# Acid-Promoted Retro-Mannich Reaction of *N*-Protected Tropenones to 2-Substituted Pyrroles

**Nicolai Cramer,[a] Jeannette Juretschke,[a] Sabine Laschat,*[a] Angelika Baro,[a] and Wolfgang Frey[a]**

*Dedicated to Professor Willi Kantlehner on the occasion of his 60th birthday*

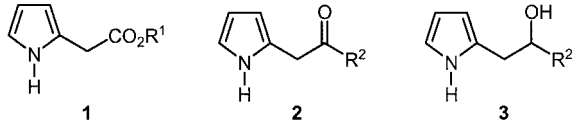
**Keywords:** Fragmentation / Ketones / Regioselectivity / Mannich reaction / Tropenones

*N*-protected tropenone **4** undergoes highly regioselective retro-Mannich reactions to 2-pyrrolyl ketones **5** and **7** in the presence of Lewis or Brønsted acids. Analogously, the pyrrole derivative **8a** was obtained by using subsequent nucleophilic trapping with TMSCN.



## Introduction

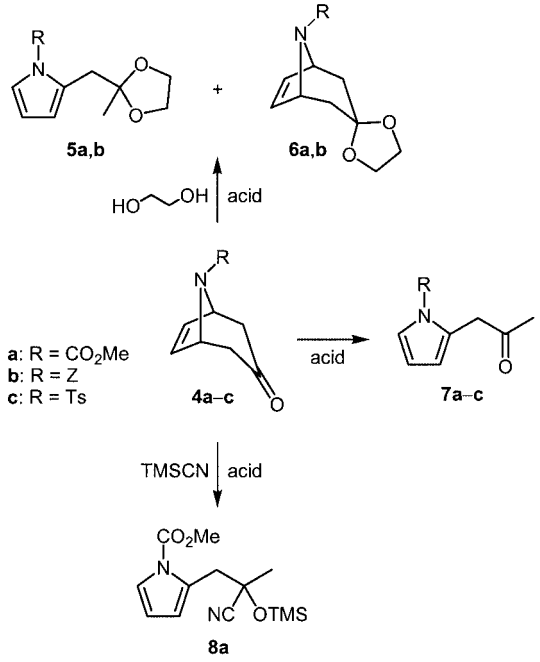
Pyrroles are important constituents of many alkaloids and pharmacologically active compounds.[1] Particularly, 2-pyrrolyl acetates **1** (Scheme 1) are valuable anti-inflammatory and analgesic agents,[2−4] and thus, a variety of synthetic approaches have been reported.[5,6] In contrast, the corresponding ketones **2**, alcohols **3**, and derivatives thereof have not been investigated as much. Among the few examples are the indium-mediated ring opening of epoxides by pyrrole to give C-alkylated pyrroles,[7] and the photooxygenation of *N*-(methoxycarbonyl)pyrrole followed by Lewis acid-catalyzed nucleophilic trapping.[8,9] This prompted us to explore a novel route to 2-substituted pyrroles by acid-promoted fragmentation of *N*-protected tropenones which was found by serendipity.




Scheme 1. Examples of 2-substituted pyrrole derivatives **1**−**3**

## Results and Discussion

Previously, we reported the enantioselective desymmetrization of *N*-protected tropenones through hydroboration.[10] In order to avoid simultaneous reduction of the carbonyl group, suitable protection was required. However, upon treatment of the tropenone derivative **4a** with ethylene glycol and catalytic amounts of *p*-TsOH in refluxing benzene the 2-substituted pyrrole **5a** was obtained as the major product in 55 % yield, whereas the desired acetal **6a** could be isolated only as a minor by-product (Scheme 2; Table 1, Entry 1).




