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Synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives from 2-(2-bromoallyl)-1,3-dicarbonyl compounds

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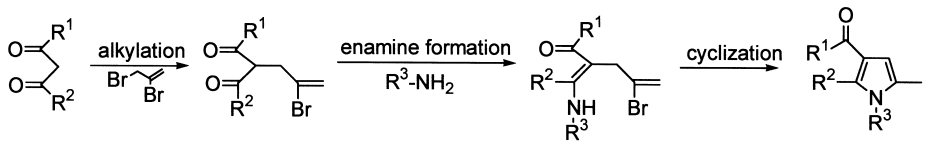
Abstract—2-(2-Bromoallyl)-1,3-dicarbonyl compounds are converted into β-enamino, β-hydrazino esters and ketones, followed by base-promoted cyclization, leading to the formation of the corresponding 1,2,3,5-tetrasubstituted pyrroles. 1,2,4- and 1,2,3,4-Substituted pyrroles are also isolated as minor products. Starting from the 2-(2-bromoallyl)-cyclohexane-1,3-dione the corresponding tetrahydro indolone is prepared in good yield.

1. Introduction

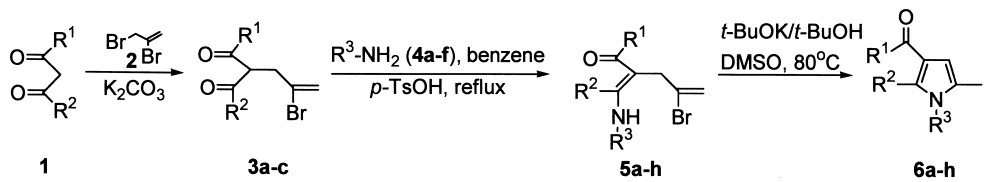
Pyrroles are very important compounds as they occur in a large number of natural products and display a variety of physiological activities;[1] in particular, 1,2,3,5-tetrasubstituted pyrrole derivatives[2] are biologically active and have been proven to display antibacterial,[3] antiviral,[4] antiinflammatory[5] and antioxidant activities and to inhibit cytokine-mediated diseases.[6] Additionally, they have been found to show potent inhibiting platelet aggregation[7] and antihypertensive activities.[8]

1,3-Dicarbonyl compounds are versatile intermediates for the synthesis of pyrrole derivatives.[9] Pioneering work on the synthesis of pyrroles from 1,3-dicarbonyl compounds was carried out by Hantzsch in 1890. Hantzsch's pyrrole synthesis is the condensation of α-haloketones with 1,3-dicarbonyl compounds in the presence of ammonia. In this reaction, alkylation of 1,3-dicarbonyl compounds with α-haloketones followed by enaminone formation and cyclization furnishes pyrroles. Many studies have been published on the synthesis of pyrroles using the principle of Hantzsch's method starting from 1,3-dicarbonyl compounds.[10] Ferraz et al. described the synthesis of *N*-substituted pyrrole and tetrahydroindole derivatives from alkenyl 1,3-dicarbonyl compounds via the formation of iodo-1,3-enamino esters followed by dehydroiodination.[11] Lightner et al. described the regioselective synthesis of substituted α-cyanopyrroles using oximino cyanoacetate esters in a Knorr-type reductive condensation with 1,3-diketones in the presence of water.[12]

Recently, Arcadi et al.[13] described the synthesis of chiral 1,2,3,5-substituted pyrrole derivatives via gold catalyzed amination/annulation reactions of 2-propynyl-1,3-dicarbonyl compounds. Pyrroles with the same substitution pattern



Scheme 1.



Scheme 2.

Keywords: nitrogen heterocycles; pyrroles; enamine esters; cyclization.

