 268 (25), 88 (29), 75 (100).


Ethyl 3-[1-(2,2-Diethoxyethyl)amino]tridec-2-enoate (3p)

Starting with ethyl 3-oxotetradecanoate (1o) (0.413 g, 2.0 mmol), 2-azido-1,1-diethylylethylene (2a) (0.382 g, 2.4 mmol) and Ph₃P (0.787 g, 3.0 mmol) in THF (10 mL), 3p was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 3:1) as a slightly light yellow oil (0.703 g, 91%).

IR (neat): 3280 (w), 2926 (s), 2859 (s), 1700 (m), 1653 (s), 1607 (s), 1510 (m), 1458 (m), 1377 (m), 1283 (m), 1233 (m), 1172 (s), 1133 (s), 1059 (s), 789 (m), 715 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 0.88 (t, J = 7.5 Hz, 3 H, CH₃), 1.20–1.33 (m, 25 H, 3 × CH₂, 8 × CH₃), 1.48–1.59 (m, 2 H, CH₂), 2.18 (t, J = 7.5 Hz, 2 H, CH₂), 3.32 (dd, J = 6.0, 5.7 Hz, 2 H, NCH₂), 3.50–3.60 (m, 2 H, OCH₂), 3.68–3.78 (m, 2 H, OCH₂), 4.09 (q, J = 7.2 Hz, 2 H, OCH₂), 4.47 (s, 1 H, CH=CH), 4.51 (t, J = 5.7 Hz, 1 H, OCH), 8.62 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 13.7, 14.2, 14.9 (2 C, CH₂), 22.3, 27.7, 29.01 (2 C), 29.03, 29.16, 29.28 (2 C), 31.6, 32.2 (CH₂), 45.3 (NCH₂), 57.8, 62.6 (2 C, OCH₂), 81.9 (CH=CH), 101.6 (OCH), 164.9 (N=C=CH), 170.1 (O=C–O).

MS (EL, 70 eV): m/z (%) = 358 (M⁺, 1), 340 (6), 326 (82), 295 (22), 282 (6), 267 (25), 223 (2), 199 (6), 186 (14), 157 (10), 125 (8), 116 (5), 103 (100).


Ethyl 7-Chloro-3-[1-(2,2-diethoxyethyl)amino]hept-2-enoate (3s)

Starting with ethyl 7-chloro-3-oxoheptanoate (1p) (0.413 g, 2.0 mmol), 2-azido-1,1-diethylylethylene (2a) (0.382 g, 2.4 mmol) and Ph₃P (0.787 g, 3.0 mmol) in THF (10 mL), 3s was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 5:1) as a light yellow oil (0.537 g, 83%).

IR (neat): 2976 (s), 2938 (s), 2876 (s), 1730 (w), 1682 (s), 1568 (s), 1449 (m), 1377 (m), 1354 (m), 1269 (s), 1139 (s), 1056 (s), 992 (m), 792 cm⁻¹ (m).

1H NMR (CDCl₃, 300 MHz): δ = 1.21 (t, J = 7.2 Hz, 6 H, 2 × CH₃), 1.24 (t, J = 7.2 Hz, 3 H, CH₃), 1.63 (quint, J = 6.6 Hz, 2 H, CH₂), 1.75 (quint, J = 6.6 Hz, 2 H, CH₂), 3.12 (t, J = 6.6 Hz, 2 H, CH₂), 3.30 (d, J = 5.4 Hz, 2 H, NCH₂), 3.36 (t, J = 6.6 Hz, 2 H, CH₂), 3.50–3.60 (m, 2 H, OCH₂), 3.68–3.78 (m, 2 H, OCH₂), 4.07 (q, J = 7.2 Hz, 2 H, OCH₂), 4.61 (s, 1 H, CH), 4.77 (t, J = 5.4 Hz, 1 H, OCH), 8.62 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 14.6, 15.3 (2 C, CH₂), 19.1, 23.1, 26.2 (CH₂), 51.2 (NCH₂), 55.2 (CH₃), 57.9, 63.3 (2 C, OCH), 81.3 (CH=CH), 99.2 (OCH), 162.3 (N=C=CH), 168.8 (O=C–O).

