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The chemistry of vicinal tricarbonyls: an expedient route to fully-substituted 3-aminopyrroles

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Dedication to Professor Harry Wasserman for his contribution to the chemistry of vicinal tricarbonyls

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ABSTRACT

A one-pot, three-component reaction between a 2,3-diketoester, an imine, and an aldehyde, catalyzed by *p*-toluenesulfonic acid, produces fully-substituted 3-aminopyrroles that can be converted to pyrrolo [3,2-*d*]pyrimidine-2,4-dione.

Introduction

The highly electrophilic nature of the central carbonyl carbon in vicinal tricarbonyl (VTC) compounds allows for the versatile construction of new carbon–carbon bonds.[1] Among others,[2] Wasserman and coworkers have been pioneers in the applications of VTC compounds in organic syntheses.[1c] Besides using VTC compounds for the synthesis of carbocyclic and heterocyclic frameworks,[3] Wasserman and co-workers have demonstrated their importance in the synthesis of natural products and biological relevant compounds such as (±)-PS-5,[4] prodigiosin,[5] vasicine,[6] papaveraldine,[7] YM-47141, YM-47142[8] and others.[9]

Our research group has been focused on the chemistry of enol silyldiazoacetates of type **1** as a coupling partner with other electrophiles toward the synthesis of highly functionalized α-diazo-β-ketoesters **2**.[10] We thought that oxidation of these complex diazo compounds **2** would give us access to functionalized VTC **3** that would allow us to study intramolecular reactions between the newly installed functional group and the central carbonyl (Scheme 1). This strategy allowed us to develop an efficient methodology to highly functionalized furans.[11] Furthermore, we have reported the first diastereoselective[12] and enantioselective[13] nucleophilic addition reactions that occur at the central carbonyl carbon of VTC compounds.

We envisioned that a condensation reaction at the β-carbonyl of 2,3-diketoesters **3** with a primary amine would generate enamine **4** that can be viewed as a 1,3-dipolar equivalent species, as demonstrated by the resonance structures **A** and **B**, for cycloaddition with other dipolarophiles (Scheme 2). Herein, we wish to report an application of VTC **3** in an acid-catalyzed three-component reaction for the synthesis of highly substituted 3-aminopyrroles **5**, important nitrogen heterocycles present in natural products and biologically active compounds.[14] Conventionally, multi-step syntheses were required for their preparation[15].

Results and discussion

Our synthesis began with a one-pot reaction involving benzyl 2,3-dioxobutanoate **3a**, aniline, and benzaldehyde under acid-catalyzed conditions. Trifluoroacetic acid, $Zn(OTf)_2$, and *p*-toluenesulfonic acid (*p*-TsOH) catalysis provided pyrrole **5a** in 65%, 50%, and 71% yield, respectively, (Table 1, entries 2–4). Lowering the amount of *p*-TsOH to 10 mol % did not have an effect on product yields. However, increasing the amount of *p*-TsOH to 50 mol % and 100 mol % decreased the formation of **5a** to 55% and 20% yield respectively, (entries 6 and 7). These results indicate that complete protonation of aniline inhibited the reaction pathway. The reaction

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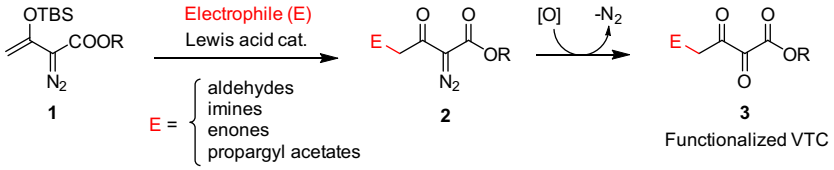
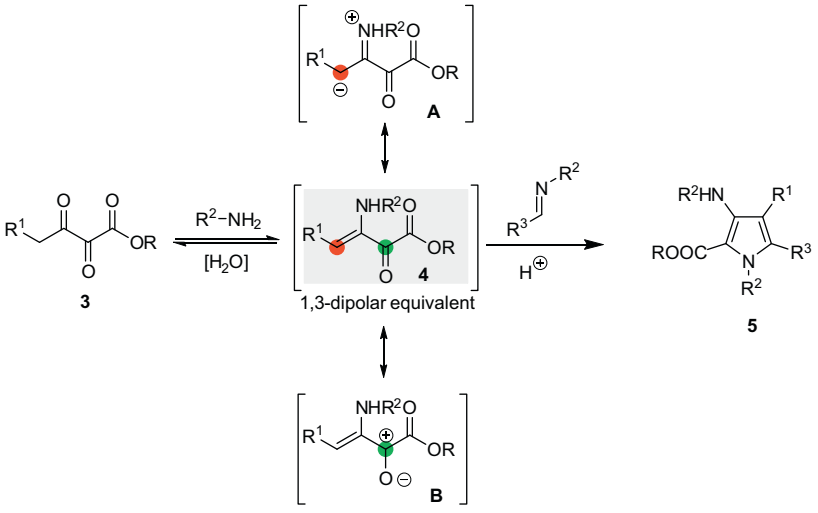
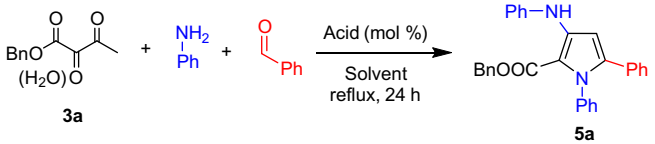


