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One-Pot Synthesis of 3,4-Disubstituted 1*H*-Pyrroles from 2-Tropanones

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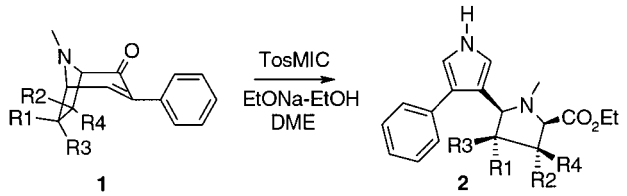
Abstract: 3,4-Disubstituted pyrroles (**2**, **3**) were prepared from 6/7-carboxyethyl-3-phenyl-3-tropen-2-ones (**1**) regioselectively and with high yields by using tosylmethyl isocyanide (TosMIC). This procedure enables the synthesis of pyrroles substituted with two distinct groups: a phenyl group and a substituted pyrrolidine analogue. The crystal structure of product **2a** was determined, and the analogous derivatives were identified by ^{1}H and ^{13}C NMR spectroscopy.

The 3,4-disubstituted pyrroles are important targets as intermediates in the synthesis of natural products and pharmaceutical drugs.[1,2] Synthesis of β-disubstituted pyrroles is known to be laborious due to their tendency to react in aromatic substitution reactions at the more electronically favorable α-positions of the heterocyclic ring.[3] In the literature, multistep synthetic routes of 3,4-disubstituted pyrroles have been reported, e.g., by coupling of imines and nitroalkanes or using Friedel−Crafts acylation with an electron-withdrawing group on the pyrrole nitrogen or from 3,4-silylated precursors.[4−6] However, these synthetic routes are often complicated and limited to only some substituent families. Previously, 3,4-disubstituted pyrroles have also been synthesized from Michael acceptors with tosylmethyl isocyanide (TosMIC),[7,8] which is a multipurpose synthetic reagent. This has been used, e.g., in the synthesis of oxazoles, imidazoles, thiazoles, and indoles and in reductive cyanation.[9] Here, we report a new regioselective one-step procedure to prepare a series of 3-aryl-4-pyrrolidinepyrroles with good yields by using TosMIC.

SCHEME 1



1a, 2a: R_1 = -CO_2Et; R_2, R_3, R_4 = -H
1b, 2b: R_2 = -CO_2Et; R_1, R_3, R_4 = -H
1c, 2c: R_3 = -CO_2Et; R_1, R_2, R_4 = -H
1d, 2d: R_4 = -CO_2Et; R_1, R_2, R_3 = -H

The starting materials were racemic 6- and 7-substituted 3-phenyl-3-tropen-2-ones (**1a**−**d**), synthesized by Diels−Alder reaction of 1-methyl-4-phenyl-3-hydroxypyridinium salt and ethylacrylate.[10] The reaction produced four isomers, in which the carboxyethyl group was attached at the 6 or 7 position of the tropinone ring with endo or exo configurations (**1a**−**d**). The products were separated by column chromatography with the known method.[10]

The reaction between the tropinones (**1a**−**d**) and TosMIC using EtONa−EtOH solution as a base produced racemic 3-phenyl-4-pyrrolidinepyrroles (**2a**−**d**) at room temperature under nitrogen atmosphere (Scheme 1). Yields were moderate, varying from 32% to 98% without any side products (Table 1). Possible side reactions, such as reductive cyanation of the ketone, were not observed. This indicates that TosMIC attacks only to the C=C double bond; hence, the reaction was found to be regioselective. Meta- and para-iodinated aryl analogues of **1** were also used, but they did not yield the desired pyrroles, but rather gave intractable mixtures.

Interestingly, if a smaller amount of EtONa was used and some moisture was present, the proline analogue **3** was also formed. According to ^{1}H NMR measured before purification steps, the yield of **3** was moderate, 50%, but after the purification a great loss occurred, apparently due to the zwitterion character of the product (Scheme 2.). Attempts were made to increase the yield of **3** by using a small amount of water or NaOH in the reaction mixture, without any success.

The structure of **2a** was analyzed by X-ray spectroscopy, and the analogous structures of other products were determined by ^{1}H and ^{13}C NMR spectroscopy. The pyrrole ring was identified from ^{1}H NMR spectra on the basis of a typical N−H shift at 8.8−8.4 ppm and on the small coupling constants of the α-protons characteristic for five-membered pyrrole rings. Configurations of the pyrrolidine ring substituents were derived from those of the starting materials.[10] The acid analogue **3** was identified by the loss of ethyl ester signals.