MS (EL, 70 eV): m/z (%) = 285 (M–Cl⁻)⁺, 161, 256 (19), 240 (60), 212 (7), 194 (11), 182 (51), 166 (16), 154 (29), 138 (12), 124 (8), 122 (29), 116 (82), 103 (100), 89 (31), 75 (92).


Ethyl 9-Chloro-3-[1-(2,2-diethoxyethyl)amino]non-2-enoate (3t)

Starting with ethyl 9-chloro-3-oxononanoate (1q) (0.470 g, 2.0 mmol), 2-azido-1,1-diethylylethylene (2a) (0.382 g, 2.4 mmol) and Ph₃P (0.787 g, 3.0 mmol) in THF (10 mL), 3t was isolated after...
chromatography (silica gel, n-hexane–EtOAc, 100:1 → 5:1) as a slightly light yellow oil (0.569 g, 81%).

IR (neat): 2977 (s), 2935 (s), 2869 (s), 1741 (m), 1721 (m), 1652 (s), 1605 (s), 1501 (m), 1453 (m), 1347 (m), 1285 (s), 1235 (s), 1175 (s), 1132 (s), 1058 (s), 789 (m), 731 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 1.22 (t, J = 7.2 Hz, 6 H, 2 × CH₂), 2.94 (t, J = 7.2 Hz, 3 H, CH), 2.30 (t, J = 7.5 Hz, 2 H, CH₂), 3.53–3.61 (m, 2 H, OCH₂), 3.69–3.78 (m, 2 H, OCH₂), 4.09 (q, J = 6.0, 5.7 Hz, 2 H, NCH₂), 4.34 (s, 1 H, OCH2), 4.47 (s, 1 H, CH), 4.51 (t, J = 5.7 Hz, 1 H, OCH), 5.00 (s, 1 H, CH=O), 5.68 (s, 1 H, CH=C), 7.40 (m, 3 H, 2 × CH of Ph), 8.63 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 21.5 (CH₂), 28.1, 31.9, 32.0 (CH₂), 44.4 (CH₂Cl), 45.1 (NCH₂), 57.6 (OCH₂), 62.5 (2 C, OCH₂), 81.8 (CH=O), 104.1 (OCH), 164.9 (N–CH=O), 169.9 (O=CH–O).

MS (EI, 70 eV): m/z (%) = 277 (M⁺, 7), 232 (6), 199 (7), 174 (7), 173 (6), 159 (8), 158 (6), 144 (1), 115 (10), 75 (45).

HRMS (ESI): m/z calculated for C₁₁H₁₉NO₃ [M⁺]: 243.1829; found: 243.1832.

3-(2,2-Diethoxyethyl)amino)-5,5-dimethylcyclohex-2-en-1-one (6b)
Starting with dimedone (5b) (0.421 g, 3.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.573 g, 3.6 mmol), and Ph,P (1.180 g, 4.5 mmol) in THF (15 mL), 6b was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1→EtOAc→acetone) as a light yellow oil (0.703 g, 92%).

IR (neat): 3259 (m), 3069 (s), 2967 (s), 2935 (s), 2878 (s), 1738 (m), 1540 (s), 1452 (s), 1425 (m), 1410 (m), 1376 (s), 1271 (s), 1242 (s), 1151 (s), 1065 (s), 960 (w), 932 (w), 891 (w), 809 (m), 732 (m), 703 (w), 660 (w), 607 (m), 560 (m), 482 cm$^{-1}$ (w).

