A CONVENIENT NEW SYNTHESIS OF 1,2-DIARYLPYRROLES FROM 3-ETHOXYCARBONYL-4-OXO-4-PHENYLIBUTRALDEHYDE

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Abstract – An efficient four-step synthesis of ethyl 1,2-diaryl-3-pyrrole carboxylates (4), an isomeric scaffold of pharmacologically active natural products, is reported. The key synthon 3-ethoxycarboxyl-4-oxo-4-phenylbutyraldehyde (3), whose new synthesis is detailed here, reacts conveniently with anilines to create the pyrrole ring.

The isolation and synthesis of pyrrole-containing alkaloids remain a very active research area because of their highly potent activity against various cancer cell lines.¹ This is the case, for example, for lamellarin O and lukianol A derivatives,² or for ningalin B (Figure 1),³ a natural marine product which was found to act as a multi-drug resistant reversal agent.⁴ All of these compounds possess a common 3,4-diaryl-substituted pyrrole nucleus with a carboxylate on C 2. Several elegant syntheses have been reported for this scaffold.²,³,⁵-⁹

![Figure 1]
In the field of our continuing search for new therapeutic agents potentially useful in cancer treatment, we recently published the synthesis of new compounds containing the pyrrole scaffold.\textsuperscript{10-14} We report here a flexible method to accede to the 1,2-diarylpyrrole structure bearing a carboxylate on C 3, an isomer of the above cited heterocycles and an analogue of the diarylpyrazole-3-carboxylate, an efficient precursor of COX-2/5-LOX inhibitors described as cell proliferation inhibitors of human prostate cancer cell lines.\textsuperscript{15}

The selected reaction sequence is shown in Scheme 1. To our knowledge, only one approach has been described for the preparation of 3-ethoxycarbonyl-4-oxo-4-phenylbutyraldehyde (3), the inconvenient ozonolysis of the corresponding alkene.\textsuperscript{16} We have developed a more versatile and efficient approach to obtain this tricarbonyl aromatic molecule through a three-step synthesis. 3-Benzoyl-3-ethoxycarboxylpropionic acid (1) was first obtained by alkylation of ethyl benzoylacetate with 2-bromoacetic acid in the presence of sodium ethoxide, as previously described.\textsuperscript{17} The main problem was to reduce the carboxylic acid function into formyl group - rather poorly described in publications - which must here be chemoselective as regards the presence of carbonyl and ester groups. A few reagents such as lithium in dimethylamine,\textsuperscript{18} thexylborane,\textsuperscript{19} isobutylmagnesium bromide/dichloro bis (η-cyclopentadienyl)titanium\textsuperscript{20} and bis(4-methylpiperazinyl)aluminium hydride\textsuperscript{21} have been mentioned but generally lack selectivity and are inconvenient to use.

One-pot conversion with DIBALH\textsuperscript{22} seemed to be the most appropriate process, but here, surprisingly, the reaction did not evolve. Using BH\textsubscript{3}•Me\textsubscript{2}S complex enabled us to selectively reduce the carboxylic

\begin{center}
\textbf{Scheme 1}\textsuperscript{†}
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\textsuperscript{†}Reagents and conditions: a) 1. BrCH\textsubscript{2}COOH, EtONa, EtOH, reflux, 15 h; 2. 3N HCl, 0°C, 15 min b) BH\textsubscript{3}•Me\textsubscript{2}S, THF, reflux, 1 h c) 1. K\textsubscript{2}CrO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, 30% H\textsubscript{2}SO\textsubscript{4}, n-Bu\textsubscript{4}N\textsuperscript{+}HSO\textsubscript{4}\textsuperscript{−}, 0°C, 15 min; 2. 10% FeSO\textsubscript{4}, rt, 10 min.
\end{center}
function of compound (1) into a primary hydroxy group which, in turn, was immediately converted into formyl function. This oxidation step was found effective with potassium chromate under phase-transfer catalysis, at 0°C. Under these conditions the primary alcohol, insoluble in the aqueous phase, was rapidly oxidized into aldehyde (15 min), without over-reaction into the corresponding carboxylic acid.

