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Intramolecular Wittig reactions with esters utilising triphenylphosphine and dimethyl acetylenedicarboxylate

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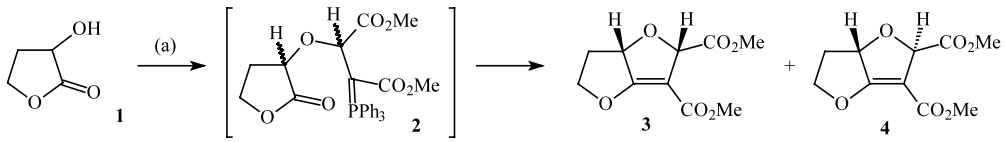
Abstract—The intramolecular Wittig olefination of α-hydroxy- and α-amino esters has been effected in high yield using a combination of triphenylphosphine and dimethyl acetylenedicarboxylate.

We previously reported[1] that reaction of α-hydroxybutyrolactones, for example **1**, with triphenylphosphine (TPP) and dimethyl acetylenedicarboxylate (DMAD) in dioxane at reflux led to the formation of two bicyclic products **3** and **4** in a 2:1 ratio via the ylide intermediate **2** (Scheme 1).

In order to test the generality of this reaction, we investigated the corresponding reaction of esters and thus treated ethyl glycolate **5a** under similar conditions[2] and were pleased to observe the formation of the expected Wittig product **6a** in 57% yield together with **8a**, the product from the conjugate addition of ethyl glycolate to DMAD, in 26% yield (Table 1, entry 1). This was a particularly encouraging result as we had envisaged that more forcing conditions might have been required to effect the cyclisation, as is often the case with esters.[3] We attempted to minimise the formation of the by-product **8a** by increasing the relative amounts of TPP and DMAD and allowing the reaction to stir at room temperature for longer periods of time, however, this had little effect on the overall outcome of the process. Structural determination of the product **6a** was aided by the characteristic $^5J_{H-H}$ coupling found in 2,5-dihydrofurans, which is of the order of 4–5 Hz for the *cis*-protons and 1–2 Hz for the corresponding *trans*-protons.[4] In the case of **6**/**7a**, these values were found to be $J=4.6$ and 1.8 Hz, respectively (Scheme 2).

When the reaction was repeated using ethyl lactate **5b** (Table 1, entry 2) a similar result was observed with the cyclisation products **6**/**7b** being isolated in 90% yield and in a 5:1 ratio, together with a smaller amount of **8b** (8%). These again were identified on the basis of the magnitude of their $^5J_{H-H}$ values. The relative ratio of these two compounds remained constant (ca. 4.5–5:1) over several reactions indicating that the selectivity for the *cis*-product probably has its origins in the step leading to the formation of the intermediate ylide. This might also suggest that the products are stable to epimerisation under the reaction conditions. Finally, reaction of ethyl mandelate **5c** (Table 1, entry 3) under identical conditions gave **6**/**7c** in 78% yield and in a 25:1 ratio, together with the addition product **8c** in 15% yield (Scheme 2).

We next turned our attention to the formation of the corresponding dihydropyrroles and initially looked at the series of Boc-protected amino acid esters **9a–c** (Table 2, entries 1–3 and Scheme 3).[5] We were encouraged to see that reaction of *N*-Boc glycine ethyl ester **9a** under the standard conditions gave a respectable 46%



Scheme 1. (a) PPh_3/DMAD/dioxane/10°C, 1 h, then reflux 3 h 84% (2:1).

Keywords: intramolecular Wittig reaction; 2,5-dihydrofurans; 2,5-dihydropyrroles.

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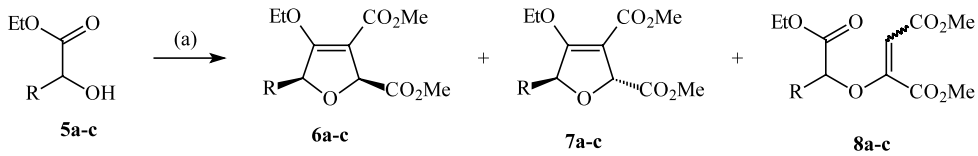
Table 1.

Entry	5	R	6/7 (%)	6:7	8 (%)	$^5J_{H-H}$ *cis* (Hz)	$^5J_{H-H}$ *trans* (Hz)
1	**a**	H	57	–	26	$J=4.6$	$J=1.8$
2	**b**[a]	Me	90	5:1[b]	8	$J=3.9$	$J=1.5$
3	**c**	Ph	78	25:1[b]	15	$J=4.1$	$J=2.6$

[a] Ethyl (*S*)-(−)-lactate was used.
[b] Inseparable by column chromatography.