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.07$ (s, 6 H, 2 CH$_3$), 1.22 (t, $J = 7.2$ Hz, 6 H, 2 $\times$ CH$_2$), 2.17 (s, 2 H, CH$_2$), 2.27 (s, 2 H, CH$_2$), 3.23 (dd, $J = 5.4$, 5.4 Hz, 2 H, NCH$_2$), 3.50–3.60 (m, 2 H, OCH$_2$), 3.65–3.75 (m, 2 H, OCH$_2$), 4.67 (t, $J = 5.4$ Hz, 1 H, OCH$_2$), 5.12 (s, 1 H, CH=C), 5.89 (br s, 1 H, NH).

1C NMR (CDCl$_3$, 75 MHz): $\delta = 14.9$ (2 H, CH$_2$), 27.8 (2 H, CH$_2$), 32.3 (C), 42.8 (CH$_3$), 44.9 (NCH$_2$), 49.9 (CH$_2$), 62.2 (2 $\times$ OCH$_2$), 94.6 (CH=C), 99.1 (O=CH), 163.2 (N=C=CH), 196.2 (C=O).

MS (EL, 70 eV): $m/z$ (%) = 255 (M$^+$, 8), 210 (2), 181 (2), 164 (6), 151 (2), 138 (2), 122 (1), 103 (77), 84 (100), 75 (47).

HRMS (ESI): $m/z$ calcd for C$_{14}$H$_{25}$NO$_3$ [M$^+$]: 255.1829; found: 255.1824.

3-(2,2-Diethoxyethyl)amino)-5-methylcyclohex-2-en-1-one (6c)
Starting with 5-methyl-1,3-cyclohexanedione (5e) (0.386 g, 3.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.573 g, 3.6 mmol) and Ph,P (1.180, 4.5 mmol) in THF (15 mL), 6c was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1→EtOAc→acetone) as a light brown oil (0.724 g, 94%).

IR (neat): 3260 (m), 3070 (m), 2968 (s), 2933 (s), 2882 (m), 1547 (s), 1451 (s), 1427 (m), 1412 (m), 1372 (s), 1304 (s), 1272 (s), 1245 (m), 1134 (m), 1067 (s), 808 cm$^{-1}$ (w).

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.03$–1.13 (m, 3 H, CH$_3$), 1.23 (dt, $J = 7.2$, 1.2 Hz, 6 H, 2 $\times$ CH$_2$), 2.00–2.34 (m, 5 H, 2 $\times$ CH$_2$), 3.22 (dd, $J = 5.4$, 5.4 Hz, 2 H, NCH$_2$), 3.50–3.60 (m, 2 H, OCH$_2$), 3.65–3.75 (m, 2 H, OCH$_2$), 4.66 (t, $J = 5.4$ Hz, 1 H, OCH$_2$), 4.80 (br s, 1 H, NH), 5.13 (s, 1 H, CH=C).

1C NMR (CDCl$_3$, 75 MHz): $\delta = 15.1$ (2 CH$_3$), 20.3 (CH$_3$), 27.5 (CH$_3$), 35.4, 42.1 (CH$_3$), 44.8 (NCH$_2$), 62.2 (2 $\times$ OCH$_2$), 95.8 (CH=C), 99.8 (O=CH), 163.4 (N=C=CH), 196.0 (C=O).

MS (EL, 70 eV): $m/z$ (%) = 241 (M$^+$, 5), 196 (1), 151 (5), 138 (3), 124 (2), 103 (100), 74 (38).

HRMS (ESI): $m/z$ calcd for C$_{13}$H$_{23}$NO$_3$ [M$^+$]: 324.16777; found: 324.16770.

3-(2,2-Diethoxyethyl)amino)-5-phenylcyclohex-2-en-1-one (6d)
Starting with 5-phenyl-1,3-cyclohexanedione (5d) (0.588 g, 3.0 mmol), 2-azido-1,1-diethoxyethane (2a) (0.573 g, 3.6 mmol) and Ph,P (1.180, 4.5 mmol) in THF (15 mL), 6d was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1→EtOAc) as a light brown solid (0.838 g, 92%).