Although all the reactions can be scaled up to 5 g without any difficulty, aldehyde (3) is not stable enough to be purified (chromatography or crystallization). Due to the formation of two unidentified side products, the yield of the oxidation reaction cannot be determined; nevertheless the IR spectrum of 3 is consistent with the formation of aldehyde as the major product: \( \nu = 1764 \text{ cm}^{-1} \) (formyl), 1729 cm\(^{-1} \) (ester) and 1683 cm\(^{-1} \) (carbonyl), while disappearance of \( \nu = 3490 \text{ cm}^{-1} \) (hydroxy).

For these reasons, 3-ethoxycarbonyl-4-oxo-4-phenylbutyraldehyde (3) must be immediately reacted with substituted anilines to give the expected pyrroles (4) in moderate yields (50% from alcohol (2)), via an acetic acid-catalysed Paal-Knorr condensation (Scheme 2).

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\begin{align*}
R & \quad \text{EtOH, CH₃COOH, reflux, 3 h} \quad \text{EtOH, CH₃COOH} \\
\text{R} & \text{NH₂} \quad 3 \quad \text{EtOH, CH₃COOH} \quad \text{EtOH, CH₃COOH} \\
& \quad \text{COOEt} \quad \text{CHO} \quad \text{COOEt} \\
& \quad \text{4a R = H} \quad \text{4b R = SO₂Me}
\end{align*}
\]

**Scheme 2**

In conclusion, we have developed a new procedure for the preparation of ethyl 1,2-diaryl-3-pyrrole-carboxylates, by condensing anilines with 3-ethoxycarbonyl-4-oxo-4-phenylbutyraldehyde (3). This method offers several advantages including an easier experimental work-up procedure than previously described, shorter reaction times and good yields. Apart from pyrrole, the 1,4-dicarbonyl electrophile (3) represents a key intermediate for the synthesis of various and potentially active heterocycles substituted by an ester, a flexible and reactive functional group.

**EXPERIMENTAL**

**General.** THF was distilled from sodium/benzophenone prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Analytical TLC was performed on precoated Kieselgel 60F\(_{254}\) plates (Merck); compounds were visualized by UV and/or with
iodine. Silica gel Kieselgel Si 60 (230-400 mesh, Merck) was used for chromatography. Melting points were determined with a Büchi 530 capillary melting point apparatus and remain uncorrected. The structures of all compounds were supported by IR spectrum (FT-Bruker Vector 22 instrument) and, if possible, by $^1$H NMR spectrum at 300 MHz on a Bruker DPX-300 spectrometer. Chemical shifts (δ) are reported in ppm downfield from TMS, $J$ values are in hertz. APCI$^+$ mass spectra were obtained on a LC-MS system Thermo Electron Surveyor MSQ. Elemental analyses were performed by the “Service Central d’Analyses” at the CNRS, Vernaison, France.

3-Benzoyl-3-ethoxycarbonylpropionic acid (1) - Ethyl benzoylacetate (5.0 mL, 28.9 mmol) was added dropwise to a stirred solution of EtONa (prepared from 2.0 g (86.9 mmol) of Na and 45 mL of EtOH). After stirring for 30 min at rt, 2-bromoacetic acid (10.0 g, 71.0 mmol) was added. The mixture was refluxed for 15 h. EtOH was then removed under reduced pressure and the viscous residue was diluted with H$_2$O (30 mL). After acidification to pH 1 with 3 N aqueous HCl, the product was extracted with EtOAc ($2 \times 30$ mL). The organic layer was dried (MgSO$_4$) and the solvent was removed under vacuum to give acid (1) as a yellow oil (5.7 g, 79%); IR (neat) 1736, 1712, 1687 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 1.11 (t, 3H, $J$ = 7.1), 3.05 (d, 1H, $J$ = 7.0), 3.10 (d, 1H, $J$ = 7.0), 4.10 (q, 2H, $J$ = 7.1), 4.82 (t, 1H, $J$ = 7.0), 7.46 (dd, 2H, $J = J' = 7.4$), 7.55 (dd, 1H, $J = J' = 7.4$), 8.00 (m, 2H).

