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

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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-ethoxycarbonyl-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}

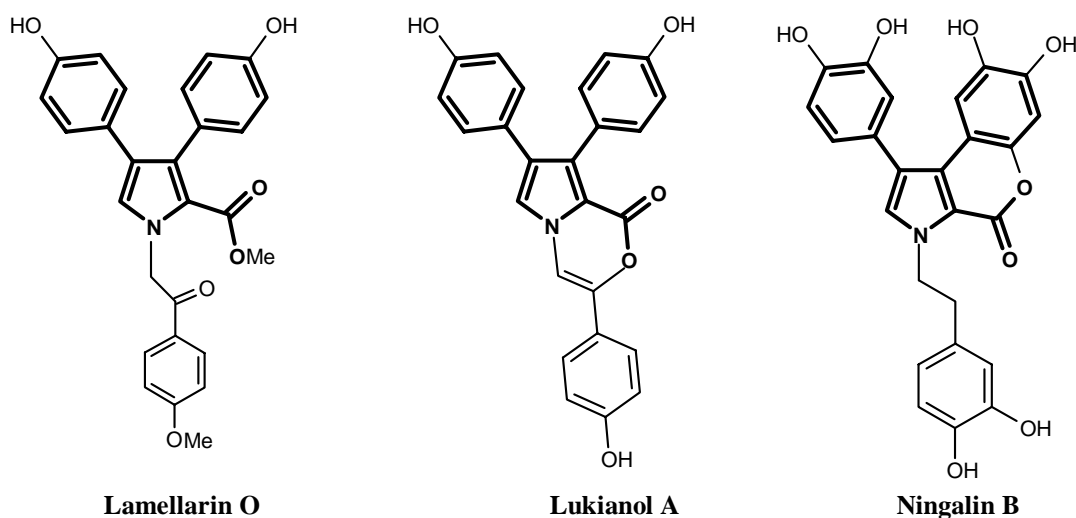
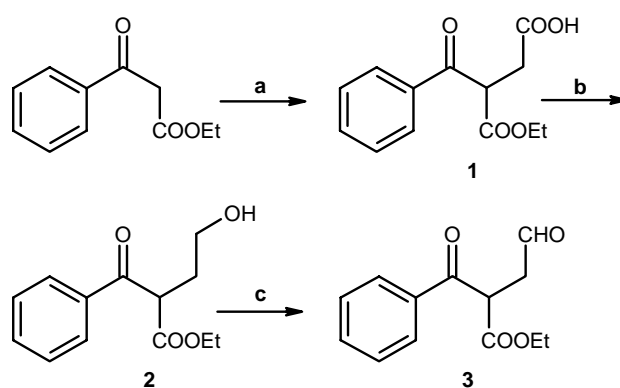


Figure 1

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.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.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.¹⁶ We have developed a more versatile and efficient approach to obtain this tricarbonyl aromatic molecule through a three-step synthesis. 3-Benzoyl-3-ethoxycarbonylpropionic acid (**1**) was first obtained by alkylation of ethyl benzoylacetate with 2-bromoacetic acid in the presence of sodium ethoxide, as previously described.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,¹⁸ hexylborane,¹⁹ isobutylmagnesium bromide/dichloro bis (η -cyclopentadienyl)titanium²⁰ and bis(4-methylpiperazinyl)aluminium hydride²¹ have been mentioned but generally lack selectivity and are inconvenient to use.



† Reagents and conditions: a) 1. BrCH₂COOH, EtONa, EtOH, reflux, 15 h; 2. 3N HCl, 0°C, 15 min b) BH₃•Me₂S, THF, reflux, 1 h c) 1. K₂CrO₄, CH₂Cl₂, 30% H₂SO₄, *n*-Bu₄N⁺HSO₄⁻, 0°C, 15 min; 2. 10% FeSO₄, rt, 10 min.

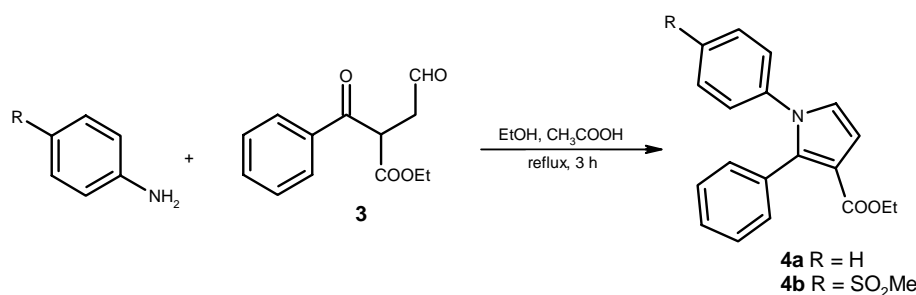
Scheme 1[†]

One-pot conversion with DIBALH²² seemed to be the most appropriate process, but here, surprisingly, the reaction did not evolve. Using BH₃•Me₂S complex enabled us to selectively reduce the carboxylic

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.²³ 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).



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,¹⁶ 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.²⁴⁻²⁷

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 60F₂₅₄ 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 ^1H 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 H₂O (30 mL). After acidification to pH 1 with 3 N aqueous HCl, the product was extracted with EtOAc (2 × 30 mL). The organic layer was dried (MgSO₄) 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; ^1H NMR (CDCl₃) 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) - BH₃•Me₂S 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 H₂O were added cautiously to quench the reaction. The product was extracted with EtOAc (3 × 50 mL). The organic layer was washed successively with 10% aqueous NaHCO₃, brine and dried (MgSO₄). 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; ^1H NMR (CDCl₃) 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 K₂CrO₄ (2.8 g, 14.9 mmol) in 30% aqueous H₂SO₄ (30 mL) was added dropwise to a stirred solution of ester (**2**) (4.4 g, 18.6 mmol) and *n*-Bu₄N⁺HSO₄⁻ (0.6 g, 1.8 mmol) in 80 mL CH₂Cl₂, 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% FeSO₄ was added. After 10 min of additional stirring, the layers were separated. The organic layer was washed successively with 10% aqueous K₂CO₃, brine and then dried (MgSO₄). 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 (MgSO_4). 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 (CDCl_3) 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 $\text{C}_{19}\text{H}_{17}\text{NO}_2$: 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 (CDCl_3) 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 $\text{C}_{20}\text{H}_{19}\text{NO}_4\text{S}$: C, 65.02; H, 5.18; N, 3.79. Found: C, 65.36; H, 5.20; N, 3.77.

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