The expected reaction mechanism explains the fragmentation of the tropane ring and the regiochemistry (Figure 1). The reaction is started by the 1,3-dipolar cycloaddition of the base-activated nucleophilic TosMIC

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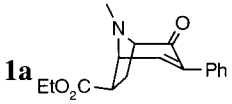
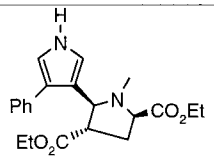
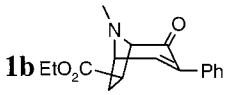
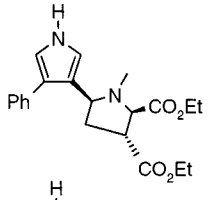
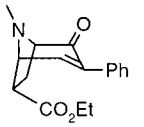
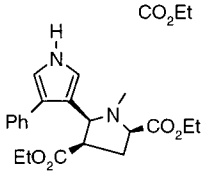
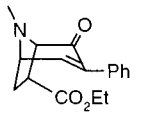
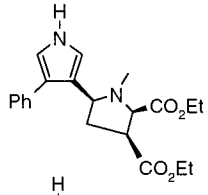
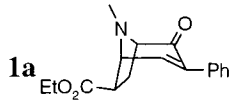
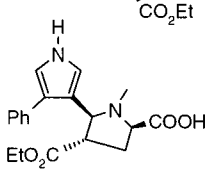
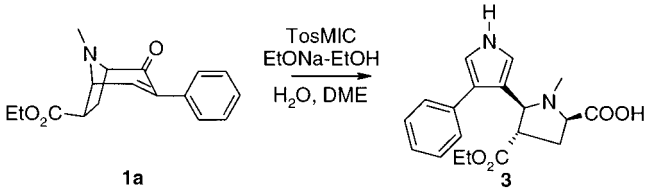
TABLE 1. Synthesis of 3,4-Pyrrole Derivatives with TosMIC

Michael acceptor	Product	Yield[a]
1a 	**2a** 	62%
1b 	**2b** 	84%
1c 	**2c** 	32%
1d 	**2d** 	98%
1a 	**3**[b] 	6%

[a] Total isolated yield. [b] Formed only if moisture was present.

SCHEME 2



1a **3**

to the double bond, which is a Michael acceptor. After protonation, attack of nucleophilic EtO^- to the polarized carbonyl C-2 and the leaving tendency of the tosyl group initiates an electron-transfer reaction as a variation of the Grob fragmentation.[11] Bond cleavage between carbons 2 and 3 generates the pyrrole ring as a stable end product, with a phenyl ring and the disubstituted *N*-methylproline analogue as substituents. According to the mechanism, the reaction does not affect chirality centers. The mechanism for the formation of acid **3** is analogous, except that the carbonyl attacking nucleophile is a hydroxyl ion.

In conclusion, the developed one-step synthetic procedure enables the synthesis of 3,4-disubstituted pyrroles with two distinct substituents: phenyl group and pyrrolidine analogue. The procedure also provides a new route for synthesis of modified prolines for modern peptide synthesis, though some further development may be needed.

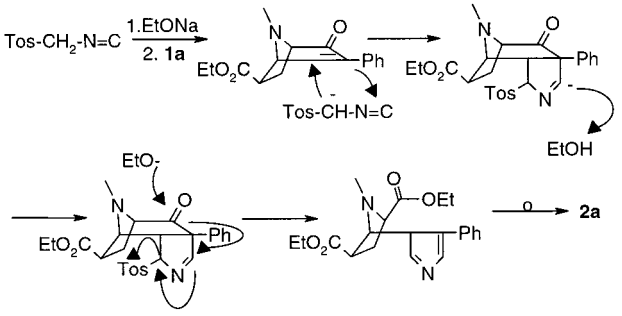


FIGURE 1. Expected reaction mechanism.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 400 or 500 MHz with TMS as an internal reference and $CDCl_3$ as solvent. *J* values are reported in Hz. All chemicals for synthesis were purchased from commercial suppliers, and solvents were purified according to standard procedures.[12] Column chromatography and TLC purification were performed with Kieselgel 60.

General Procedure for Synthesis of 2a−d. The reaction was carried out under a nitrogen atmosphere. The starting material **1a**−**d** (1 mmol) and tosylmethyl isocyanide (1.32 mmol) were dissolved into 6 mL of dimethoxyethane. A solution of EtONa in dry EtOH (1.88 mmol of EtONa/mL of EtOH, 1.44 mL, 2.68 mmol of EtONa) was added dropwise, and the mixture was stirred for 1 h at rt. The mixture was evaporated to dryness, dissolved into saturated $NaHCO_3$, and extracted with dichloromethane five times. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to dryness. The product was purified with column chromatography using EtOAc−hexane (1:1): **2a**, yield 62%, $R_f = 0.78$; **2b**, yield 84%, $R_f = 0.66$; **2c**, yield 32%, $R_f = 0.52$; **2d**, yield 98%, $R_f = 0.55$.

1-Methyl-4′-phenyl-2,3,4,5-tetrahydro-1*H*,1′*H*-[2,3′]bipyrrolyl-*trans*-3,5-dicarboxylic acid diethyl ester (2a): ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.48−7.55 (m, 2H), 7.29−7.35 (m, 2H), 7.18−7.24 (m, 1H), 6.87 (t, $J = 2.4$ Hz, 1H), 6.78 (t, $J = 2.4$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 3.92 (q, $J = 7.2$, 2H), 3.86 (d, $J = 8.5$ Hz, 1H), 3.22 (t, $J = 8.4$ Hz, 1H), 3.00 (m, 1H), 2.24 (s, 3H), 2.19−2.34 (m, 2H), 1.29 (t, 3H), 1.09 (t, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.1, 165.5, 135.2, 129.2, 128.8, 126.6, 126.1, 121.9, 117.3, 108.6, 68.4, 65.6, 63.0, 61.9, 45.9, 37.7, 29.4, 14.1, 14.0.

