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Phosphoric Acid-Promoted Synthesis of 4-Acylpyrrole-2-carboxylic Esters and Dipyrryl Ketones from Mixed Anhydrides

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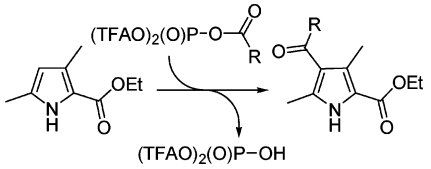

An efficient synthesis of 4-acylpyrrole-2-carboxylic esters utilizing a phosphoric acid-catalyzed mixed anhydride system is described. The new route also enables the preparation of dipyrryl ketones and *N*-confused dipyrryl ketones.

4-Acylpyrrole-2-carboxylic esters[1] are useful intermediates for the synthesis of a wide range of pyrrolic compounds. The acylation of pyrrole-2-carboxylic esters is most easily achieved by using acid chlorides, catalyzed by Lewis acids such as $SnCl_4$.[2] The use of trifluoroacetic anhydride (TFAA) to produce mixed anhydrides for use in acylation chemistry is well-known[3] and the use of phosphoric acid as a catalyst in TFAA/mixed anhydride chemistry was first described by Galli.[4] Knight and coworkers have recently described a method[5] for the 2-acylation of *N*-substituted pyrroles involving carboxylic acids and TFAA (Figure 1). The reaction proceeds via the formation of the mixed anhydride that results from the reaction of TFAA with a carboxylic acid. Knight's method is similar to those reported by Galli (thiophene)[6] and Kakushima (pyrrole)[7] and produces good yields of 2-acylated pyrroles.

As part of our research into the synthesis of homochiral bis(dipyrromethene)s,[8] we needed a route by which to prepare 4-trifluoroacetylpyrrole-2-carboxylic esters. Our first attempt to synthesize **2**, by the trifluoroacetylation of **1** using TFAA and DMAP in DCM (method A, Scheme 1),[9] resulted in a disappointing product yield of 51%. Treating **1** with trifluoroacetic acid (TFA) in the presence of TFAA (method B, Scheme 1), according to Knight's procedure,[5] gave the pyrrole **2** in excellent yield. Encouraged by this success we attempted to apply Knight's methodology to the preparation of other 4-acylpyrrole-2-carboxylic esters. Thus, several attempts with pyrrole **1**, using a carboxylic acid in place of TFA, were made and the results are presented in Table 1.

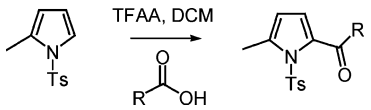

FIGURE 1. Knight's acylation methodology.[5]

SCHEME 1. Trifluoroacetylation of 1

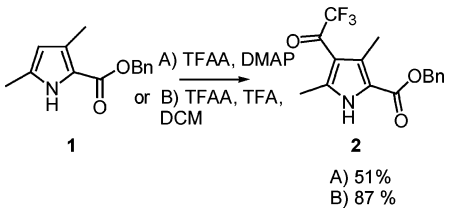

TABLE 1. Attempted Syntheses of 4-Acylpyrrole-2-carboxylic Esters with RCO_2H and TFAA

entry	acid	temp (°C)	product	yield[a] (%)
1	4-nitrocinnamic	20	**4a**	NR
2	3,5-dimethoxybenzoic	20	**4b**	NR
3	benzoic	20	**4c**	NR
4	4-ethoxybenzoic	20	**4d**	60
5	palmitic	20	**4e**	60
6	propanoic	20[b]	**4f**	96

[a] NR: no reaction. [b] Carboxylic acid used in 5-fold excess.

Analysis of Table 1 reveals that electron-poor aryl acids (entries 1 and 2), or even benzoic acid itself (entry 3), did not result in acylated pyrrole. Aliphatic and electron-rich aryl carboxylic acids gave good yields (entries 4−6). Given the lack of reactivity of electron-poor carboxylic acids under these conditions, it became clear that Knight's method was not general for the acylation of pyrrole-2-carboxylic esters unsubstituted in the 4-position.