Scheme 2. Acid-mediated fragmentation of *N*-protected tropenones **4a**−**c**; for details see Table 1

[a] Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany,
Fax: (internat.) + 49-711-685-4285
E-mail: sabine.laschat@po.uni-stuttgart.de

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Table 1. Fragmentation of tropenones **4**

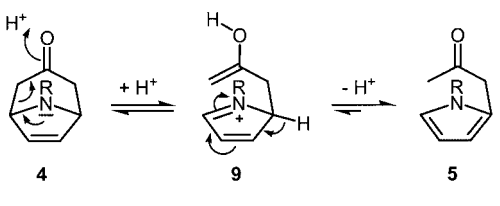
| Entry[a] | **4** | Acid[b] | Solvent | Temp. (°C) | Time (h) | Pyrrole | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | TsOH[c] | $C_6H_6$ | reflux | 24 | **5a** | 55[d][e] |
| 2 | **4a** | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | −10 → room temp. | 4 | **5a** | 42[e][f] |
| 3 | **4a** | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | −10 → room temp. | 0.5 | **5a** | 18[e][g] |
| 4 | **4a** | TsOH[c] | $C_6H_6$ | reflux | 5 | **7a** | 73 |
| 5 | **4a** | TMSBr | MeCN | room temp. | 2 | **7a** | 72 |
| 6 | **4a** | $ZnI_2$ | $C_6H_6$ | 0 → room temp. | 2 | **8a** | 64[h] |
| 7 | **4b** | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | −10 → room temp. | 24 | **5b** | 29[e][i] |
| 8 | **4b** | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | −10 → room temp. | 2 | **7b** | 50 |
| 9 | **4b** | TsOH[c] | $C_6H_6$ | reflux | 1 | **7b** | 57 |
| 10 | **4b** | TMSBr | MeCN | room temp. | 3 | **7b** | 68 |
| 11 | **4c** | TsOH[c] | $C_6H_6$ | reflux | 3 | **7c** | 77 |
| 12 | **4c** | TMSOTf | MeCN | room temp. | 5 | **7c** | 77 |

[a] The conversion, determined by capillary GC, was 100 % apart from Entries 1 (92 %), 3 (76 %), and 7 (65 %). Yields refer to isolated yields (calculated for re-isolated starting material). [b] Addition of acid: 8−10 mol % (Entries 1,4,9,11), 1/5 of the solvent (Entries 2,3,7,8), 2 equivalents (Entries 5,10,12), and 10 mol % (Entry 6). [c] Monohydrate. [d] 17% of tropenone **6a**. [e] With ethylene glycol as nucleophile. [f] 19 % of **6a**. [g] 49 % of **6a**. [h] With TMSCN as nucleophile. [i] 31 % of **6b**.

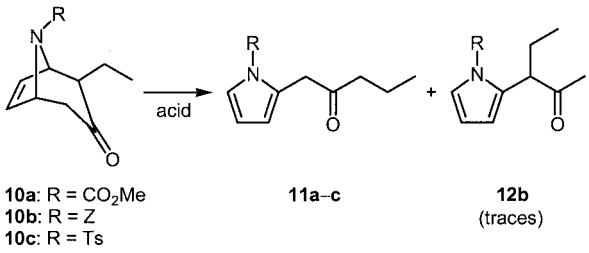
This surprising discovery was further investigated. Carrying out the acetalization with ethylene glycol in $CH_2Cl_2$ in the presence of $BF_3{\cdot}OEt_2$ for 4 h gave a similar product ratio with the pyrrole **5a** as the major product (Table 1, Entry 2). However, when the reaction time was reduced to 30 min, the acetal **6a** was isolated in 49 % yield together with 18 % of the pyrrole **5a** (Entry 3). Under similar conditions, the corresponding *Z*-protected tropenone **4b** afforded equimolar amounts of the pyrrole **5b** (29 %) and the tropenone acetal **6b** (31 %) (Entry 7).

In order to find out whether the tropenone acetal **6a** or the ketone **4a** undergo acid-catalyzed fragmentation, tropenone **4a** was treated directly with TsOH in refluxing benzene for 5 h. Indeed, pyrrolyl ketone **7a** could be isolated in 73 % yield (Entry 4). The use of the Lewis acid TMSBr instead of TsOH proved to be equally effective (Entry 5). The *Z*- and *N*-tosyl-protected tropenone **4b** and **4c** gave similar results upon treatment with Brønsted or Lewis acids (Entries 9−12). It should be mentioned that the corresponding *N*-alkyl-substituted tropenones did not undergo any fragmentation under similar conditions.