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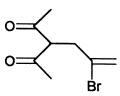
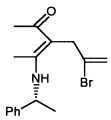
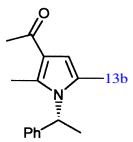
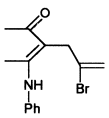
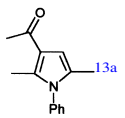
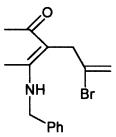
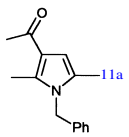
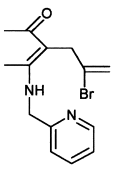
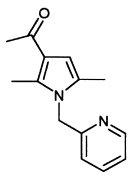
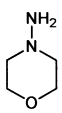
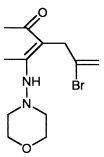
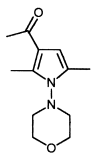
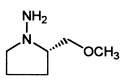
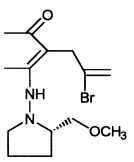
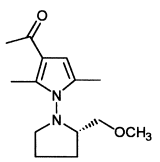
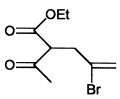
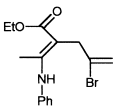
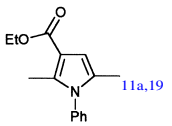
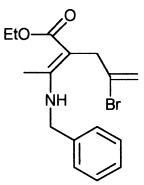
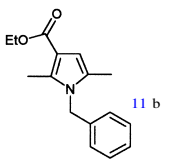
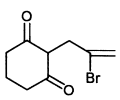
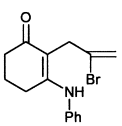
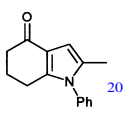
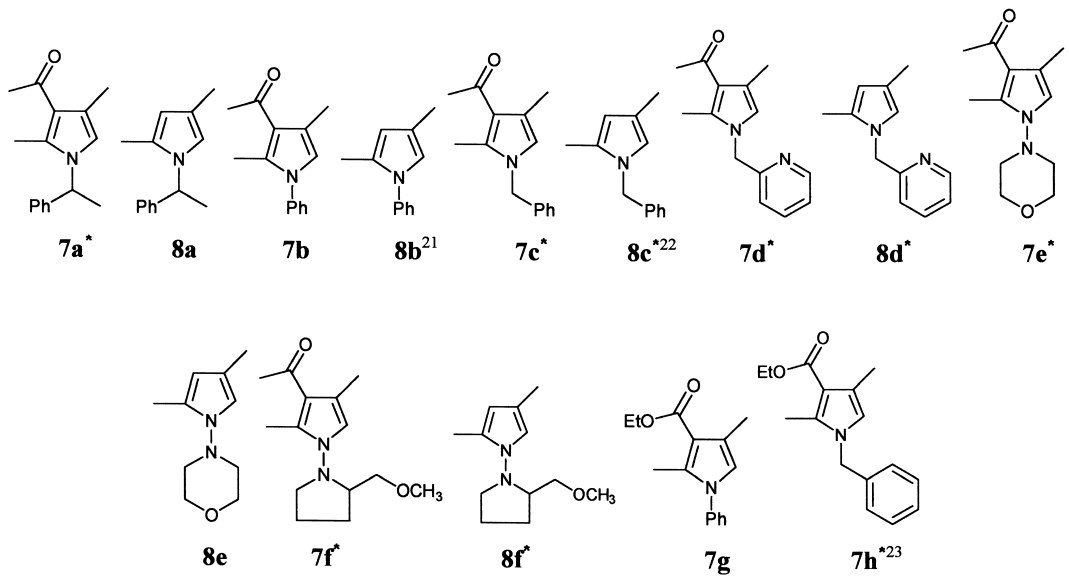
Table 1. Synthesized enamines and pyrroles

1,3-Dicarbonyl compounds (**3**)	Amines (**4**)	Enamines		Pyrroles	
		5	Yield (%)	**6**	Yield (%)[a]
 **a**	 **a**	 **a**	87	 **a**	75
a	 **b**	 **b**	93	 **b**	82
a	 **c**	 **c**	94	 **c**	85
a	 **d**	 **d**	87	 **d**	65
a	 **e**	 **e**	83	 **e**	67
a	 **f**	 **f**	90	 **f**	76
 **b**	 **b**	 **g**	88	 **g**	87
b	 **c**	 **h**	95	 **h**	80
 **c**	 **b**	 **i**	95	 **i**	87



* Trace amount is detected by GC–MS.
[a] Yields refer to those of pure isolated products.
[b] Small amount of free carboxylic acid is detected by GC–MS.

were synthesized by Müller et al. in good yields in a one-pot, three-step, four-component process by a coupling-isomerization-Stetter reaction Paal–Knorr sequence of an electron-poor aryl halide, a terminal propargyl alcohol, an aldehyde, and a primary amine.[14]

In our work on pyrrole chemistry[15] we found a convenient method for the synthesis of 1,2,3,5-tetrasubstituted pyrroles through enamines from 2-(2-bromoallyl)-1,3-dicarbonyl compounds.

2. Results and discussion

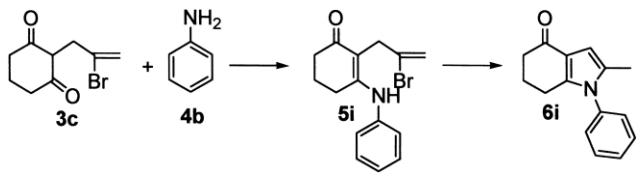
From a synthetic point of view, 1,2,5-trisubstituted-3-acyl pyrroles can be synthesized via a reaction sequence involving α-alkylation of carbonyl compounds with 2,3-dibromoprop-1-ene, enamine formation, and finally a ring closure reaction (Scheme 1). This seems a very attractive route because of the wide variety of substituents (R^1, R^2 and R^3) that can be used, originating from readily accessible starting materials.