Ethyl 2-benzoyl-4-hydroxybutanoate (2) - BH$_3$•Me$_2$S in THF (2 M, 15.0 mL, 30.0 mmol) was added to a solution of acid (1) (5.0 g, 20.0 mmol) in 100 mL of THF and the mixture was stirred at reflux. After 1 h, the reaction mixture was cooled to rt, then 1 N aqueous HCl and H$_2$O were added cautiously to quench the reaction. The product was extracted with EtOAc ($3 \times 50$ mL). The organic layer was washed successively with 10% aqueous NaHCO$_3$, brine and dried (MgSO$_4$). The solvent was removed under vacuum to give ester (2) as a yellow oil (4.4 g, 94%); IR (neat) 3490, 1734, 1684 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 1.21 (t, 3H, $J$ = 7.1), 3.13 (td, 2H, $J = 9.8, J' = 8.7$), 4.14 (q, 2H, $J$ = 7.1), 4.54 (t, 2H, $J = 9.8$), 4.83 (t, 1H, $J =$ 8.8), 7.27-7.40 (m, 3H), 7.76 (m, 2H).

3-Ethoxycarbonyl-4-oxo-4-phenylbutyraldehyde (3) - A solution of K$_2$CrO$_4$ (2.8 g, 14.9 mmol) in 30% aqueous H$_2$SO$_4$ (30 mL) was added dropwise to a stirred solution of ester (2) (4.4 g, 18.6 mmol) and $n$-Bu$_4$N$^+$HSO$_4$$^-$ (0.6 g, 1.8 mmol) in 80 mL CH$_2$Cl$_2$, keeping the inner temperature between –5°C and 0°C. The mixture was stirred vigorously for 15 min, then 30 mL of an aqueous solution of 10% FeSO$_4$ was added. After 10 min of additional stirring, the layers were separated. The organic layer was washed successively with 10% aqueous K$_2$CO$_3$, brine and then dried (MgSO$_4$). The solvent was removed under
vacuum to give a reddish oil, which was immediately used in the next reaction. IR (neat) 1764, 1729, 1683 cm⁻¹.

**Ethyl 1,5-diphenyl-1H-pyrrole-2-carboxylate (4a)** - A solution of crude aldehyde (3) (4.5 g), aniline (2.1 mL, 22.9 mmol) and AcOH (0.2 mL) in 25 mL EtOH was refluxed for 3 h. The solvent was removed under vacuum and the residue diluted with 40 mL of EtOAc. The organic layer was washed successively with 1 N aqueous HCl, brine and then dried (MgSO₄). The crude product was purified by chromatography on silica gel using heptane/EtOAc (95/5 v/v) as eluent. Recrystallization from MeOH gave pyrrole (4a) as white crystals (2.9 g, 54% from 2); mp 107-109°C; IR (neat) 1686 cm⁻¹; ¹H NMR (CDCl₃) 1.20 (t, 3H, J = 7.0), 4.19 (q, 2H, J = 7.0), 6.85 (d, 1H, J = 2.9), 6.90 (d, 1H, J = 2.9), 7.06 (m, 2H), 7.28 (m, 3H), 7.32 (m, 5H); MS m/z 292 (MH⁺). Anal. Calcd for C₁₉H₁₇NO₂: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.21; H, 5.80; N, 4.80.

**Ethyl 5-(4-methanesulfonylphenyl)-1-phenyl-1H-pyrrole-2-carboxylate (4b)** - Prepared from aldehyde (3) (4.5 g, 19.1 mmol) and 4-methanesulfonylaniline (3.6 g, 21.1 mmol) in a similar way to that described above for the preparation of pyrrole (4a). The crude product was purified by chromatography on silica gel using heptane/EtOAc (8/2 v/v) as eluent. Solvent evaporation gave pyrrole (4b) as a yellow oil (3.4 g, 49% from 2); IR (neat) 1735 cm⁻¹; ¹H NMR (CDCl₃) 1.17 (t, 3H, J = 7.2), 3.03 (s, 3H), 4.15 (q, 2H, J = 7.2), 6.87 (d, 1H, J = 2.5), 6.91 (d, 1H, J = 2.5), 7.21-7.30 (m, 7H), 7.81 (d, 2H, J = 8.3); MS m/z 370 (MH⁺). Anal. Calcd for C₂₀H₁₉NO₄S: C, 65.02; H, 5.18; N, 3.79. Found: C, 65.36; H, 5.20; N, 3.77.

**REFERENCES**