Next, Lewis acid-catalyzed fragmentation with subsequent nucleophilic trapping with TMSCN was performed. Indeed, the resulting cyanohydrin **8a** was obtained in 64 % yield (Entry 6). Our mechanistic rationale for the observed pyrrole fragmentation is shown in Scheme 3. Brønsted or Lewis acids may catalyze a retro-Mannich reaction through the enol intermediate **9**. In the case of substituted tropenone derivatives, one would expect a preferred cleavage at the α-substituted carbon due to the increased stability of substituted enols as compared to unsubstituted ones. The reaction can also be considered as a Lewis acid-catalyzed Grob fragmentation.[11,12] In order to investigate this hypothesis, 2-ethyltropenones **10a**−**c**[13] were submitted to acidic fragmentation (Scheme 4, Table 2).




Scheme 3. Mechanistic proposal




Scheme 4. Fragmentation of 2-ethyl-substituted tropenones **10**; for details see Table 2

Table 2. Fragmentation of compounds **10**

| Entry | **10** | Conditions[a] | Pyrrole | Yield (%) |
|---|---|---|---|---|
| 1 | **10a** | TsOH,[b] $C_6H_6$, reflux, 4 h | **11a** | 67 |
| 2 | **10b** | TsOH,[b] $C_6H_6$, reflux, 6 h | **11b** | 56[c] |
| 3 | **10b** | TMSBr, MeCN, room temp., 3 h | **11b** | 52[c] |
| 4 | **10c** | TMSBr, MeCN, room temp., 3 h | **11c** | 64 |

[a] Yields refer to isolated yields. [b] Monohydrate. [c] GC-MS of the crude product revealed trace amounts of the branched regioisomer **12b**.

As shown in Scheme 4, irrespective of the protecting group on nitrogen, the 2-ethyltropenones **10a**−**c** underwent fragmentation to the linear 2-pyrrolyl ketones **11a**−**c** from which **11c** gave single crystals suitable for X-ray crystallographic analysis (Figure 1).[14] In case of the *Z*-protected tropenone **10b**, the crude product contained trace amounts (< 1−2 %) of the branched pyrrolyl ketone **12b**.

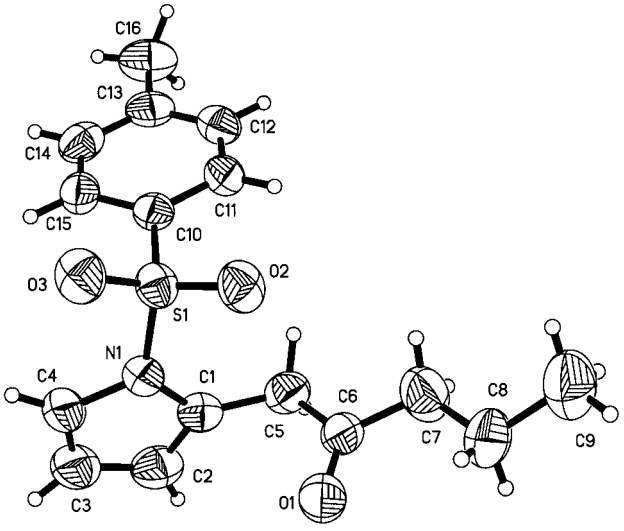



Figure 1. ORTEP view of 2-pyrrolyl ketone **11c**

Thus, the retro-Mannich reaction proceeded with high regioselectivity. Although this type of pyrrole formation has not been described previously in the literature, a related fragmentation of 2-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones to 2-substituted furans has been reported.[15,16] In conclusion, we have demonstrated the synthetic utility of acid-promoted retro-Mannich reaction of tropenones to 2-substituted pyrroles.

## Experimental Section

**General:** Melting points were determined on a Differential Scanning Calorimeter DSC822 (Mettler-Toledo). NMR spectra were recorded on a Bruker ARX 300 ($^1$H: 300 MHz, $^{13}$C: 75 MHz) and ARX 500 ($^1$H: 500 MHz, $^{13}$C: 125 MHz) instrument and are referenced to residual $CHCl_3$. IR spectra were recorded on a Bruker FT-IR spectrometer Vektor 22. Mass spectra were recorded on a Finnigan MAT 95 or a Varian MAT 711 apparatus. Flash chromatography was performed with silica gel 60 (Fluka, grain size 40−63 μm). Hexanes (petroleum ether, PE, boiling range 30−75 °C) and ethyl acetate (EtOAc) were distilled prior to use; benzene and $CH_2Cl_2$ were distilled over $CaH_2$, $CH_3CN$ was dried over $P_2O_5$ before distillation.