As shown in Scheme 2, 2-(2-bromoallyl)-1,3-dicarbonyl compounds **3a–c** were synthesized by regiospecific alkylation of 1,3-dicarbonyl compounds with 2,3-dibromoprop-1-ene according to the literature procedure in 85–92% yields.[16] The enamine derivatives **5a–h** were easily prepared from amines **4a–d**, hydrazines **4e**,**f** and 2-(2-bromoallyl)-1,3-dicarbonyl compounds in refluxing benzene with the addition of a catalytical amount of *p*-TsOH in 83–95% yields after purification of the crude products by column chromatography (Table 1). 2-(2-Bromoallyl)-1,3-diketones are versatile intermediates for the formation of furan rings. Zefirov et al. showed that the reaction of 2-(2-bromoallyl)-1,3-diketones can be converted into substituted furans by the use of K_2CO_3/DMSO.[16] According to this procedure the reaction of enamine **5a** with K_2CO_3/DMSO yielded no products. After many trials, we found that potassium *t*-butoxide in a mixture of DMSO and *t*-BuOH is the best choice for the conversion of enamine **5a** to pyrrole **6a**. This solvent mixture with potassium *t*-butoxide is used by Jiang et al.[17] for the preparation of (*Z*)-β-trifluoromethyl enamines by the reaction of 2-bromo-3,3,3-trifluropropene with *N*-alkyl toluenesulfonamides via Michael addition and elimination processes.

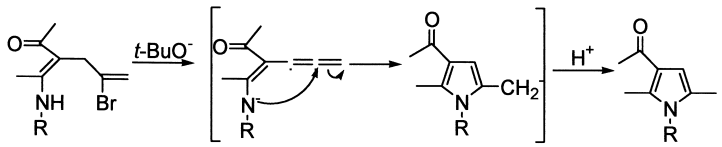
The reaction of 2-(2-bromoallyl) enaminones and enhydrazinones **5a–h** with *t*-BuOK/*t*-BuOH/DMSO at 80°C furnished the pyrrole derivatives **6a–h** in 65–87% yields as major products. In addition to these products, the enamine derivatives **5a–f** furnished 2,4-dimethyl-3-acetyl derivative of pyrroles **7a–f** (5–7%) and the corresponding 2,4-dimethyl pyrrole derivatives **8a–f**[22] (2–3%) as minor products. The enamine derivatives **5g**,**h** from β-ketoester gave 2,4-dimethyl-3-carbethoxy derivatives **7g**,**h**[23] as minor products (4–5%) (Table 1).

All of the pyrrole derivatives were identified by spectroscopic methods. Under conditions similar to those described above, starting from cyclohexane-1,3-dione derivative **3i** and aniline (**4b**) 2-methyl-1-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (**6i**) was synthesized in 87% yield as a colorless solid (Scheme 3).

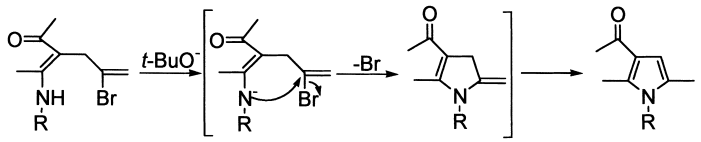
For the formation of the pyrrole ring from enamines we



Scheme 3.



Scheme 4.



Scheme 5.

suggest two possible mechanisms. The enamine could form either the allene or alkyne intermediate after HBr elimination. The formation of allene is more likely than the formation of alkyne because of the higher acidity of the allylic proton. Then the reaction of *N*-deprotonated enamine with allene can give the carbanion intermediate, which furnishes the desired product after protonation (Scheme 4). By the other possible mechanism the deprotonated enamine can react with the vinylic carbon to form a 5-methylene pyrrole derivative via a nucleophilic vinylic substitution reaction. This compound then isomerizes to the pyrrole derivatives (Scheme 5). As shown in Scheme 6, for the formation of 2,4-dimethyl-3-acetyl-substituted pyrroles **7**, first isomerization of enamine into imine, and then formation of α-carbanion and intramolecular cyclization furnishes the cyclopropane derivative, which then forms the methylene derivative via ring opening and a cyclization reaction. Isomerization of the methylene compound forms a pyrrole ring. A similar mechanism is suggested by Zefirov et al. for the formation of a furan derivative starting with 2-bromoallyl-1,3-diketone derivatives.[16b] Careful monitoring of this reaction with GC–MS showed that during the formation of 2,4-dimethylpyrrole derivative **8** first 3-acetyl derivative **7** is formed and then a deacetylation reaction occurred.[18] This deacetylation process works only with 2,4-dimethyl-3-acetyl pyrrole derivatives, not with 1,2,5-trisubstituted 3-acetyl pyrroles. This different course of the reactions is currently being investigated.