IR (KBr): 3243 (s), 3065 (s), 2975 (m), 2934 (m), 2888 (m), 1545 (s), 1441 (s), 1374 (m), 1234 (s), 1133 (s), 1069 (s), 757 (w), 701 cm$^{-1}$ (w).

1H NMR (CDCl$_3$, 300 MHz): $\delta = 1.23$ (dt, $J = 7.2$, 1.4 Hz, 6 H, 2 $\times$ CH$_2$), 2.44–2.75 (m, 4 H, 2 $\times$ CH$_2$), 3.24 (dd, $J = 5.1$, 5.1 Hz, 2 H, NCH$_2$), 3.29–3.41 (m, 1 H, CH$_3$), 3.50–3.61 (m, 2 H, OCH$_2$), 3.66–3.76 (m, 2 H, OCH$_2$), 4.65 (t, $J = 5.1$ Hz, 1 H, OCH$_2$), 4.81 (br s, 1 H, NH), 5.22 (s, 1 H, CH=C), 7.23–7.27 (m, 3 H, 3 $\times$ CH of Ph), 7.31–7.34 (m, 2 H, 2 $\times$ CH of Ph).

Starting with 3a (0.100 g, 0.4 mmol) and Me 3SiOTf (0.172 g, 0.8 mmol) TFA (0.33 mL, a 1:1) as a light brown oil was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1). HRMS (ESI): m/z calcd for C8H11NO2: 153.0790 [M+]; found: 153.0790 ± 2 ppm.

Isopropyl 2-Methyl-1H-pyrrrole-3-carboxylate (4c)
Starting with 3c (0.200 g, 0.8 mmol) and Me3SiOTf (0.172 g, 0.8 mmol) in CH2Cl2 (10 mL), 4c was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1) as a light brown oil (0.064 g, 50%).

IR (neat): 3318 (m), 2925 (m), 1703 (m), 1609 (m), 1553 (s), 1402 (s), 1306 (s), 1251 (m), 1212 (s), 1155 (m), 1053 (m), 902 (w), 788 (w), 724 cm−1 (w).

1H NMR (CDCl3, 300 MHz): δ = 1.26 (d, J = 6.8, 2 H, 2 CH3), 2.53 (s, 3 H, CH3), 5.04 (sept, J = 6.3 Hz, 1 H, OCH3), 6.55 (d, J = 2.7 Hz, 1 H, CH), 8.58 (bs r s, 1 H, NH).

13C NMR (CDCl3, 75 MHz): δ = 13.2, 16.1 (2 C, CH3), 53.8 (CH3), 110.3 (CH), 111.9 (C), 135.3 (13C, O=C=O–C=O–).

MS (EI, 70 eV): m/z (%) = 167 (M+, 96), 124 (19), 107 (100), 88 (73).

IR (neat): 3321 (m), 2983 (s), 2941 (w), 2897 (w), 1705 (s), 1691 (s), 1673 (s), 1577 (m), 1491 (w), 1414 (w), 1371 (m), 1331 (m), 1272 (m), 1223 (w), 1200 (m), 1126 (s), 1087 (m), 1054 (m), 901 (w), 786 (w), 722 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 0.98 (d, J = 6.9 Hz, 6 H, 2 × CH₃), 1.98 (m, J = 6.9 Hz, 1 H, CH₂), 2.53 (s, 3 H, CH₃), 3.87 (d, J = 6.9 Hz, 2 H, OCH₂), 6.54–6.58 (m, 2 H, 2 × CH), 8.53 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 13.2, 19.1 (2 C, CH₃), 27.8 (CH), 70.4 (OCH₂), 110.5 (CH), 111.8 (C), 115.7 (CH), 135.2 (C), 165.4 (O=C–O).

MS (EI, 70 eV): m/z (%): 181 (M⁺, 70), 124 (45), 108 (100), 80 (42).

HRMS (ESI): m/z calcd for C₁₀H₁₄NO₂ [M⁺]: 181.1102; found: 181.1104.