**General Procedure for the Reaction with the Acid TsOH; a) Preparation of Pyrroles 5 with a Nucleophile:** A solution of **4** (1 mmol), ethylene glycol (200 μL, 3.6 mmol) and TsOH (16 mg, 0.08 mmol) in anhydrous benzene (4 mL) was heated at reflux under Dean−Stark conditions for the times given in Table 1. The reaction mixture was then diluted with $CH_2Cl_2$ (20 mL) and subsequently washed with $NaHCO_3$ solution (20 mL). The organic layer was dried ($Na_2SO_4$) and concentrated. Flash chromatography on $SiO_2$ with EtOAc/hexanes (1:2) yielded the products **5** and by-products **6**.

**Methyl 2-[(2-Methyl-1,3-dioxolan-2-yl)methyl]-1*H*-pyrrole-1-carboxylate (5a):** $R_f$ (EtOAc/PE 1:2; PMA) = 0.7. $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, 3-H), 3.36 (s, 2 H, 1-H), 3.59−3.75 (m, 2 H, $OCH_2$), 3.76−3.90 (m, 2 H, $OCH_2$), 3.92 (s, 3 H, $OCH_3$), 6.08−6.14 (m, 2 H, 3′-H, 4′-H), 7.21 (dd, $J$ = 3.3, $J$ = 1.7 Hz, 1 H, 5′-H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 24.5 (C-3), 36.6 (C-1), 53.6 (OMe), 64.9 ($OCH_2$), 109.2 (C-2), 110.4 (C-3′), 114.4 (C-4′), 121.3 (C-5′), 130.5 (C-2′), 151.7 (COO) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2962 (m), 2931 (m), 2882 (m), 2360 (s), 2341 (s), 1683 (vs), 1453 (vs), 1394 (vs), 1307 (vs), 1192 (s), 1110 (vs), 1090 (vs), 1055 (vs) cm$^{-1}$. MS (CI): $m/z$ (%) = 224 (0.5) [$MH^+ - H_2$], 87 (100) [$C_4H_7O_2^+$]. $C_{11}H_{15}NO_4$ (225.2): calcd. C 58.66, H 6.71, N 6.22; found C 58.66, H 6.68, N 6.14.

**b) Preparation of Pyrroles 7 or 11 without a Nucleophile:** TsOH (16 mg, 0.08 mmol) was added to a solution of **4** or **10** (1 mmol) in benzene (5 mL), and the reaction mixture was heated at reflux for the times given in Table 1 and 2. The reaction mixture was diluted with $CH_2Cl_2$ (20 mL) and subsequently washed with $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic layer was dried ($Na_2SO_4$) and concentrated. Flash chromatography on $SiO_2$ with EtOAc/hexanes (1:4) gave products **7** and **11**, respectively.

**Methyl 2-(2-Oxopropyl)-1*H*-pyrrole-1-carboxylate (7a):** Chromatography, $R_f$ (EtOAc/PE 8:1; PMA) = 0.32. $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, 3-H), 3.87 (s, 3 H, $OCH_3$), 3.92 (s, 2 H, 1-H), 6.05−6.09 (m, 1 H, 3′-H), 6.15 (t, $J$ = 3.4 Hz, 1 H, 4′-H), 7.24 (dd, $J$ = 3.4, $J$ = 1.7 Hz, 1 H, 5′-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 29.3 (C-3), 43.2 (C-1), 53.7 ($OCH_3$), 110.9 (C-3′), 114.6 (C-4′), 121.2 (C-5′), 128.3 (C-2′), 151.1 (COO), 205.1 (CO) ppm. FT-IR (ATR): $\tilde{\nu}$ = 1737 (vs), 1717 (vs), 1494 (m), 1440 (s), 1414 (m), 1310 (vs), 1223 (s), 1130 (vs), 1069 (s) cm$^{-1}$. MS (EI): $m/z$ (%) = 181 (50) [$M^+$], 138 (100) [$M^+ - CH_3CO$], 94 (25). $C_9H_{11}NO_3$ (181.2): calcd. C 59.66, H 6.12, N 7.73; found C 59.81, H 6.24, N 7.61.