3. Conclusion

In this work, we describe a simple and selective method for the formation of 1,2,3,5-tetrasubstituted pyrroles in good yields starting from simple easily accessible 2-(2-bromoallyl)-1,3-dicarbonyl compounds. In addition to these products, 1,2,3,4-tetra- and 1,2,4-tri-substituted pyrroles are formed as minor products.

4. Experimental

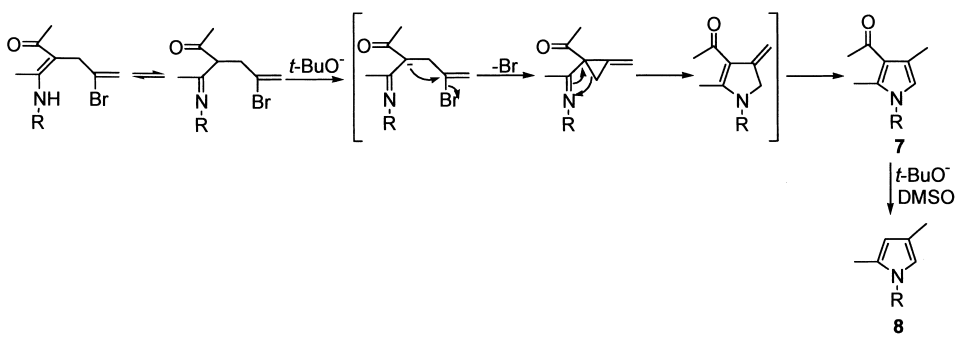
4.1. General

NMR spectra were recorded on a Bruker DPX 400 spectrometer. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). GC–MS spectra were determined on a Phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane) on a Thermo Quest Trace 2000 Series and Thermo Quest Finnigan Automass. Optical rotations were measured with an Autopol IV automatic polarimeter.

4.2. General procedure for the synthesis of enamines, 5a–i

To a mixture of 1,3-diketone (0.010 mol) **3a–c**, and amine (0.015 mol) **4a–f**, in 60 mL benzene was added a catalytic amount of *p*-TsOH and the resulting mixture was refluxed for 10 h, cooled to room temperature and stirred overnight. After evaporation of the solvent in vacuo, flash column chromatography was performed to afford enamines in 83–95% yields.

4.2.1. 5-Bromo-3-{(*E*)-1-[(*R*)-(1-phenylethyl)amino]-ethylidene}hex-5-en-2-one (5a). Viscous oil; 2.81 g



Scheme 6.

(87%); $[\alpha]_D^{20}$=+9.7 (*c* 5, $CHCl_3$); ν_{max}: 3053, 2916, 1617, 1552, 1432, 1285, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.69 (d, *J*=7.1 Hz, 3H), 1.92 (s, 3H), 2.28 (s, 3H), 3.51 (s, 2H), 4.83 (q, *J*=7.1 Hz, 1H), 5.57 (s, 1H), 5.70 (s, 1H), 7.28–7.47 (m, 5H), 12.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 15.7, 25.3, 27.9, 42.2, 53.9, 101.5, 115.9, 125.8, 127.6, 129.2, 134.4, 144.8, 163.4, 195.6. Anal. calcd for $C_{16}H_{20}BrNO$ (322.24 g/mol): C 59.64, H 6.26, N 4.35. Found: C 59.61, H 6.21, N 4.55.

4.2.2. 3-[(*E*)-1-Anilinoethylidene]-5-bromohex-5-en-2-one (5b). Viscous oil; 2.69 g (93%); ν_{max}: 3061, 2927, 1622, 1548, 1412, 1273, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.89 (s, 3H), 2.08 (s, 3H), 3.34 (s, 2H), 5.40 (s, 1H), 5.58 (s, 1H), 6.49–6.51 (m, 1H), 6.94–7.22 (m, 4H), 13.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 16.7, 27.9, 42.2, 103.1, 116.1, 125.8, 126.1, 129.5, 133.9, 139.2, 160.9, 196.7. Anal. calcd for $C_{14}H_{16}BrNO$ (294.19 g/mol): C 57.16, H 5.48, N 4.76. Found: C 57.31, H 5.26, N 4.65.

