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Low-Valent Titanium Reductive Coupling Reactions of Pyrrylaldehydes and Pyrrylketones

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Abstract: 2-Pyrrylaldehydes are shown to react under McMurry conditions to give the expected coupling products in high yield, while 3-pyrrylaldehydes and 3-pyrrylketones give in good yields either rearrangement products or reduced McMurry products, depending upon the nature of the reactant.
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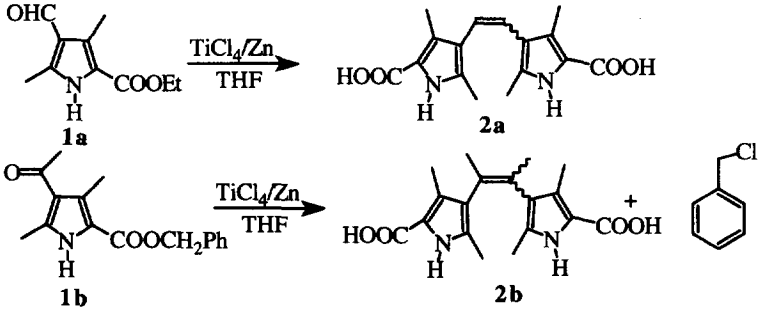
The reductive coupling of aldehydes and ketones to generate olefins using low-valent titanium species, generated *in situ*, has found wide application in the preparation of an extraordinary variety of molecules many of which are unattainable by other methods.[1,2] Aliphatic and alicyclic carbonyl groups undergo this coupling reaction very successfully with few exceptions. However, reports on the coupling reaction of heterocyclic aldehydes or ketones are rare. Newkome *et al.* reported that treatment of both *mono*-2-pyridyl ketone and *bis*-2-pyridyl ketone with either $LiAlH_4$-$TiCl_3$ or Na^0-$TiCl_3$ afforded primarily the corresponding alcohols. [3] No coupled olefins were isolated although ethane linked dimers (i.e. the products of reduction of the expected coupling products) were isolated in yields of less than 5 %. The position of the carbonyl group appeared to influence the reaction products since 3-benzoylpyridine, when treated with $TiCl_3$-$LiAlH_4$, was shown to give the expected coupled olefin in 31% yield, as a mixture of *E* and *Z* isomers. The authors suggested that complexation between titanium, the pyridyl nitrogen, and the ketone oxygen was responsible for the failure of 2-pyridyl ketone to react as expected. Reductive couplings of 2-pyrrylaldehydes and 2-furylaldehydes, although only in low yields, have also been reported.[4]

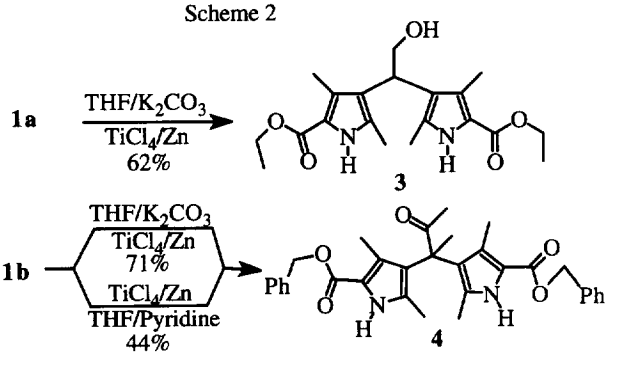
In our efforts to synthesize functionalized molecules with C_2 symmetry as precursers to tricyclic ring systems or as novel HIV protease or protein kinase C inhibitors, the reductive coupling reactions of functionalized pyrrylaldehydes and pyrrylketones were studied.

Scheme 1



Treatment of ethyl 2,4-dimethyl-3-formylpyrrole-5-carboxylate (**1a**) with $TiCl_4$-Zn^0 led to the isolation of the expected coupled product although both ester groups had also undergone hydrolysis, The corresponding acids was isolated in about 10 % yield along with a complicated mixture (Scheme 1). Treatment of benzyl 2,4-dimethyl-3-acetylpyrrole-5-carboxylate (**1b**) under the same conditions similarly gave the coupled diacid **2b** in low yield and benzyl chloride, rather than benzyl alcohol, demonstrating that ester hydrolysis was not occurring during the work-up. Addition of a base, such as pyridine or potassium bicarbonate, during the reaction prevented the hydrolysis but also changed the course of the reaction, resulting in the formation of different products.