**Methyl 2-(2-Oxopentyl)-1*H*-pyrrole-1-carboxylate (11a):** Chromatography, $R_f$ (EtOAc/PE 8:1; PMA) = 0.38. $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, $J$ = 7.3 Hz, 3 H, 5-H), 1.63 (qt, $J$ = 7.3, $J$ = 7.3 Hz, 2 H, 4-H), 2.47 (t, $J$ = 7.3 Hz, 2 H, 3-H), 3.88 (s, 3 H, $OCH_3$), 3.91 (s, 2 H, 1-H), 6.05−6.09 (m, 1 H, 3′-H), 6.15 (t, $J$ = 3.4 Hz, 1 H, 4′-H), 7.24 (dd, $J$ = 3.4, $J$ = 1.8 Hz, 1 H, 5′-H) ppm. $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ = 13.7 (C-5), 17.0 (C-4), 42.6, 43.9 (C-1, C-3), 53.7 ($OCH_3$), 110.9 (C-3′), 114.6 (C-4′), 121.3 (C-5′), 128.4 (C-2′), 151.2 (COO), 207.2 (CO) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2960 (m), 1740 (vs), 1716 (vs), 1494 (m), 1440 (s), 1407 (m), 1315 (vs), 1133 (vs) cm$^{-1}$. MS (CI): $m/z$ (%) = 209 (100) [$M^+$], 178 (12) [$M^+ - CH_3O$], 140 (50). HRMS for $C_{11}H_{15}NO_3$ (EI): calcd. 209.1052; found 209.1052 [$M^+$].

**Methyl 2-[2-Cyano-2-(trimethylsilyloxy)propyl]-1*H*-pyrrole-1-carboxylate (8a):** Ketone **4a** (108 mg, 0.603 mmol) was added to a stirred suspension of anhydrous $ZnI_2$ (ca. 15−20 mg) in anhydrous benzene (2 mL). The reaction was cooled to 0 °C and TMSCN (87 μL, 0.603 mmol) was added by syringe. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. The reaction was terminated with a saturated EDTA solution (3 mL), and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated. Chromatography on $SiO_2$ with hexanes/EtOAc [$R_f$ (EtOAc/PE, 9:1; PMA) = 0.40] gave **8a** as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.16 (s, 9 H, OTMS), 1.59 (s, 3 H, 3-H), 3.41 (d, $J$ = 14.7 Hz, 1 H, 1-H), 3.53 (d, $J$ = 14.7 Hz, 1 H, 1-H), 3.93 (s, 3 H, $OCH_3$), 6.16 (t, $J$ = 3.4 Hz, 1 H, 4′-H), 6.24−6.32 (m, 1 H, 3′-H), 7.26 (dd, $J$ = 3.4, $J$ = 1.7 Hz, 1 H, 5′-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 0.9 (OTMS), 28.7 (C-3), 40.2 (C-1), 53.7 ($OCH_3$), 110.6 (C-3′), 115.5 (C-4′), 121.7 (CN), 122.0 (C-5′), 128.6 (C-2′), 151.5 (COO) ppm. FT-IR (ATR): $\tilde{\nu}$ = 1748 (vs), 1489 (m), 1441 (s), 1416 (m), 1337 (m), 1320 (vs), 1252 (s), 1233 (s), 1170 (m), 1136 (vs), 1002 (vs), 840 (vs) cm$^{-1}$. MS (EI): $m/z$ (%) = 280 (7) [$M^+$], 138 (100)

$[M^+ - CH_3C(CN)OTMS]$. $C_{13}H_{20}N_2O_3Si$ (280.4): calcd. C 55.69, H 7.19, N 9.99; found C 55.71, H 7.26, N 9.86.

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