The use of acyl trifluoroacetates (ATFA) as mixed anhydrides for the acylation of aromatic heterocyles and activated benzene rings has been previously reported. Indeed, ATFA has been used as a successful acylating agent for thiophene, anisole, and furan but is less successful for the acylation of pyrrole.[1,10,11] Clementi's work in this area indicates that the trifluoroacetylation of pyrrole becomes competitive with acylation upon a decrease in temperature, solvent polarity, and reactant concentration.[12]

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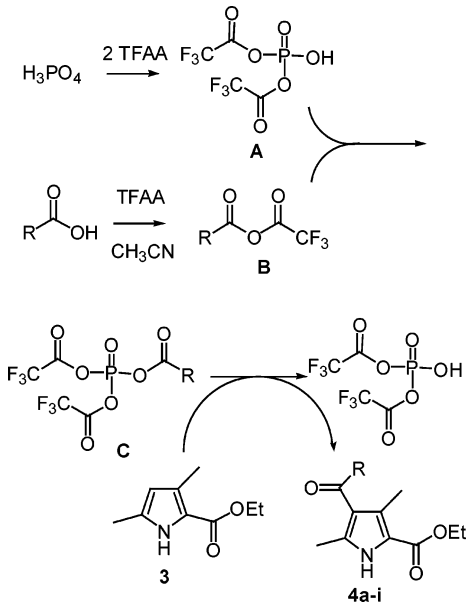
SCHEME 2. Phosphoric Acid-Promoted Synthesis of 4-Acylpyrrole-2-carboxylic Esters



Smyth and co-workers have proposed that Friedel–Crafts acylations of substituted benzenes with TFAA and phosphoric acid are a clean alternative to conventional methods utilizing Lewis acid catalysts.[13−15] Recyclability of TFAA after the reaction through treatment of the resultant TFA with a dehydrating agent (e.g., P_2O_5) contributes to the efficiency of the process. The degree of activation is significant as the activated phosphoryl mixed anhydrides react rapidly and so Lewis acid co-catalysis is unnecessary, in contrast to when using acyl chlorides.[15]

Considering the success of utilizing both phosphoric acid to promote acylations and the beneficial effects of polar solvents[12] to enhance the acylation of thiophene, we decided to merge these two approaches for the 4-acylation of pyrrole-2-carboxylic esters. In our modified procedure, pyrrole **3** was added as a solid to a solution containing, presumably, a pre-formed phosphoryl mixed anhydride **C**, synthesized stepwise in a manner similar to that of Smyth (Scheme 2).[16] The reaction, not rigorously protected from oxygen, was followed by monitoring the disappearance of **3** by TLC. Analysis of Table 2 reveals that, under these conditions, excellent yields of 4-acylpyrrole-2-carboxylic esters were obtained with carboxylic acids that were previously unsuccessful or low yielding.

Murakami and co-workers have reported similar phosphoric acid-promoted acylations of indole[17] and pyrroles[18,19] but with lower yields. The order of addition and, presumably, successful formation of the phosphoryl mixed anhydride **C**, prior to the addition of the pyrrole, is key to the higher yields obtained in our reactions. Thus in one flask we mixed phosphoric acid with 2 equiv of TFAA to generate **A**, for which Smyth has reported ^{19}F and ^{31}P NMR spectroscopic evidence.[15] In another flask, 2 equiv of TFAA were added to a solution (or suspension) of the carboxylic acid in CH_3CN to generate **B**. The TFAA/H_3PO_4 mixture (**A**) was then added to the solution containing **B**, presumably then generating the required phosphoryl mixed anhydride **C**. Pyrrole **3** was then added within 2 min and the reaction mixture was stirred for 5 min. Routine workup and purification gave the expected 4-acylpyrrole-2-carboxylic esters (Table 2).

TABLE 2. Synthesis of 4-Acylpyrrole-2-carboxylic Esters with Phosphoric Acid-Derived Mixed Anhydrides

entry	acid	temp (°C)	product	yield[a] (%)
1	palmitic	20	**4e**	77
2	propanoic	20	**4f**	90
3	acetic	20	**4g**	83
4	pivalic	20	**4h**	86
5	iso-valeric	20	**4i**	66
6	benzoic	20	**4c**	81
7	3,5-dimethoxybenzoic	20[b]	**4b**	81
8	3,5-dimethoxybenzoic	40	**4b**	62
9	4-nitrocinnamic	20	**4a**	NR

[a] NR: no reaction. [b] No solvent; heated to form **B**.