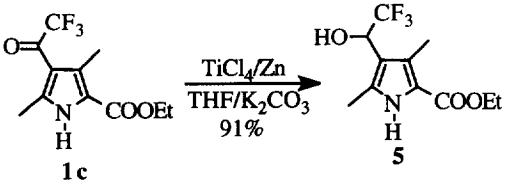
Scheme 2



In the case of **1a**, the reaction product was shown to be the dipyrrylcarbinol **3** (Scheme 2). Thus, mass spectrometry gave a molecular ion of 376 amu with fragments at m/z = 345, 299 and 253 corresponding to loss of hydroxymethyl and, sequentially, two ethoxy groups. An AM_2 coupling system was observed in the ^1H NMR spectrum of **3** while the APT spectrum included a resonance at 63.95 ppm, indicative of the hydroxymethylene carbon. A similar observation was made for reaction of **1b** which afforded the dipyrromethane analog **4**, again in good yield. Mass spectrometry of **4** gave no parent ion, however fragments at m/z = 483, 375 and 267 corresponded to loss of acetyl and sequentially two benzyloxy groups, respectively. The ^{13}C NMR spectrum of **4** showed the presence of resonances at 206 and 161 ppm which are attributed to the carbonyl carbons of a keto group and an ester group, respectively. This type of rearrangement, although rare, has been previously observed[5] and appears to be similar to the pinacol-pinacolone rearrangement, which typically requires acidic conditions.

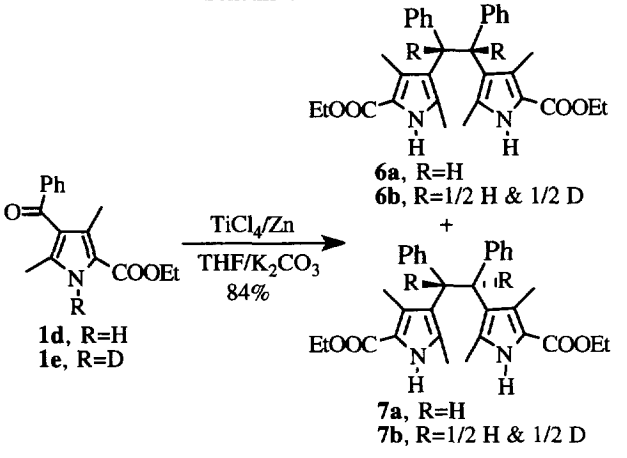
In order to extend this study, two more pyrroles, 3-trifluoroacetylpyrrole, **1c,** and 3-benzoylpyrrole, **1d,** were prepared and reacted under the same conditions as described above. However, in each case, no rearrangement products were observed. Rather, pyrrole **1c** gave only the corresponding reduced pyrrole **5** (Scheme 3) in 91 % yield as indicated by mass spectrometry and NMR spectroscopy. Thus mass spectrometry of **5** gave the parent ion at m/z = 265 , fragments at m/z = 220, 196, and 150 corresponding to the loss of the ethoxy group, trifluoromethyl group, and both these groups respectively. The ^1H, ^{13}C and ^{19}F NMR spectra showed the expected coupling between the trifluoroethanol carbons (CF_3-CH-OH) and fluorine. Particularly diagnostic were the disappearance of a quartet at δ = 177.27 ppm in the ^{13}C NMR spectrum attributable to the acetyl carbonyl carbon of the reactant and the appearance of a quartet at δ = 67.69 ppm which was diagnostic of the carbinol carbon.

Scheme 3



Pyrrole **1d** however, proceeded through a different reaction pathway to generate not the corresponding carbinol, but rather the reduced McMurry dimers **6a, 7a** in yields of 84 %, as mixtures of the *meso* and *dl* isomers (1:1 ratio), (Scheme 4). The *meso* and *dl* isomers, which could be separated by fractional crystallization were characterized spectroscopically. Both **6a** and **7a**, showed a singlet resonance for the benzyl hydrogen (R) in the ^{1}H NMR spectrum in addition to the expected resonances for the remaining protons. Mass spectrometry gave an intense peak for the facile cleavage of the central bis(benzylic) bond at m/z = 256 . The distinction between the *meso* and *dl* isomers (**6a** and **7a**) was achieved through ^{1}H NMR by the addition of the chiral shift reagent Eu(hfc)$_3$. Thus the *dl* isomers exhibited resolution of the ester group in the ^{1}H NMR spectrum upon addition of the Eu(hfc)$_3$ indicating the mixture of two enantiomers while the *meso* compound only showed downfield shifts. Although this modified McMurry reaction has been previously observed, the present study is of interest since these products are the major reaction products (84%) not minor products (2-5 %) as observed in cases of very sterically hindered phenyl ketones or diphenyl ketones.[6,7]