2-Methoxethyl 2-Methyl-1H-pyrrole-3-carboxylate (4e)

Starting with 3f (0.100 g, 0.4 mmol) in DMSO (2 mL), 4e was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 1:1 as a light brown solid (0.034 g, 51%).

IR (neat): 3139 (br), 2930 (w), 1684 (s), 1455 (m), 1322 (w), 1269 (m), 1231 (w), 1196 (w), 1099 (s), 1060 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 2.52 (s, 3 H, CH₃), 3.42 (s, 3 H, OCH₂), 3.68–3.71 (m, 2 H, OCH₂), 4.36–4.39 (m, 2 H, OCH₂), 5.64–5.68 (m, 2 H, 2 × CH), 8.35 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): δ = 13.2 (CH₂), 58.9 (OCH₂), 62.4, 70.8 (OCH₂), 110.5 (CH), 111.3 (C), 115.8 (CH), 135.5 (C), 165.5 (O=C–O).

MS (EI, 70 eV): m/z (%): 183 (M⁺, 9), 125 (23), 108 (100), 80 (14).

HRMS (EI, 70 eV): m/z calcd for C₁₀H₁₅NO₂: 183.0895 [M⁺]; found: 183.0895 ± 2 ppm.

Allyl 2-Methyl-1H-pyrrole-3-carboxylate (4f)

Starting with 3g (0.100 g, 0.4 mmol) and Me₃SiOTf (0.087 g, 0.4 mmol) in CH₂Cl₂ (5 mL) at 0 °C, 4f was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 1:1 as a light brown oil (0.024 g, 37%).

IR (neat): 3337 (br, m), 2976 (w), 2928 (m), 1703 (s), 1581 (m), 1447 (m), 1411 (m), 1327 (m), 1175 (m), 1102 (w), 994 (w), 933 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 2.53 (s, 3 H, CH₃), 4.62–4.74 (m, 2 H, CH₂, OCH₂), 5.20–5.39 (m, 2 H, CH₂, OCH₂), 5.91–6.09 (m, 1 H, CH=CH₂), 6.55–6.58 (m, 2 H, 2 × CH), 8.35 (br s, 1 H, NH).

Anal. Calcd for C₁₀H₁₅NO₂ (139.24): C, 68.73; H, 7.82. Found: C, 68.55; H, 7.58.

Methyl 2-Ethyl-1H-pyrrole-3-carboxylate (4g)

Starting with 3h (0.100 g, 0.4 mmol) and Me₃SiOTf (0.091 g, 0.4 mmol) in CH₂Cl₂ (5 mL) at 0 °C, 4g was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 1:1 as a light brown solid (0.024 g, 39%).

IR (KBr): 3296 (br, w), 2954 (m), 2929 (m), 1715 (s), 1445 (m), 1371 (m), 1226 (s), 1102 cm⁻¹ (m).

1H NMR (CDCl₃, 300 MHz): δ = 1.25 (t, J = 7.2 Hz, 3 H, CH₃), 3.00 (q, J = 7.2 Hz, 2 H, CH₂), 3.79 (s, 3 H, OCH₃), 6.55–6.58 (m, 2 H, 2 × CH), 8.28 (br s, 1 H, NH).

MS (EI, 70 eV): m/z (%): 153 (M⁺, 49), 138 (1), 94 (100), 80 (2).

1^1C NMR (CDCl₃, 75 MHz): δ = 14.1, 14.5 (CH₃), 22.6, 27.3, 29.3, 29.4, 29.47, 29.51, 29.7, 31.8 (CH₂), 59.3 (OCH₂), 110.5 (CH), 111.1 (C), 115.7 (CH), 140.0 (C), 146.5 (O=C–O).

MS (EL, 70 eV): m/z (%) = 265 (M⁺, 64), 236 (8), 220 (5), 192 (52), 166 (98), 154 (22), 138 (6), 124 (37), 120 (17), 94 (100).