4.2.3. 3-[(*E*)-1-(Benzylamino)ethylidene]-5-bromohex-5-en-2-one (5c). Viscous oil; 2.87 g (94%); ν_{max}: 3061, 2927, 1622, 1548, 1412, 1273, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.82 (s, 3H), 2.04 (s, 3H), 3.25 (s, 2H), 4.39 (d, *J*=6.1 Hz, 2H), 5.38 (d, *J*=1.4 Hz, 1H), 5.52 (d, *J*=1.4 Hz, 1H), 7.13–7.26 (m, 5H), 12.42 (br.s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 15.3, 27.9, 42.3, 47.5, 115.9, 126.9, 127.4, 128.6, 129.2, 134.4, 138.3, 164.0, 195.7. Anal. calcd for $C_{15}H_{18}BrNO$ (308.21 g/mol): C 58.45, H 5.89, N 4.54. Found: C 58.26, H 5.73, N 4.22.

4.2.4. 5-Bromo-3-{(*E*)-1-[(pyridin-2-ylmethyl)amino]-ethylidene}hex-5-en-2-one (5d). Viscous oil; 2.72 g (87%); ν_{max}: 3057, 2895, 1587, 1535, 1397, 1281, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.86 (s, 3H), 2.05 (s, 3H), 3.30 (s, 2H), 4.51 (d, *J*=9.9 Hz, 2H), 5.39 (s, 1H), 5.54 (s, 1H), 7.08–7.17 (m, 2H), 7.56–7.64 (m, 1H), 8.46 (d, *J*=4.3 Hz, 1H), 12.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 15.4, 27.9, 42.3, 49.2, 101.7, 115.9, 120.9, 122.5, 128.6, 134.4, 137.1, 149.8, 158.0, 163.8, 195.8. Anal. calcd for $C_{14}H_{17}BrN_2O$ (309.20 g/mol): C 54.38, H 5.54, N 9.06. Found: C 54.19, H 5.33, N 9.35.

4.2.5. 5-Bromo-3-[(*E*)-1-morpholin-4-ylethylidene]hex-5-en-2-one (5e). Viscous oil; 2.47 g (83%); ν_{max}: 3145, 2876, 1612, 1497, 1345, 1218, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.01 (s, 3H), 2.11 (s, 3H), 2.87–2.92 (m, 4H), 3.45 (s, 2H), 3.75–3.81 (m, 4H), 5.47 (s, 1H), 5.55 (s, 1H), 13.57 (br.s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.9, 26.7, 42.4, 56.2, 66.4, 102.1, 114.5, 134.3, 162.5, 196.4. Anal. calcd for $C_{12}H_{19}BrN_2O_2$ (303.20 g/mol): C 47.54, H 6.32, N 9.24. Found: C 47.77, H 6.51, N 8.94.

4.2.6. 5-Bromo-3-((*Z*)-1-{[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]amino}ethylidene)hex-5-en-2-one (5f). Viscous oil; 2.85 g (90%); $[\alpha]_D^{20}$=+35 (*c* 12, $CHCl_3$); ν_{max}: 3050, 3016, 2875, 2833, 2400, 2300, 1708, 1626, 1591, 1558, 1425, 1266, 1216, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.64–2.02 (m, 4H), 2.06 (s, 3H), 2.09 (s, 3H), 2.71–2.73 (m, 1H), 2.87–2.94 (m, 1H), 3.16–3.21 (m, 1H), 3.27 (s, 3H), 3.33 (s, 2H), 3.28–3.35 (m, 2H), 5.46 (s, 1H), 5.59 (s, 1H), 12.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 21.3, 26.0, 27.5, 42.2, 57.5, 59.1, 66.1, 73.9, 98.9, 115.5, 134.5, 165.7, 194.8. Anal. calcd for $C_{14}H_{23}BrN_2O_2$ (331.25 g/mol): C 50.76, H 7.00, N 8.46. Found: C 50.53, H 7.21, N 8.15.

4.2.7. Ethyl 2-[(*E*)-1-anilinoethylidene]-4-bromopent-4-enoate (5g). Viscous oil; 2.78 g (88%); ν_{max}: 3035, 2917, 2369, 1649, 1591, 1562, 1435, 1257, 1198 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.27 (t, *J*=7.1 Hz, 3H), 2.01 (s, 3H), 3.43 (s, 2H), 4.16 (q, *J*=7.1 Hz, 2H), 5.40 (s, 1H), 5.58 (s, 1H), 7.02–7.31 (m, 5H), 11.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.9, 16.9, 39.9, 59.6, 93.4, 115.2, 124.7, 125.3, 129.4, 134.4, 139.9, 158.5, 170.3. Anal. calcd for $C_{15}H_{18}BrNO_2$ (324.21 g/mol): C 55.57, H 5.60, N 4.32. Found: C 55.32, H 5.31, N 4.11.