The reaction was very rapid after the addition of pyrrole and usually complete (or close to completion) within 5 min. The use of aliphatic acids (entries 1−5) gave the corresponding 4-acylpyrrole-2-carboxylic esters in very good yield. Benzoic acid, previously unreactive (Table 1, entry 3), gave the required acylated pyrrole in 81% yield (Table 2, entry 6). In the case of 3,5-dimethoxybenzoic acid it was found that the yield could be significantly improved by conducting the reaction in the absence of solvent (entry 7), and ensuring the efficient formation of **B** by heating to reflux. Unfortunately, similar attempts with *p*-nitrocinnamic acid proved fruitless (entry 9), akin to similar reports involving indoles.[17]

Many of the reactions could also be conducted in the absence of CH_3CN, with similar yields obtained. However, on occasion we observed that the carboxylic acid was not miscible with TFAA and this lack of miscibility was usually indicative that no 4-acylpyrrole-2-carboxylic ester would be produced (if the reaction was carried out as usual). However, if acetonitrile was added to the formation of **B**, and the acylation only carried out upon the disappearance of the suspended carboxylic acid, the required 4-acylpyrrole-2-carboxylic ester was isolated in good yield. It is thus evident that the formation of the initial mixed anhydride **B** between the carboxylic acid and TFAA must occur first, before the addition of **A** and the pyrrole, if good product yields are to be obtained. As such, our preferred procedure was to routinely use CH_3CN in the preparation of **B**.

Having established that our new procedure could be used for the efficient formation of 4-acylpyrrole-2-car-

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(16) Smyth et al. (ref 14) mixed TFAA (4 equiv) with the carboxylic acid (1 equiv) followed, upon cooling to below 10 °C, by 85% phosphoric acid (1 equiv). After complete dissolution of the phosphoric acid the substrate was added. In our work, phosophoric acid (1 equiv) was added to TFAA (2 equiv) at 0 °C and the carboxylic acid (1 equiv) was stirred separately with TFAA (2 equiv) in acetonitrile at room temperature. Upon solvation of the phosphoric acid solution, the two components were mixed and then the substrate was added as a solid within 2 min.
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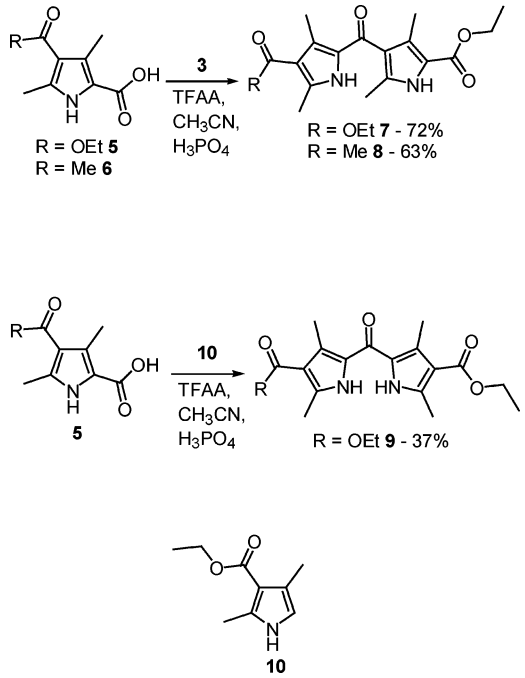
SCHEME 3. Synthesis of Dipyrryl Ketones



boxylic esters, we turned our attention to the synthesis of dipyrryl ketones. Dipyrryl ketones have been used as synthetic intermediates in the synthesis of oxophlorins/oxyporphyrins, which are themselves intermediates for biologically important protoporphyrins.[20,21] Symmetric 2,2′-dipyrryl ketones have previously been constructed through the use of phosgene,[22] or thiophosgene followed by reaction with basic hydrogen peroxide.[23] Other known synthetic routes of dipyrryl ketones include the oxidation of dipyrromethanes with lead tetraacetate/lead oxide,[12] sulfuryl chloride,[12] and ceric ammonium nitrate.[24]

To investigate the scope of the phosphoric acid-promoted mixed anhydride reaction for the synthesis of dipyrryl ketones, we reacted pyrrolyl carboxylic acids with **3**. Thus, two pyrrolyl carboxylic acids, **5** and **6**, were used in conjunction with **3** to produce *N*-confused dipyrryl ketones, **7** and **8**, potential precursors to *N*-confused and/or *N*-fused porphyrins. The same methodology was used for the construction of 2,2′-dipyrryl ketone **9** (Scheme 3). Compounds analogous to **9** have been used to construct oxophlorins (oxoporphyrins).[25] These results demonstrate that it is possible to prepare dipyrryl ketones with a variety of architectures simply by using different pyrrolyl carboxylic acids and α/β-free pyrrole nucleophiles.

In conclusion our new procedure for the synthesis of 4-acylpyrrole-2-carboxylic esters gives improved yields over existing methods and enables a new route to dipyrryl ketones, both *N*-confused and 2,2′-dipyrryl ketones. The procedure is facile to follow and the acylation proceeds rapidly.