HRMS (EL, 70 eV): m/z calc for C₁₄H₂₀N₂O₂: 279.1406 [M⁺] ± 2 ppm.

Starting with 3o (0.130 g, 0.4 mmol) and Me₃SiOTf (0.085 g, 0.4 mmol) in CH₂Cl₂ (7 mL), 4k was isolated after chromatography (silica gel, n-hexane–EtOAc, 2:1) as a light brown oil (0.061 g, 57%).

Starting with 3o (0.300 g, 0.81 mmol) and Me₃SiOTf (0.191 g, 0.9 mmol) in CH₂Cl₂ (15 mL), 4k was isolated after chromatography (silica gel, n-hexane–EtOAc, 1:1) as a light brown oil (0.122 g, 54%).

IR (neat): 3377 (m), 2956 (s), 2926 (s), 2854 (s), 1676 (s), 1463 (s), 1185 (m), 1183 (m), 1131 (m). MS (EI, 70 eV): m/z (%) = 279 (M⁺, 55), 250 (5), 234 (3), 206 (42), 197 (2), 166 (100), 138 (6), 120 (12), 94 (98).

HRMS (EL, 70 eV): m/z calc for C₁₄H₂₀N₂O₂: 279.1406 [M⁺] ± 2 ppm.

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was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1 → 1:1) as a light yellow solid (0.130 g, 70%).

IR (KBr): 3232 (w), 2924 (w), 1608 (s), 1561 (m), 1446 (s), 1367 (m), 2851 (w), 1646 (s), 1571 (m), 1493 (s), 1475 (s), 1412 (s), 1367 (m), 1331 (w), 1282 (m), 1220 (m), 1150 (w), 954 (m), 902 (w), 885 (w), 796 (m), 733 (m), 675 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): "δ = 1.18 (t, J = 7.2 Hz, 3 H, CH₃), 1.20 (t, J = 7.2 Hz, 3 H, CH₃), 2.70 (q, J = 7.2 Hz, 2 H, CH₂), 2.97 (q, J = 7.2 Hz, 2 H, CH₂), 6.38–6.41 (m, 1 H, CH), 6.45–6.49 (m, 1 H, CH), 8.27 (br s, 1 H, NH).

13C NMR (CDCl₃, 75 MHz): "δ = 101.1, 13.8 (CH₃), 20.2, 35.4 (CH₃), 110.7, 115.8 (CH), 119.8, 146.1 (C), 199.4 (C=O).

MS (EI, 70 eV): m/z (%) = 151 (M⁺, 51), 122 (3), 107 (100), 94 (3), 80 (25), 66 (2), 43 (11).

Anal. Calcd for C₅H₅NO (123.15): C, 68.27; H, 7.37. Found: C, 68.12; H, 7.15.

1-(2-Methyl-1H-pyrrol-3-yl)propan-1-one (4p)

Starting with 3w (0.300 g, 1.2 mmol) and TFA (0.96 mL, 12.3 mmol) in CHCl₃ (15 mL), 1H was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1 → 1:1) as a light yellow solid (0.130 g, 70%).

IR (KBr): 3212 (s), 3112 (s), 3023 (m), 2978 (w), 2959 (m), 2927 (m), 2851 (w), 1646 (s), 1571 (m), 1493 (s), 1475 (s), 1412 (s), 1367 (s), 1331 (w), 1282 (m), 1220 (m), 1150 (w), 954 (m), 902 (w), 885 (w), 796 (m), 733 (m), 675 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): "δ = 1.24 (s, 3 H, CH₃), 2.55 (s, 3 H, CH₃), 6.52–6.54 (m, 1 H, CH), 6.57–6.59 (m, 1 H, CH), 8.52 (br s, 1 H, NH).

13C NMR (CDCl₃, 62 MHz): "δ = 11.6, 15.2 (2 C), 29.7 (CH₃), 49.7 (NCH₂), 63.9 (2 C, OCH₂), 102.0 (OCH), 110.0, 120.8 (CH), 121.2, 135.6 (C), 195.1 (C=O).