4.2.8. Ethyl 2-[(*E*)-1-(benzylamino)ethylidene]-4-bromopent-4-enoate (5h). Viscous oil; 3.18 g (95%); ν_{max}: 2927, 1587, 1512, 1397, 1265, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.24 (t, *J*=7.1 Hz, 3H), 1.89 (s, 3H), 3.37 (s, 2H), 4.08 (q, *J*=7.1 Hz, 2H), 4.42 (d, *J*=6.1 Hz, 2H), 5.35 (s, 1H), 5.51 (s, 1H), 7.22–7.31 (m, 5H), 9.94 (br.s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.6, 14.9, 39.5, 46.9, 58.7, 89.9, 114.5, 126.4, 127.2, 128.6, 134.7, 138.7, 161.3, 170.0. Anal. calcd for $C_{16}H_{20}BrNO_2$ (338.24 g/mol): C 56.82, H 5.96, N 4.14. Found: C 56.58, H 5.91, N 4.33.

4.2.9. 3-Anilino-2-(2-bromoallyl)cyclohex-2-en-1-one (5i). Colorless solid; 2.88 g (95%); ν_{max}: 3102, 2945, 1612, 1557, 1487, 1312, 1161 cm^{-1}; mp 118–120°C; ^1H NMR (400 MHz, $CDCl_3$): 1.90–1.96 (m, 2H), 2.36–2.40 (m, 2H), 2.47–2.50 (m, 2H), 3.61 (s, 2H), 5.46 (s, 1H), 5.69 (s, 1H), 6.79 (br.s, 1H), 7.05–7.07 (m, 2H), 7.18–7.22 (m, 1H), 7.32–7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.8, 27.2, 35.0, 36.5, 108.6, 116.4, 125.0, 125.7, 129.2, 131.6, 138.4, 159.7, 194.2. Anal. calcd for $C_{15}H_{16}BrNO$ (306.20 g/mol): C 58.84, H 5.27, N 4.57. Found: C 58.66, H 5.37, N 4.33.

4.3. General procedure for the synthesis of pyrroles

2.2 g (6.8 mmol) enamine **5a–i** was dissolved in a mixture of 7 mL *t*-BuOH and 14 mL DMSO. Then 1.15 g *t*-BuOK (10.2 mmol) was added, followed by heating at 80°C for 4–5 h. After cooling to room temperature, the mixture was poured into 50 mL water and extracted with ether. Combined organic layers were dried over $MgSO_4$, concentrated and purified by flash column chromatography to afford pyrroles.

4.3.1. 1-[2,5-Dimethyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl]ethan-1-one, 6a.[13b] Viscous oil; 1.23 g (75%); $[\alpha]_D^{20}$=+11.9° (*c* 0.7, $CHCl_3$); ν_{max}: 3051, 3011, 1671, 1501, 1411, 1312, 1287 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.72 (d, *J*=7.1 Hz, 3H), 1.86 (s, 3H), 2.19 (s, 3H), 2.30 (s, 3H), 5.39 (q, *J*=7.1 Hz, 1H), 6.03 (s, 1H), 6.69–6.85 (m, 2H), 7.07–7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.9, 14.1, 19.2, 28.9, 52.7, 110.0, 120.6, 126.2, 127.6, 127.8, 129.1, 135.4, 141.2, 194.7. Anal. calcd for $C_{16}H_{19}NO$ (241.33 g/mol): C 79.63, H 7.94, N 5.80. Found: C 79.60, H 7.91, N 5.75.

4.3.2. 2,4-Dimethyl-1-(1-phenylethyl)-1*H*-pyrrole, 8a. Viscous oil; 27 mg (2%); ν_{max}: 3106, 1505, 1419, 1342,

1297, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.67 (d, J=7.1 Hz, 3H9, 1.96 (s, 3H), 2.00 (8s, 3H), 5.10 (q, J= 7.1 Hz, 2H), 5.63 (s, 1H), 6.42 (s, 1H), 6.87–6.89 (m, 2H), 7.12–7.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.6, 14.3, 22.8, 54.9, 106.8, 109.2, 115.0, 117.6, 126.0, 126.4, 127.3, 128.9, 144.4. Anal. calcd for $C_{14}H_{17}N$ (199.29 g/mol): C 84.37, H 8.60, N 7.03. Found: C 84.15, H 8.51, N 6.83.