5a-c **6a-c** **7a-c** **8a-c**

Scheme 2. (a) PPh_3/DMAD/dioxane/10°C, 1 h, then reflux 16 h.

yield of the expected 2,5-dihydropyrrole **10a**, together with a considerable amount of recovered **9a** which raised the yield, based on conversion, to 90%. Again, structural determination of **9a** was aided by the characteristic $^5J_{H-H}$ coupling found in 2,5-dihydropyrroles.[3] Following on from this, we attempted a similar reaction with *N*-Boc alanine ethyl ester **9b** and were disappointed to achieve only a 13% yield of the desired products **10**/**11b** in ca. 1:1 ratio. Again, based on recovered starting material this yield rose to 93%. Finally, we reacted *N*-Boc-2-phenylglycine methyl ester **9c** under identical conditions to give **10**/**11c** in 46% yield in a 1.4:1 ratio. Again the yield was found to be very high when recovered starting material was taken into account.

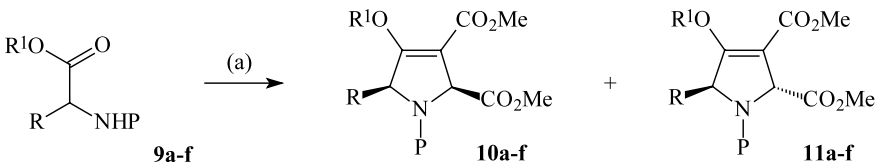
We felt that the low conversion of substrates **9a–c** was probably due to a steric effect related to the Boc protecting group. We thus performed a series of reactions on the corresponding series of *Z*-protected amino acid esters **9d–f**. We were pleased to find that these substrates were far more suitable for the reaction leading to the dihydropyrroles **10**/**11d–f** in 75–96% overall yield (Table 2, entries 4–6), with only **9e** (entry 5) being recovered in any appreciable amount (Scheme 3). As observed with the dihydrofuran examples, in all these reactions, there appeared to be a bias towards the formation of the *cis*-products **10**, however, the effect was not as pronounced.

We next investigated the reaction of ethyl thioglycolate **12** under these conditions and not surprisingly obtained only the addition product **13** in high yield. We attempted to prevent the formation of this product by firstly generating the vinyl phosphonium salt **14**[6] in situ from DMAD and triphenylphosphonium hydrobromide. This was then reacted with **12** in the presence of pyridine or DBU to effect the formation of the intermediate ylide. Despite considerable effort, we were unable to isolate any of the required 2,5-dihydrothiophene, the only major product obtained being triphenylphosphine sulphide, suggesting that desulfurisation of the starting material and/or product is a competetive process (Scheme 4).

Table 2. [a]

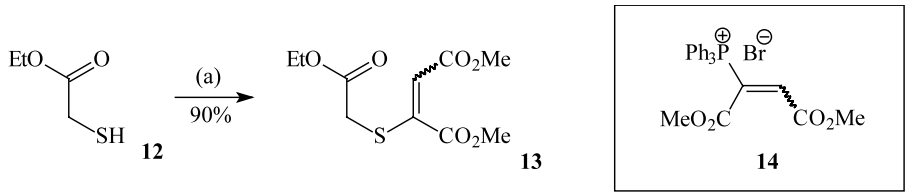
Entry	9	R	R^1	P	10/11 (%)	10:11	$^5J_{H-H}$-*cis* (Hz)	$^5J_{H-H}$-*trans* (Hz)
1	**a**	H	Et	Boc	46 (90)	–	$J=4.4$	$J=1.7$
2	**b**	Me	Et	Boc	13 (93)[b]	ca. 1:1	–[c]	–[c]
3	**c**	Ph	Me	Boc	46 (99)	1.4:1	$J=4.6$	$J=\sim 0$
4	**d**	H	Et	*Z*	91	–	$J=4.2$	$J=1.3$
5	**e**	Me	Et	*Z*	75 (96)[b]	ca. 1:1	–[c]	–[c]
6	**f**	Ph	Me	*Z*	96	1.2:1	$J=4.4$	$J=\sim 0$

[a] Yields in parentheses are based on recovered starting material.
[b] Inseparable by column chromatography.
[c] Signals obscured.



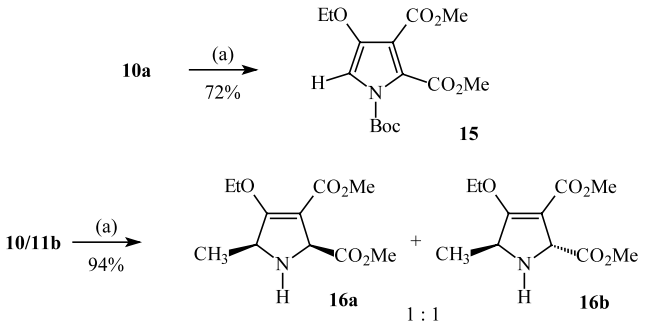
9a-f **10a-f** **11a-f**

Scheme 3. (a) PPh_3/DMAD/dioxane/10°C, 1 h, then reflux 16 h.