MS (EI, 70 eV): m/z (%) = 239 (M⁺, 31), 224 (2), 194 (6), 178 (2), 165 (18), 149 (10), 136 (5), 123 (14), 107 (60), 103 (100), 94 (14), 75 (83).

HRMS (ESI): m/z calcd for C₇H₁₅NO₄ [M⁺]: 239.15119; found: 239.15119.

1-(2-Methyl-1H-pyrrol-3-yl)ethanone (4o)

Starting with method B (0.120 g, 0.1 mmol) and TFA (0.32 mL, 4.3 mmol) in CH₂Cl₂ (6.4 mL), 4s was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1 → 1:1) as a light yellow oil (0.07 g, 79%).

IR (KBr): 3270 (w), 3054 (w), 2926 (w), 1958 (m), 1498 (s), 1283 (s), 1021 (w), 735 cm⁻¹ (s).

1H NMR (CDCl₃, 250 MHz): "δ = 2.43 (s, 3 H, CH₃), 3.72 (s, 3 H, OCH₃), 6.17–6.19 (m, 1 H, CH₂), 6.43–6.45 (m, 1 H, CH₂), 6.88–6.94 (m, 2 H, CH₂), 7.24 (dd, J = 7.7 Hz, J = 2.0 Hz, 1 H, CH₂), 8.35 (dd, J = 2.0 Hz, J = 1.7 Hz, 1 H, CH₂), 8.35 (br s, 1 H, NH).

13C NMR (CDCl₃, 62 MHz): "δ = 13.8 (CH₃), 55.7 (OCH₃), 111.3 (CH₃), 112.5 (CH₂), 120.2 (CH₂), 121.1 (C₆), 128.3, 128.7, 130.5 (C₆), 136.4 (C₆), 156.5 (C₆), 192.1 (C = O).


1,5,6,7-Tetrahydro-4H-indol-4-one (7a)

Method A: Starting with 6a (0.070 g, 0.33 mmol) and TFA (0.24 mL, 3.1 mmol) in CH₂Cl₂ (5 mL), 7a was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1 → EtOAc) as a slightly light yellow solid (0.040 g, 95%).

Method C: Starting with 6a (0.300 g, 1.32 mmol) in DMSO (5 mL), 4r was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1 → 1:1) as a light brown solid (0.048 g, 72%).

IR (KBr): 3183 (w), 3105 (s), 2949 (s), 2889 (w), 2846 (w), 1683 (w), 1622 (s), 1493 (s), 1477 (s), 1310 (w), 1197 (w), 1146 (w), 893 (w), 854 (w), 804 (w), 705 cm⁻¹ (w).

1H NMR (CDCl₃–DMSO-d₆, 250 MHz): "δ = 2.12 (quint, J = 6.3 Hz, 2 H, CH₂), 2.44 (t, J = 6.3 Hz, 2 H, CH₂), 2.81 (t, J = 6.3 Hz, 2 H, CH₂), 6.44 (m, 1 H, CH), 6.64 (m, 1 H, CH), 10.71 (br s, 1 H, NH).

Starting with acetonylacetone (8) (0.21 mL, 1.8 mmol), 2-azido-1,1-diethoxypropane (10) (0.35 g, 2.1 mmol) and Ph₃P (0.708 g, 2.7 mmol) in THF (15 mL), 9 was isolated after chromatography (silica gel, n-hexane–EtOAc, 100:1 → 10:1) as a slightly light yellow oil (0.353 g, 93%).

IR (neat): 2976 (s), 2925 (s), 2901 (s), 1521 (w), 1447 (m), 1409 (s), 1383 (m), 1303 (m), 1107 (s), 1076 (s), 1019 (m), 752 cm⁻¹ (w).

HRMS (ESI): m/z (%) = 211 (M⁺, 58), 166 (21), 138 (10), 122 (12), 107 (39), 103 (100), 76 (94).