Scheme 1. Strategy to functionalize VTC **3**.



Scheme 2. Synthesis of 3-aminopyrroles.

Table 1
Optimization of conditions for the synthesis of **5a**[a]



Entry	Acid (mol %)	Solvent	Yield[b] (%)
1	None	DCM	0
2	TFA (20)	DCM	65
3	$Zn(OTf)_2$ (20)	DCM	50
4	*p*-TsOH (20)	DCM	71
5	*p*-TsOH (10)	DCM	70
6	*p*-TsOH (50)	DCM	55
7	*p*-TsOH (100)	DCM	20
8	*p*-TsOH (20)	Toluene	12
9	*p*-TsOH (20)	THF	94

[a] Reactions were performed on a 1.0 mmol scale: A solution of **3a** (1.2 equiv), aniline (2.1 equiv), benzaldehyde (1.0 equiv), and acid (X mol %) was refluxed in 5 mL of solvent for 24 h.
[b] Isolated yield after column chromatography.

was elevated to a higher temperature by refluxing in toluene; however, a complex mixture was obtained due to decomposition of **3a**, and only a 12% yield of **5a** was isolated (entry 8). When the solvent was switched to THF, the desired pyrrole **5a** was obtained in 94% yield (entry 9).

The proposed mechanism for the formation of 3-aminopyrrole **5a** is given in Scheme 3. Enamine **4a** and iminium ion **6** are generated in situ by condensation reactions of aniline with the β-carbonyl of **3a** and benzaldehyde, respectively. Subsequent nucleophilic addition of enamine **4a** to the iminium ion **6** produces intermediate **7**, which cyclizes to the hemiaminal **8**. The cyclic hemiaminal **8** tautomerizes to the enamine **9**, and dehydration by 1,4-elimination generates the 3-aminopyrrole **5**. THF appears to be sufficiently polar to promote the proton exchange reactions required in this transformation. Overall three components comprising four molecules are involved.

The generality of this reaction was evaluated under the optimized conditions, and the results are reported in Table 2. *p*-Anisidine and aniline provided excellent yields of pyrroles **5a** and **5b**, respectively, (Table 2, entries 1 and 2). Unfortunately, no reaction occurs when the less nucleophilic tosylamide or the more basic benzylamine is employed. The latter result is probably the consequence of base strength of benzylamine (entries 3 and 4). Next, the reaction scope of the aldehyde was examined. The reaction tolerates a wide variety of aryl aldehydes including electron poor, halogen, *ortho*-substituted, providing excellent yields of 3-aminopyrroles. Electron rich-substituted aryl aldehydes provided the product in moderate yields (entries 5–8). In addition, paraformaldehyde also provided 90% yield of the 5-*H*-3-aminopyrrole **5g** (entry 9). Examination of the R^1 substituent of 2,3-diketoester **3** further demonstrated the broad applicability of this methodology to furnish fully substituted 3-aminopyrroles. High yields were obtained when R^1 = methyl, which allows for the installation of a methyl substituent at the C-4 position (entries 10–12). However, no reaction occurs when R^1 = Ph, probably due to the less reactive, conjugated enamine intermediate (entry 13).

To demonstrate one use of 3-aminopyrroles, **5e** was further reacted with phenylisocyanate for the synthesis of pyrrolo[3,2-*d*]pyrimidine-2,4-dione **10** (Scheme 4). This structural motif that is a core structural feature of pyrrolo[3,2-*d*]pyrimidine-2,4-dione **11** has been recently found to have remarkable high affinity and selectivity toward the α_1-adrenoceptor, which controls smooth muscle in the cardiovascular system and the prostate.[16]