Extending the Scope of a Known Furan Synthesis – A Novel Route to 1,2,4-Trisubstituted Pyrroles

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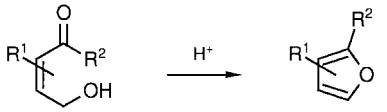
Abstract: 2-(Acylmethylene)propanediol diacetates, which cyclize readily under acidic conditions to give furans (76–84%) react with primary amines under palladium catalysis to give 1,2,4-trisubstituted pyrroles in moderate to good yields (39–53%). When glycine methyl ester is used as the amine, substituted methyl pyrrol-1-ylacetates (31–82%) are obtained.

Key words: heterocycles, Wittig olefination, palladium catalysis, allylic substitution

Probably the best known access to furans and pyrroles is by the Paal–Knorr synthesis.[1] 1,4-Dicarbonyl compounds are cyclized under acid catalysis and with dehydration to give furans; in the presence of primary amines or ammonium salts, the corresponding pyrroles are formed. By a similar mechanism, but under much milder conditions, furans are also formed under acid catalysis from α,β-unsaturated γ-hydroxyketones of type **1** (Scheme 1).[2] Starting from readily available dihydroxyacetone diacetate **3**,[3] we have extended a known access[4] to functionally substituted furans **6** and developed an analogous, yet palladium-catalyzed reaction leading to pyrroles.



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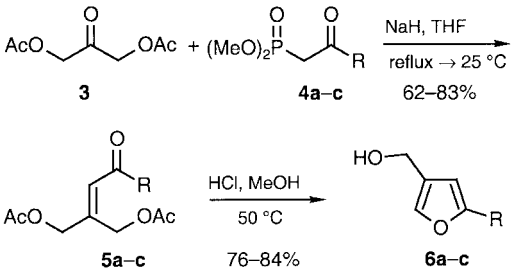
Scheme 1 Furans from α,β-unsaturated γ-hydroxyketones

In this extension of the furan synthesis, α,β-unsaturated γ-acetoxyketones **5a**–**c** which were obtained by Horner–Wadsworth–Emmons olefination of 1,3-diacetoxy-2-propanone (**3**) with β-ketophosphonates **4a**–**c** in 62–83% yield, were used as precursors (Scheme 2, Table 1).[5]

Upon treatment of the 3,3-bis(acetoxymethyl)-substituted enones **5** with hydrochloric acid in methanol at 50 °C for 30–60 minutes, the corresponding 2-substituted 4-hydroxymethylfurans **6a**–**c** were formed in 76–84% yield.[5] This reaction involves the hydrolysis of the two acetoxy moieties to give the bisallylic alcohol which, under the acidic conditions, forms the furan. Formation of the 4-fluorophenyl-substituted furan **6c** proceeded much faster than the formation of the methyl- and ethyl-substituted furans **6a**,**b**.



Scheme 2 Horner–Wadsworth–Emmons olefination of 1,3-diacetoxy-2-propanone (**3**) and subsequent cyclization to 2,4-disubstituted furans. For details see Table 1.

Table 1 Horner–Wadsworth–Emmons Olefination of 1,3-Diacetoxy-2-propanone (**3**) with β-Ketophosphonates **4a**–**c** and Subsequent Cyclization of Products **5a**–**c** to Furans **6a**–**c**

R	Reaction Time [h]	Product	Yield (%)	Reaction Time [h]	Product	Yield (%)
Me	2.5	**5a**	76	1	**6a**	76
Et	18	**5b**	83	1	**6b**	79
4-F-C_6H_4	48	**5c**	62	0.5	**6c**	84

In a first attempt to further extend the scope of this reaction to the synthesis of pyrroles, the simple addition of primary amines and ammonium salts to precursors **5a**–**c** was tested under acidic and basic conditions. But no trace of a pyrrole could be detected in any case. Since pyrroles can only be formed after nucleophilic substitution of at least one of the allylic acetoxy groups in **5** by an amine, and this kind of substitution is generally catalyzed by palladium(0),[6,7] compounds **5a**,**c** were treated with two equivalents of benzylamine and 5 mol% of tetrakis(triphenylphosphine)palladium in refluxing tetrahydrofuran to give the desired pyrroles **7a**,**c** as orange oils in 53 and 39% yield, respectively (Scheme 3, Table 2).[5]

The low yields of isolated products must be partly due to the low stability of the pyrroles **7a**,**c** towards air and moisture, as was indicated by the appearance of deeply colored zones on the flash-chromatography column. The chroma-

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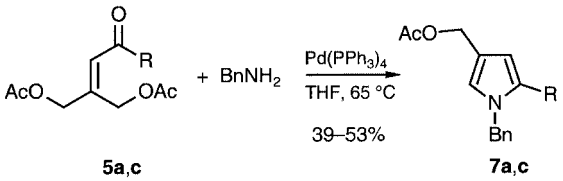


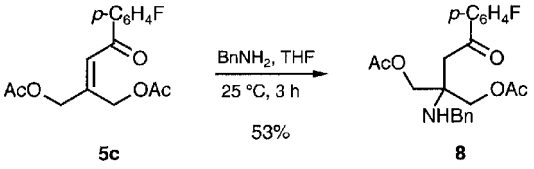
Scheme 3 Synthesis of pyrroles **7a**,**c** from enones **5a**,**c**. For details see Table 2.

tography therefore had to be performed with a column as short as possible, longer retention of the compounds **7a**,**c** on the column resulted in even lower yields.