3-Azido-1,1-diethoxypropane (10)
Sodium azide (9.752 g, 150 mmol) and potassium iodide (1.669 g, 10 mmol) were added to 3-chloropropionaldehyde diethyl acetal (16.8 mL, 100 mmol) in DMSO (100 mL) at r.t. The reaction mixture was heated to 90 °C and stirred for 72 h at 90 °C. After cooling to r.t., H₂O (200 mL) and Et₂O (200 mL) were added, the organic layer was separated and the aqueous layer was repeatedly extracted with Et₂O (3 × 200 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and the filtrate was concentrated to dryness in vacuo. Product 10 was isolated without further purification as a slightly light yellow oil (15.271 g, 88%).

IR (neat): 3415 (br), 2998 (w), 2950 (w), 2909 (w), 1547 (s), 1442 (m), 1379 (m), 1299 (s), 1226 (w), 1127 (s) cm⁻¹.

HRMS (ESI): m/z (%) = 163 (M⁺, 29), 106 (29), 103 (100), 79 (57), 59 (13), 57 (13), 45 (93), 28 (100).

3-(3,3-Diethoxypropyl)amino)-1-phenylbut-2-en-1-one (11)
The reaction was carried by application of the procedure given for the synthesis of products 3. Starting with benzoylaceton (1u) (0.487 g, 3.0 mmol), 10 (0.624 g, 3.6 mmol) and Ph₃P (1.180 g, 4.5 mmol) in THF (15 mL), 11 was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1 → 3:1) as a light yellow oil (0.805 g, 95%).

IR (neat): 3463 (br), 3061 (w), 2974 (m), 2929 (m), 2882 (m), 1601 (s), 1547 (s), 1442 (m), 1379 (m), 1317 (s), 1299 (s), 1226 (w), 1127 (s), 1064 (s), 809 (w), 739 (m), 689 cm⁻¹ (w).

HRMS (ESI): m/z (%) = 147 (M⁺, 27), 132 (C₂H₇), 46.9 (CH₃N₂), 61.2 (2 C, OCH₃), 99.9 (CH).
(2-Methylpyridin-3-yl)phenyl)methanone (12)

The reaction was carried by application of the procedures given for the synthesis of products 3 and 4 (method A). Starting with 11 (0.146 g, 0.5 mmol) and TFA (0.4 mL, 5.0 mmol) in CH₂Cl₂ (3 mL) (0–20 °C), 12 was isolated after chromatography (silica gel, n-hexane–EtOAc, 50:1 to EtOAc as a light yellow solid (0.095 g, 96%).

IR (KBr): 3004 (w), 1721 (s), 1667 (s), 1616 (m), 1414 (w), 1382 (w), 1283 (s), 1198 (s), 1131 (s), 1070 (m), 965 (m), 898 (w), 822 (s), 706 (m), 638 (m), 574 (w), 545 cm⁻¹ (w).

1H NMR (CDCl₃, 300 MHz): δ = 2.76 (s, 3 H, CH₃), 7.55 (s, 1 H, CH₃), 7.69–7.79 (m, 4 H, 4 × CH), 7.95 (q, 1 H, CH₂), 8.16 (d, J = 7.5 Hz, 1 H, CH), 8.96 (d, J = 4.8 Hz, 1 H, CH).

13C NMR (CDCl₃, 75 MHz): δ = 19.2 (CH₃), 123.1, 129.2 (C), 130.0 (C), 134.8 (CH), 154.1 (C), 193.0 (C=O).

MS (EI, 70 eV): m/z (%): 197 (M⁺, 100), 182 (12), 105 (50), 92 (24), 77 (57).

HRMS (ESI): m/z calc for C₁₃H₁₁NO [M +]: 197.0841; found: 197 (M +, 100), 182 (3), 120 (12), 105 (4), 92 (2), 77 (15), 60 (12), 55 (10), 42 (9), 32 (9), 20 (8), 17 (5).

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References