Scheme 4



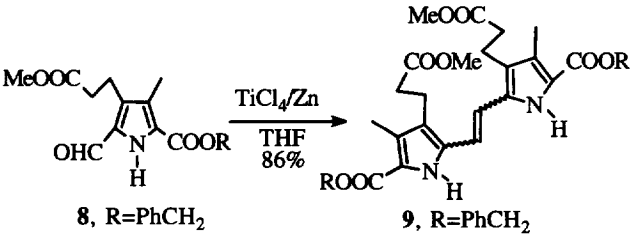
Two experiments were performed to establish the hydrogen source (R) for the reduction occurring during reaction. In the first experiment, after the reaction mixture had been stirred at reflux for five hours, deuterium oxide was added to quench the reaction. No deuterium was detected by ^{1}H NMR spectroscopy in the isolated products. In the second experiment, 3-benzoylpyrrole derivative **1d** was exchanged with deuterium oxide to afford the N-deuterobenzoylpyrrole derivative **1e**, which was then allowed to undergo the same McMurry reaction. After quenching the reaction mixture with water and work-up, both isolated diastereomers **6b** and **7b** were found to contain 50 % deuterium at the benzyl position by ^{1}H NMR spectroscopy (Scheme 4). Both **6b** and **7b** also showed a singlet resonance in the ^{2}H NMR spectrum.

An additional observation made during the reaction of **1a-d** was that if the reaction was not quenched by aqueous base, a red complex, soluble in organic solvents, was isolated. This complex was relatively stable toward alcohols but reacted slowly with water to give the products. This type of complex was not observed when acetophenone (which lacks -NH protons) was subjected to the same conditions, and the expected McMurry product stilbene was isolated without basic work-up. Coupling of acetophenone under the same conditions with the addition of a hydrogen source, such as one equivalent of water, ethanol, or diphenylamine also led to the normal McMurry coupling product along with a small amount of glycol by-product. No reduced McMurry product was detected by ^{1}H NMR spectroscopy.

In light of these results, It was surprising to observe that the coupling of 2-pyrrylaldehyde **8** under the same conditions gave the normal McMurry olefin coupling products **9** in 86 % yield, with a *Z* to *E* ratio of 1:4 as indicated by ^{1}H NMR spectroscopy (Scheme 5). Each isomer was readily separated by fractional

recrystallization. The yield of **9** was not affected by the addition of base. In addition, although **8** has two ester groups, hydrolysis during the McMurry reaction was not observed. Thus these pyrroles appear to behave differently from the 3-formylpyrrole **1a** and 3-acetylpyrrole **1b** described above where hydrolysis in the absence of base was observed.

Scheme 5



8, R=$PhCH_2$ **9**, R=$PhCH_2$

These current results cannot be explained by the titanium-amine-carbonyl transition state postulated by Newkome to explain the lack of McMurry reaction with 2-pyridyl ketone. If they were, pyrrole-3-carbonyl compounds should be more likely to give normal coupling products because they are less likely to form stable complexes. Since the product of the reaction appears to be influenced by the electronic nature of the group bonded to the carbonyl and the McMurry reaction involves a radical pathway, [8] factors which affect the stability of the radical intermediate may play an important role in these reactions. In summary, our studies indicate that 2-pyrrylaldehyde gives normal McMurry coupling products in high yield, while 3-pyrrylaldehyde and 3-pyrrylketones give either rearrangement products or reduced McMurry coupling products, depending upon the nature of any substituent, also in good yields.

EXPERIMENTAL DATA

3. ^{1}H NMR: δ = 8.91 (2H, b), 4.78 (1H, b), 4.26 (4H, q), 4.04 (3H, m), 2.17 (6H, s), 2.16 (6H, s), 1.32 (6H, t). m/z 376 (8 %), 345 (78 %), 299 (100 %), 253 (68 %); **4.** ^{1}H NMR: δ = 9.18 (1H, b), 7.22-7.42 (10H, m), 5.28 (4H, s), 2.17 (6H, s), 2.14 (3H, s), 1.95 (6H, s), 1.8 (3H, s). m/z: 483 (82 %), 375 (75 %), 267 (71 %), 91 (100 %); **5.** ^{1}H NMR: δ = 9.01 (1H, b), 5.03 (H, q, J = 7.2 Hz), 4.29 (2H, q, J = 7.2 Hz), 2.33 (6H, s), 1.34 (3H, t, J = 7.2 Hz); **6a.** ^{1}H NMR: δ = 8.32 (2H, b), 6.94-7.14 (10H, m), 4.74 (2H, s), 4.20 (4H, q, J = 7.2 Hz), 2.18 (6H, s), 2.05 (6H, b), 1.27 (6H, t, J = 7.2 Hz). m/z: 467 (2 %), 256 (100 %), 210 (71 %). **7a.** ^{1}H NMR: δ = 8.68 (2H, b), 6.90-7.10 (10H, m), 4.68 (2H, s), 4.23 (4H, q, J = 7.2 Hz), 2.17 (6H, s), 2.14 (6H, s), 1.30 (6H, t, J = 7.2 Hz).

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