Table 2 Reaction of Precursors **5** with Benzylamine to Yield Pyrroles **7**

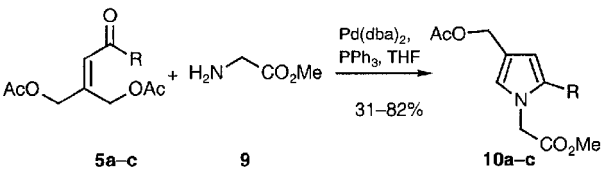
Starting Material	R	Reaction Time [h]	Product	Yield (%)
5a	Me	10	**7a**	53
5c	4-F-C_6H_4	3	**7c**	39

The attempted conversions of **5a**,**c** with benzylamine to **7a**,**c** did not succeed at ambient temperature. In the case of **5a**, no product was formed, while the treatment of **5c** with benzylamine at ambient temperature gave the Michael adduct **8** as the only product in 53% yield (Scheme 4). The same reaction took place in the absence of the palladium catalyst. Since this Michael addition is reversible, treatment of **8** with tetrakis(triphenylphosphine)palladium at 65 °C also gave the pyrrole **7c**.



Scheme 4 Michael addition of benzylamine to **5c**

The reaction of the bisallylic diacetates **5a**–**c** with glycine methyl ester (**9**) in the presence of a palladium catalyst gave the corresponding methyl 2-pyrrol-1-ylacetates **10a**–**c** in 31–82% yield (Scheme 5, Table 3). In this case, the best precatalyst system turned out to be bis(dibenzylideneacetone)palladium with triphenylphosphine.



Scheme 5 Synthesis of substituted pyrrol-1-ylacetates **14**. For details see Table 3.

While the reactions of **5a**,**b** with glycine methyl ester proceeded cleanly at room temperature to give the pyrroles **10a**,**b** in 80% and 82% yield, that of precursor **5c** required a temperature of 65 °C, and led to a more complex product mixture, from which the pyrrole **10c** could be isolated in only 31% yield.[5] At room temperature, again, only the Michael adduct of methyl glycinate to **5** was formed.

Table 3 Reaction of Bisallylic Diacetates **5** with Methyl Glycinate (**9**) to Pyrroles **10a**–**c**

Enone	R	Conditions	Product	Yield (%)
5a	Me	25 °C, 2 d	**10a**	80
5b	Et	25 °C, 2 d	**10b**	82
5c	4-F-C_6H_4	65 °C, 15 h	**10c**	31

The possibility to incorporate the amino function of an amino acid ester into a pyrrole ring gives access to a class of compounds known as pyrallic acids, which recently have gained attention for their antibiotic properties.[8]

Acknowledgement

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(5) All new compounds were fully characterized by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, MS); bulk purity was established in most cases by satisfactory elemental analysis data. Spectroscopic data of representative examples are: **4-Hydroxymethyl-2-methylfuran (6a)**: IR (KBr): 3357 (OH), 2923, 2878, 1740, 1557, 1449, 1385, 1272, 1234, 1123, 1021, 977, 918, 809, 737 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.90 (s, 1 H, OH), 2.28 (s, 3 H, 2-CH_3), 4.51 (s, 2 H, CH_2OH), 6.03 (br s, 1 H, 3-H), 7.26 (br s, 1 H, 5-H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 13.36 (+, 2-CH_3), 56.36 (–, CH_2OH), 105.70 (+, C-3), 125.84 (C_{quat}, C-4), 137.87 (+, C-5), 152.87 (C_{quat}, C-2). MS (EI, 70 eV): *m*/*z* (%) = 112(9) [M$^+$], 88(10), 61(16), 45(15), 43(100). Calcd for $C_6H_8O_2$: 112.0524; (correct HRMS). ***N*-Benzyl-4-acetoxymethyl-2-methylpyrrole (7a)**: IR (film): 3088, 3063, 3030, 2934, 1734 (CO), 1662, 1605, 1521, 1496, 1454, 1416, 1366, 1238, 1149, 1021, 943, 796, 734, 696 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.06 (s, 3 H),

2.12 (s, 3 H), 4.93 (s, 2 H), 4.98 (s, 2 H), 5.99 (s, 1 H, 3-H), 6.67 (br s, 1 H, 5-H), 7.01–7.04 (m, 2 H), 7.26–7.32 (m, 3 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 11.94 (+, 2-CH_3), 21.27 (+, CO*C*H_3), 50.36 (–), 60.42 (–), 108.04 (+, C-3), 117.13 (C_{quat}, C-4), 121.06 (+, C-5), 126.47 (+), 127.42 (+), 128.71 (+), 129.57 (C_{quat}, C-2), 137.77 (C_{quat}), 171.25 (C_{quat}, *C*OMe). MS (EI, 70 eV): *m/z* (%) = 243(70) [M^+], 201(25), 184(43) [M^+ – OCOMe], 172(12), 91(100) [$C_7H_7^+$]. **Methyl (4-Acetoxymethyl-2-methylpyrrol-1-yl)acetate (10a)**: IR(film): 3443, 2952, 1732 (CO), 1666, 1525, 1436, 1419, 1368, 1347, 1232, 1158, 1141, 1023, 943, 798, 731, 694, 658 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.05 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, 2-CH_3), 3.77 (s, 3 H, CO_2CH_3), 4.52 (s, 2 H, N-CH_2), 4.94 (s, 2 H, CH_2OAc), 5.97 (br s, 1 H, 3-H), 6.63 (br s, 1 H, 5-H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 11.63 (+, 2-CH_3), 21.20 (+, CO*C*H_3), 48.03 (–, N-CH_2), 52.51 (+, CO_2*C*H_3), 60.21 (–, *C*H_2OAc), 108.32 (+, C-3), 117.80 (C_{quat}, C-4), 121.30 (+, C-5), 129.72 (C_{quat}, C-2), 168.99 (C_{quat}), 171.25 (C_{quat}).

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