1-Methyl-4′-phenyl-2,3,4,5-tetrahydro-1*H*,1′*H*-[2,3′]bipyrrolyl-*trans*-4,5-dicarboxylic acid diethyl ester (2b): ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.48−7.51 (m, 2H), 7.31−7.36 (m, 2H), 7.20−7.36 (m, 1H), 6.88 (t, $J = 2.5$ Hz, 1H), 6.80 (t, $J = 2.5$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.71 (dd, $J = 9.0$ Hz, 7.7 Hz, 1H), 3.33 (d, $J = 7.8$ Hz, 1H), 3.27 (t, $J = 2.4$ Hz, 1H), 2.34 (m, 1H), 2.28 (s, 3H), 2.14 (m, 1H), 1.29 (t, 3H), 1.24 (t, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.9, 172.4, 136.3, 128.8, 128.2, 125.8, 125.0, 122.0, 117.6, 116.6, 71.0, 63.1, 60.9, 60.9, 45.7, 39.6, 36.7, 14.3, 14.2.

1-Methyl-4′-phenyl-2,3,4,5-tetrahydro-1*H*,1′*H*-[2,3′]bipyrrolyl-*cis*-3,5-dicarboxylic acid diethyl ester (2c): ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.51−7.55 (m, 2H), 7.30−7.35 (m, 2H), 7.20−7.24 (m, 1H), 6.90 (t, $J = 2.5$ Hz, 1H), 6.79 (t, $J = 2.5$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.92 (q, $J = 7.1$ Hz, 2H), 3.85 (d, $J = 8.5$ Hz, 1H), 3.22 (t, $J = 8.5$ Hz, 1H), 3.00 (m, 1H), 2.26 (s, 3H), 2.23−2.32 (m, 2H), 1.29 (t, 3H), 1.08 (t, 3H);

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^{13}C NMR (500 MHz, $CDCl_3$) δ 174.3, 173.3, 136.3, 129.2, 128.1, 125.8, 125.4, 120.7, 118.2, 116.7, 67.2, 66.5, 60.7, 60.5, 49.8, 39.3, 32.1, 14.3, 14.0.

1-Methyl-4′-phenyl-2,3,4,5-tetrahydro-1*H*,1′*H*-[2,3′]bipyrrolyl-*cis*-4,5-dicarboxylic acid diethyl ester (2d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 7.49−7.52 (m, 2H), 7.32−7.36 (m, 2H), 7.21−7.25 (m, 1H), 6.91 (t, J = 2.5 Hz, 1H), 6.82 (t, J = 2.5 Hz, 1H), 4.24 (q, J = 7.0 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.71 (dd, J = 9.3 Hz, 7.7 Hz, 1H), 3.32 (d, J = 7.9 Hz, 1H), 3.25 (m, 1H), 2.34 (m, 1H), 2.28 (s, 3H), 2.13 (m, 1H),1.30 (t, 3H), 1.24 (t, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.9, 172.4, 136.2, 128.8, 128.2, 125.8, 125.0, 122.3, 117.6, 116.6, 71.0, 63.2, 60.9, 60.9, 45.7, 39.6, 36.8, 14.3, 14.2.

1-Methyl-4′-phenyl-2,3,4,5-tetrahydro-1*H*,1′*H*-[2,3′]bipyrrolyl-*trans*-3,5-dicarboxylic Acid 3-Ethyl Ester (3). The synthesis was performed according to the general procedure, but without nitrogen atmosphere, and only 1.33 mmol of EtONa was used (EtOH not dried). EtOAc was used in extractions, instead of dichloromethane. The product was purified with TLC using EtOAc−hexane (1:1). **3**: yield 6%, R_f = 0.62 (yield before purification steps 50%, determined by ^{1}H NMR before extractions); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.49−7.53 (m, 2H), 7.30−7.35 (m, 2H), 7.20−7.24 (m, 1H), 6.88 (t, J = 2.5 Hz, 1H), 6.77 (t, J = 2.5 Hz, 1H), 3.92 (q, J = 7.1 Hz, 2H), 3.86 (d, J = 8.4 Hz, 1H), 3.25 (t, J = 9.4 Hz, 8.4 Hz, 1H), 2.99 (m, 1H), 2.21−2.34 (m, 2H), 2.25 (s, 3H), 1.08 (t, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 174.1, 173.5, 136.2, 129.2, 128.1, 125.8, 125.5, 120.6, 118.2, 116.7, 67.0, 66.5, 60.6, 49.8, 39.3, 32.0, 14.0.

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Supporting Information Available: X-ray data of **2a**. ^{1}H and ^{13}C NMR data of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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