4.3.3. 1-(2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)ethan-1-one, 6b.[13a] Viscous oil; 1.18 g (82%); ν_{max}: 3052, 3018, 2985, 1649, 1503, 1419, 1261, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.97 (s, 3H), 2.29 (s, 3H), 2.38 (s, 3H), 6.27 (s, 1H), 7.15–7.17 (m, 2H), 7.34–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.1, 13.3, 28.8, 108.7, 121.0, 122.9, 126.8, 128.5, 128.9, 129.7, 136.2, 195.4. Anal. calcd for $C_{14}H_{15}NO$ (213.28 g/mol): C 78.84, H 7.09, N 6.57. Found: C 78.79, H 7.01, N 6.49.

4.3.4. 1-(2,4-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)ethan-1-one, 7b. Viscous oil; 58 mg (4%); ν_{max}: 3052, 2987, 1420, 1261, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.29 (s, 3H), 2.38 (s, 3H), 2.44 (s, 3H), 6.44 (s, 1H), 7.21–7.23 (m, 2H), 7.35–7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 14.0, 31.5, 108.5, 121.0, 126.7, 128.6, 128.9, 129.6, 135.9, 137.9, 195.3. Anal. calcd for $C_{14}H_{15}NO$ (213.28 g/mol): C 78.84, H 7.09, N 6.57. Found: C 78.73, H 7.18, N 6.32.

4.3.5. 2,4-Dimethyl-1-phenyl-1*H*-pyrrole, 8b.[21] Viscous oil; 23 mg (2%); ν_{max}: 3035, 2897, 1417, 1272, 1116, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.09 (s, 3H), 2.17 (s, 3H), 5.83 (s, 1H), 6.49 (s, 1H), 7.19–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.4, 13.3, 110.7, 118.9, 119.4, 125.9, 126.7, 128.9, 129.3. Anal. calcd for $C_{12}H_{13}N$ (171.24 g/mol): C 84.17, H 7.65, N 8.18. Found: C 84.06, H 7.58, N 8.09.

4.3.6. 1-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)ethan-1-one, 6c.[11a] Viscous oil; 1.31 g (85%); ν_{max}: 3053, 2985, 1649, 1520, 1420, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.11 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 5.01 (s, 2H), 6.24 (s, 1H), 6.84–6.86 (m, 2H), 7.19–7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.1, 12.6, 28.8, 46.9, 108.9, 120.7, 125.8, 127.8, 127.9, 129.3, 135.3, 137.2, 194.7. Anal. calcd for $C_{15}H_{17}NO$ (227.30 g/mol): C 79.26, H 7.54, N 6.16. Found: C 79.18, H 7.48, N 6.07.

4.3.7. 1-[2,5-Dimethyl-1-(pyridin-2-ylmethyl)-1*H*-pyrrol-3-yl]ethan-1-one, 6d. Viscous oil; 1.01 g (65%); ν_{max}: 3057, 2847, 1649, 1591, 1521, 1418, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.16 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 5.12 (s, 2H), 6.26 (s, 1H), 6.52 (d, J=7.8 Hz, 1H), 7.15–7.19 (m, 1H), 7.57–7.61 (m, 1H), 8.54 (br.s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.6, 12.1, 28.3, 48.4, 108.5, 119.5, 120.3, 120.4, 127.4, 134.7, 137.0, 149.3, 156.8, 194.1. Anal. calcd for $C_{14}H_{16}N_2O$ (228.29 g/mol): C 73.66, H 7.06, N 12.27. Found: C 73.61, H 7.21, N 11.97.

4.3.8. 1-(2,5-Dimethyl-1-morpholin-4-yl-1*H*-pyrrol-3-yl)ethan-1-one, 6e. Viscous oil; 1.03 g (67%); ν_{max}: 3052, 2985, 2305, 1650, 1542, 1420, 1264, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.99 (s, 3H), 2.12 (s, 3H), 2.27 (s, 3H), 2.93–3.01 (m, 4H), 3.75–3.81 (m, 4H), 6.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.3, 13.4, 28.5, 57.5, 69.7, 108.5, 119.4, 127.6, 129.9, 197.5. Anal. calcd for $C_{12}H_{18}N_2O_2$ (222.28 g/mol): C 64.84, H 8.16, N 12.60. Found: C 64.65, H 8.33, N 12.38.

4.3.9. 4-(2,4-Dimethyl-1*H*-pyrrol-1-yl)morpholine, 8e. Viscous oil; 37 mg (3%); ν_{max}: 3048, 2987, 1462, 1312, 1227, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.02 (s, 3H), 2.14 (s, 3H), 2.96–2.98 (m, 4H), 3.79–3.82 (m, 4H), 5.49 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 10.9, 12.2, 55.9, 66.9, 104.5, 109.3, 116.5, 127.9. Anal. calcd for $C_{10}H_{16}N_2O$ (180.25 g/mol): C 66.63, H 8.95, N 15.54. Found: C 66.44, H 8.78, N 15.35.