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Experimental Section

General Procedure for the Synthesis of Ketones. Formation of A: H_3PO_4 (85%, 0.041 mL, 0.59 mmol) was added jet-wise to TFAA (0.166 mL, 1.2 mmol) that was being stirred at 0 °C. The solution was allowed to stir at this temperature until homogeneous (the reaction mixture goes through a white precipitous stage prior to the achievement of complete homogeneity). Concurrent with the formation of **A**, **B** was prepared. **Formation of B:** TFAA (0.166 mL, 1.2 mmol) was added to a solution/suspension of carboxylic acid (0.59 mmol) and CH_3CN (1 mL). The reaction mixture was stirred for 10 min (or until the disappearance of insoluble suspended carboxylic acids). Mixture **A** was then added to the solution of **B** in one portion. This mixture was allowed to stir briefly (30 s to 2 min) and pyrrole **3** (0.100 g, 0.59 mmol) was then added as a solid. The reaction was then allowed to stir until the disappearance of **3** was confirmed by TLC analysis (5 min; 3:7 ethyl acetate:hexanes, R_f 0.69). Upon completion, the reaction was quenched with 10% aqueous Na_2CO_3 (added dropwise slowly) until the cessation of effervescence, followed by an additional 20 mL. Note: Some ketones precipitated at this point and were filtered, while others were extracted with CH_2Cl_2 (3 × 10 mL). Purification with flash chromatography on silica gel and a gradient elution (19:1 hexanes:ethyl acetate−4:1 hexanes:ethyl acetate) gave the required compound.

4-Benzoyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4c). Light yellow solid (0.132 g, 81%). Mp 111−112 °C. NMR ($CDCl_3$) δ_H 1.37 (3H, t, J = 7 Hz), 2.24 (3H, s), 2.25 (3H, s), 4.34 (2H, q, J = 7 Hz), 7.43 (2H, t, J = 1.5 Hz), 7.54 (1H, t, J = 1.5 Hz), 7.73 (2H, d, J = 1.5 Hz), 9.56 (1H, br s); NMR ($CDCl_3$) δ_C 12.6, 13.9, 14.9, 60.7, 118.8, 123.5, 128.6, 129.5, 129.6, 132.5, 137.3, 140.7, 162.3, 194.3. *m/z* 564.9 (dimer as Na adduct). R_f 0.39.

4-(3,5-Dimethoxybenzoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4b). White solid (0.121 g, 81%). Starting material (0.025 g) was recovered under solvent-free conditions. Mp 183−185 °C. NMR ($CDCl_3$) δ_H 1.38 (3H, t, J = 7 Hz), 2.28 (6H, s), 3.83 (6H, s), 4.34 (2H, q, J = 7 Hz), 6.64 (1H, t, J = 2.5 Hz), 6.90 (2H, d, J = 2.5 Hz), 9.05 (1H, br s); NMR ($CDCl_3$) δ_C 12.2, 13.6, 14.5, 55.6, 60.4, 104.6, 106.5, 118.5, 123.2, 129.3, 136.6, 142.3, 160.8, 161.6, 193.4. *m/z* 684.8 (dimer as Na adduct). R_f 0.26.

4-Hexadecanoyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4e). White solid (0.185 g, 77%). Mp 93−94 °C. NMR ($CDCl_3$) δ_H 0.88 (3H, t, J = 7 Hz), 1.25 (24H, m), 1.35 (3H, t, J = 7 Hz), 1.68 (2H, p, J = 7 Hz), 2.51 (3H, s), 2.59 (3H, s), 2.72 (2H, t, J = 7 Hz), 4.33 (2H, q, J = 7 Hz), 9.06 (1H, br s); NMR ($CDCl_3$) δ_C 13.05, 14.6, 14.8, 15.5, 23.0, 24.6, 29.7, 29.8, 29.9, 29.9, 30.0, 32.3, 43.3, 60.7, 118.2, 124.0, 129.3, 138.0, 162.0, 198.9. *m/z* 833.1 (dimer as Na adduct). R_f 0.60.

3,5-Dimethyl-4-propionyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4f). White solid (0.120 g, 90%). Mp 143−144 °C. NMR ($CDCl_3$) δ_H: 1.17 (3H, t, J = 7.5), 1.38 (3H, t, J = 7 Hz), 2.53 (3H, s), 2.60 (3H, s), 2.76 (2H, q, J = 7.5 Hz), 4.34 (2H, q, J = 7 Hz), 9.27 (1H, br s); NMR ($CDCl_3$) δ_C 8.5, 13.1, 14.8, 15.5, 36.3, 60.7, 118.2, 123.7, 129.4, 138.2, 162.1, 199.0. *m/z* 468.9 (dimer as sodium adduct). R_f 0.39.