Scheme 4. (a) PPh_3, DMAD, dioxane, 10°C, 1 h; then reflux, 16 h.

In conclusion, we have demonstrated that the intramolecular Wittig reaction of the ylide generated from the reaction of α-hydroxy or *Z*-protected α-aminoesters leads to the formation of 2,5-dihydrofurans or 2,5-dihydropyrroles, respectively, in high yields. In addition, the preferential formation of the *cis*-heterocycles in these reactions and their apparent stability to epimerisation would suggest that this reaction could be utilised in an asymmetric manner. We intend to investigate this eventuality, as well as other transformations, for example preliminary results include the aromatisation of **10a** to the pyrrole **15** and the deprotection of **10**/**11b** to give **16a**/**b**, both of which proceeded in high yield (Scheme 5).



Scheme 5. (a) DDQ, toluene, reflux 16 h; (b) CF_3COOH, DCM, 2 h.

Acknowledgements

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2. **General procedure**: The required α-hydroxy ester or protected amino acid ester (1 equiv., typically 10 mmol) was dissolved in dry dioxane (20 ml) together with triphenylphosphine (1.1–3.0 equiv.) and cooled in ice water (to ca. 10°C). DMAD (1.0–1.5 equiv.) was then added dropwise over 5 min and the reaction warmed to rt over 1 h. The reaction was refluxed overnight (16 h), cooled to rt which was followed by the addition of silica gel (8–10 g) and evaporation of the solvent. The resulting free flowing powder was applied to a silica gel column and the products eluted with a diethyl ether/petroleum ether mix. All compounds displayed satisfactory analytical data.
4,5-Dicarbomethoxy-3-ethoxy-2,5-dihydrofuran 6a. ^1H NMR: δ 5.25 (dd, 1H, $J=4.6$, 1.8 Hz, CH), 4.88 (dd, 1H, $J=13.7$, 4.6 Hz, $C\underline{H}_aH_b$), 4.70 (dd, 1H, $J=13.7$, 1.8 Hz, $CH_a\underline{H}_b$), 4.15 (q, 2H, $J=7.0$ Hz, CH_2), 3.90 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 1.37 (t, 3H, $J=7.0$ Hz, CH_3). ^{13}C NMR: $\delta=171.52$ (C), 166.06 (C), 162.31 (C), 99.51 (C), 83.33 (CH), 71.96 (CH_2), 68.64 (CH_2), 52.31 (CH_3), 51.28 (CH_3), 15.37 (CH_3). IR: $\nu_{max}=2984$, 2953, 2911, 2860 (C-H), 1745, 1724 (C=O), 1650 (C=C). MS (CI): $m/z=171$ (10%, $[M-CO_2Me]^+$), 231 (100%, $[M+H]^+$), 248 (80%, $[M+NH_4]^+$). HRMS (CI): $C_{10}H_{15}O_6$ ($[M+H]^+$) requires 231.0868; found: 231.0868.
***N*-Boc-4,5-dicarbomethoxy-3-ethoxy-2,5-dihydropyrrole 10a**. (The Boc and *Z*-protected derivatives were found to exist as atropisomers, figures in parentheses represent chemical shift values for the alternate isomer where given.) ^1H NMR: δ 5.05 (5.09) (dd, 1H, $J=4.4$, 1.7 Hz, CH), 4.52 (4.49) (dd, 1H, $J=16.0$, 4.4 Hz, $C\underline{H}_aH_b$), 4.40 (4.32) (dd, 1H, $J=16.0$, 1.7 Hz, $CH_a\underline{H}_b$), 4.18 (m, 2H, CH_2), 3.74 (3.76) (s, 3H, CH_3), 3.72 (3.73) (s, 3H, CH_3), 1.44 (m, 12H, *t*-Bu+CH_3). ^{13}C NMR: $\delta=171.92$ (C), 164.59 (C), 162.52 (C), 152.98 (C), 100.44 (C), 81.17 (C), 67.95 (CH_2), 63.72 (CH), 52.37 (CH_3), 51.24 (CH_3), 50.33 (CH_2), 28.28 (3× CH_3), 15.27 (CH_3). IR: $\nu_{max}=2979$, 2951, 2868 (C-H), 1748, 1708 (C=O), 1639 (C=C). MS (CI): $m/z=230$ (40%, $[M+H\text{-Boc}]^+$), 291 (100%, $[M+NH_4-C_4H_8]^+$), 330 (30%, $[M+H]^+$), 347 (35%, $[M+NH_4]^+$). HRMS (CI): $C_{15}H_{24}NO_7$ ($[M+H]^+$) requires 330.1553; found: 330.1556.
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