4.3.10. 1-{1-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-2,5-dimethyl-1*H*-pyrrol-3-yl}ethan-1-one, 6f. Viscous oil; 1.29 g (76%); $[\alpha]_D^{20}$=+13 (*c* 9, $CHCl_3$); ν_{max}: 3041, 3016, 2976, 2401, 2309, 1633, 1416, 1267, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.78–1.84 (m, 2H), 1.91–1.94 (m, 2H), 2.05–2.11 (m, 2H), 2.24 (s, 3H), 2.38 (s, 3H), 2.45 (s, 3H), 3.00–3.07 (m, 1H), 3.12–3.19 (m, 1H), 3.25 (s, 3H), 3.26–3.29 (m, 1H), 6.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.6, 13.9, 21.6, 26.6, 30.9, 55.9, 58.8, 65.9, 73.6, 115.2, 118.2, 119.2, 137.9, 194.2. Anal. calcd for $C_{14}H_{22}N_2O_2$ (250.34 g/mol): C 67.17, H 8.86, N 11.19. Found: C 67.23, H 8.76, N 10.91.

4.3.11. Ethyl 2,5-dimethyl-1-phenyl-1*H*-pyrrole-3-carboxylate, 6g.[11a,19] Colorless solid; 1.44 g (87%); mp 42–44°C (lit. 45–46° (MeOH)); ν_{max}: 3035, 2986, 2311, 1685, 1536, 1420, 1269, 1219, 1163, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.27 (t, J=7.1 Hz, 3H), 1.96 (s, 3H), 2.27 (s, 3H), 4.27 (q, J=7.1 Hz, 2H), 6.32 (s, 1H), 7.23–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.2, 12.6, 14.6, 58.9, 107.7, 115.7, 119.9, 126.2, 128.1, 129.0, 137.8, 165.2. Anal. calcd for $C_{15}H_{17}NO_2$ (243.30 g/mol): C 74.05, H 7.04, N 5.76. Found: C 74.01, H 6.98, N 5.68.

4.3.12. Ethyl 2,4-dimethyl-1-phenyl-1*H*-pyrrole-3-carboxylate, 7g. Viscous oil; 83 mg (5%); ν_{max}: 3037, 2979, 2319, 1687, 1542, 1402, 1305, 1212, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.37 (t, J=7.1 Hz, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 4.28 (q, J=7.1 Hz, 2H), 6.44 (s, 1H), 7.24–7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.4, 12.5, 14.4, 58.7, 112.3, 119.8, 120.9, 126.0, 127.4, 128.0, 128.7, 139.1, 165.4. Anal. calcd for $C_{15}H_{17}NO_2$ (243.30 g/mol): C 74.05, H 7.04, N 5.76. Found: C 74.11, H 7.21, N 5.48.

4.3.13. Ethyl 1-benzyl-2,5-dimethyl-1*H*-pyrrole-3-carboxylate, 6h.[11] Viscous oil; 1.39 g (80%); ν_{max}: 3029, 2987, 2317, 1647, 1567, 1418, 1326, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.33 (t, J=7.1 Hz, 3H), 2.09 (s, 3H), 2.43 (s, 3H), 4.23 (q, J=7.13 Hz, 2H), 5.00 (s, 2H), 6.31 (s, 1H), 6.83–6.85 (m, 2H), 7.18–7.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.6, 12.5, 15.0, 47.1, 59.3, 108.4, 111.7, 125.9, 127.7, 127.9, 129.2, 135.7, 137.4, 165.8. Anal. calcd for $C_{16}H_{19}NO_2$ (257.33 g/mol): C 74.68, H 7.44, N 5.44. Found: C 74.55, H 7.37, N 5.38.

4.3.14. 2-Methyl-1-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one, 6i.[20] Colorless solid; 1.33 g (87%); mp 150–152°C

(lit. 150–151° (hexane)); ν_{max}: 3048, 2979, 2310, 1650, 1547, 1419, 1268 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.04 (s, 3H), 2.06–2.11 (m, 2H), 2.43–2.45 (m, 2H), 2.51–2.54 (m, 2H), 6.34 (s, 1H), 7.22–7.27 (m, 2H), 7.43–7.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.6, 22.7, 23.8, 37.8, 103.8, 120.8, 127.5, 128.5, 129.4, 130.9, 137.2, 143.8, 193.5. Anal. calcd for $C_{15}H_{15}NO$ (225.29 g/mol): C 79.97, H 6.71, N 6.22. Found: C 79.89, H 6.65, N 6.14.

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