4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4g). White solid (0.104 g, 83%). Mp 143−145 °C. NMR ($CDCl_3$) δ_H 1.38 (3H, t, J = 7 Hz), 2.45 (3H, s), 2.53 (3H, s), 2.59 (3H, s), 4.34 (2H, q, J = 7 Hz), 9.14 (1H, br s); NMR ($CDCl_3$) δ_C 13.0, 14.8, 15.5, 31.6, 60.7, 118.3, 123.9, 129.6, 138.5, 162.0, 195.8. *m/z* 440.9 (dimer as Na adduct). R_f 0.26.

4-(2,2-Dimethylpropionyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4h). White solid (0.129 g, 86%). Mp 144−146 °C. NMR ($CDCl_3$) δ_H 1.24 (9H, s), 1.39 (3H, t, J = 7 Hz), 2.24 (3H, s), 2.27 (3H, s), 4.34 (2H, q, J = 7 Hz), 9.12 (1H, br s); NMR ($CDCl_3$) δ_C 12.7, 13.4, 14.8, 27.3, 45.8, 60.4, 118.2, 125.8, 126.1, 129.5, 162.0, 213.0. *m/z* 524.9 (dimer as Na adduct). R_f 0.49.

3,5-Dimethyl-4-(3-methylbutyryl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4i). White solid (0.099 g, 66%). Mp 97−99 °C. NMR ($CDCl_3$) δ_H 0.97 (6H, d, J = 7 Hz), 1.37 (3H, t, J =

7 Hz), 2.24 (1H, n, J = 7 Hz), 2.51 (3H, s), 2.57 (3H, s), 2.61 (2H, d, J = 7 Hz), 4.34 (2H, q, J = 7 Hz), 9.27 (1H, br s); NMR ($CDCl_3$) δ_C 12.7, 14.8, 15.0, 22.8, 25.0, 51.9, 60.4, 117.9, 124.0, 128.9, 137.6, 161.8, 198.4. *m/z* 524.9 (dimer as Na adduct). R_f 0.49.

4-(3,5-Dimethyl-1*H*-pyrrole-2-carbonyl-4-carboxylic acid ethyl ester)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (7). Off-white solid (0.155 g, 72%). Mp 213-214 °C. NMR ($CDCl_3$) δ_H 1.35 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 2.22 (3H, s), 2.30 (3H, s), 2.31 (3H, s), 2.60 (3H, s), 4.28 (2H, q, J = 7 Hz), 4.35 (2H, q, J = 7 Hz), 9.52 (1H, br s), 10.06 (1H, br s); NMR ($CDCl_3$) δ_C 11.6, 12.3, 12.6, 14.7, 14.8, 14.8, 59.9, 60.7, 114.4, 118.8, 124.6, 128.3, 129.9, 131.7, 134.8, 141.6, 162.3, 165.8, 183.3. *m/z* 742.9 (dimer as Na adduct). R_f 0.14.

4-(4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (8). Isolation of the title compound as an off white solid (0.099 g, 63%). Mp 256−257 °C dec. NMR (DMSO-d_6) δ_H 1.31 (3H, t, J = 7 Hz), 2.10 (3H, s), 2.16 (3H, s), 2.24 (3H, s), 2.36 (3H, s), 2.46 (3H, s), 4.24 (2H, q, J = 7 Hz), 11.60 (1H, br s), 11.72 (1H, br s); NMR (DMSO-d_6) δ_C 11.6, 12.4, 12.7, 14.8, 14.9, 31.7, 59.8, 118.0, 123.1, 124.3, 127.6, 127.8, 129.6, 135.6, 139.6, 161.2, 183.0, 195.0. *m/z* 682.9 (dimer as Na adduct). R_f 0.07.

2,2′-Bis(3,5-dimethyl-1*H*-pyrrole-4-carboxylic acid ethyl ester)carbonyl (9). Isolation of the title compound as an orange solid (0.88 g, 37%). Fischer reported colorless needles.[26] Mp 226−227 °C (lit.[26] mp 221 °C). NMR (DMSO-d_6) δ_H 1.28 (3H, t, J = 7 Hz), 2.21 (3H, s), 2.44 (3H, s), 4.19 (2H, q, J = 7 Hz), 11.74 (1H, br s); NMR (DMSO-d_6) δ_C 12.5, 14.0, 14.8, 59.3, 112.7, 128.0, 128.4, 139.9, 165.2, 179.7. *m/z* 742.8 (dimer as Na adduct). R_f 0.16.

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Supporting Information Available: General experiment details, characterization data for **4d**, and ^{13}C NMR spectra for **4b**−**i**, **7**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051906W

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