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An efficient and convenient synthesis of pentasubstituted pyrroles from alkyl acetoacetates, dialkyl acetylenedicarboxylates and amines

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Abstract- A simple and efficient synthesis of pentasubstituted pyrroles has been developed using a one-pot, two-step reaction. The synthesis of a series of 4-hydroxypenta-1,3-diene-tricarboxylates from alkyl acetoacetates and dialkyl acetylenedicarboxylates in the presence of K_2CO_3, followed by cyclization with amines, gave the corresponding pyrroles in excellent yields.

Keywords: pentasubstituted pyrroles; alkyl acetoacetates; dialkyl acetylenedicarboxylates; amines.

Polysubstituted pyrroles are molecular frameworks which have significant importance in materials science.[1] They have also been employed as anti-oxidants,[2a] antibacterial,[2b,c] ionotropic,[2d,e] antitumor,[2f] anti-inflammatory,[2g,h] and antifungal agents.[2i] Moreover, they are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry.[3]

The growing importance and wide utility of polysubstituted pyrroles has led to the search for new methods for the efficient synthesis of these heterocycles.

Pyrroles have been prepared via several classical methods,[4a] such as the Barton-Zard,[4b] Hantzsch,[4c,d] Knorr,[5a,b] Trofimov,[5c] Paal-Knorr,[6a,b] and Clauson-Kaas[6c-e] reactions and their modifications. In addition, these heterocycles have also been synthesized from Huisgen 1,3-

dipoles, derived from the addition of alkyl(aryl) isocyanides to dimethyl acetylenedicarboxylate, which are trapped by succinimide,[7] cyclobutene-1,2-diones,[8] and benzoyl chloride.[9] Triarylphosphine-induced domino reactions of acetylenedicarboxylates with unsaturated compounds,[10] oxidative free radical reactions of enamino esters,[11] primary aliphatic amines, alkynoates and 1,2-diaza-1,3-dienes,[12] and tertiary amines as well as other catalyst-assisted domino reactions,[13] have also been described for their preparation. Various catalysts and/or reagents such as $FeCl_3$,[14] palladium,[15] $NiCl_2 \cdot 6H_2O$,[16] $CeCl_3 \cdot 7H_2O$ (under microwave),[17] silica-supported tungstic acid,[18] and TiO_2,[19] have been employed for this purpose. All these methods have their merits, but many involve the use of a metal catalyst, the removal of which often requires cumbersome work-up and purifications. Herein we report a metal-free, one-pot, two-step synthesis of pentasubstituted pyrroles from alkyl acetoacetates, dialkyl acetylenedicarboxylates and amines as starting materials.

We began our investigation with the construction of 4-hydroxypenta-1,3-diene-tricarboxylates, which are versatile synthetic intermediates, from alkyl acetoacetates and dialkyl acetylenedicarboxylates (Table 1). The initial reaction was attempted using ethyl acetoacetate (**1a**) and dimethyl acetylenedicarboxylate (**2a**) (Table 1, entry 1). When **1a** and **2a** were treated in the presence of K_2CO_3 as a base in ethanol at room temperature, methyl 4-ethoxycarbonyl-5-hydroxy-3-methoxycarbonylhexa-2,4-dienoate (**3a**) was obtained in 98% yield. Various 4-hydroxypenta-1,3-diene-1,2,3-tricarboxylates **3** were prepared in excellent yields as shown in Table 1.

Table 1.

After the successful preparation of 4-hydroxypenta-1,3-diene-1,2,3-tricarboxylates **3a-d**, and with the aim to construct pentasubstituted pyrroles, we selected **3a** as a model compound to examine its reactions with an amine under different conditions. Upon treatment of **3a** with benzylamine (**4a**) in acetic acid, the reaction furnished the desired product, 4-ethyl 2,3-dimethyl 1-benzyl-5-methyl-1*H*-pyrrole-2,3,4-tricarboxylate **(5a)** (Scheme 1).

Scheme 1.

The optimization of the reaction conditions, including the reaction solvent, equivalents of acid, time, and the temperature, was then investigated. First, solvent-free conditions and various solvents were screened (Table 2, entries 1–9), with ethanol proving to be the best for this reaction. Next, we observed that the amount of acetic acid also had an important influence on the reaction. A lower amount of acetic acid (for example, 5 mol%) in ethanol at room temperature resulted in a lower yield of 75%. A good yield of 83% was achieved using 10 mol% of acetic acid. Increasing the amounts of acid (for example, 15 and 20 mol%) did not improve the yield. When the reaction was carried out at room temperature for 12 hours, the product was obtained in 83% yield (Table 2, entry 8), but under reflux conditions, the desired product was formed in 90% yield after 12 hours (Table 2, entry 9).

Table 2.

With the optimized conditions in hand (Table 2, entry 9), we next investigated the possibility of the synthesis of pentasubstituted pyrroles via a one-pot reaction from alkyl acetoacetates, dialkyl acetylenedicarboxylates and amines. To a 25 mL round-bottom flask was added ethyl acetoacetate (**1a**) (1.0 mmol), dimethyl acetylenedicarboxylate (**2a**) (1.0 mmol), K_2CO_3 (1.0 mmol), ethanol (10.0 mL) and the mixture was stirred vigorously at room temperature. After the ethyl acetoacetate had been consumed (monitored by TLC), ethanol (5.0 mL), benzylamine (**4a**) (1.0 mmol), and acetic acid (10 mol%) were added. The mixture was allowed to stir under reflux conditions for 12 hours to give the expected product in 90% yield. To explore the scope of this novel transformation, various alkyl acetoacetates, dialkyl acetylenedicarboxylates and amines were utilized under the optimized one-pot conditions. The results in Table 3 show that all the reactions proceeded smoothly to afford the corresponding pentasubstituted pyrroles in good yields. All the products are novel, to the best of our knowledge, and were characterized by ^{1}H, ^{13}C NMR and IR spectroscopy and CHN analysis.

Table 3.

A possible mechanism for the synthesis of 4-ethyl 2,3-dimethyl 1-benzyl-5-methyl-1*H*-pyrrole-2,3,4-tricarboxylate (**5a**) is illustrated in Scheme 2. This conversion involves the initial reaction of ethyl acetoacetate (**1a**) with dimethyl acetylenedicarboxylate (**2a**) in the presence of K_2CO_3 to form 3-ethyl 1,2-dimethyl 4-hydroxypenta-1,3-diene-1,2,3-tricarboxylate (**3a**). Next, the carbonyl group in compound **3a** could be activated by acetic acid and undergo nucleophilic addition with benzylamine (**4a**) followed by elimination of a molecule of H_2O. The subsequent cyclization of this intermediate is favoured kinetically resulting in formation of the five-membered ring. The final stage in the sequence must involve an oxidation in which two hydrogens are removed to afford the final product **5a**.

Scheme 2.

In summary, we have developed an efficient and facile method for the synthesis of pentasubstituted pyrrole derivatives by treatment of alkyl acetoacetates, dialkyl acetylenedicarboxylates and amines using acetic acid. The mild reaction conditions, low cost of the starting materials, operational simplicity, and excellent yields are advantages of the protocol.

Supporting Information: full experimental details, IR, ^{1}H and ^{13}C NMR spectra and CHN data of products **5a-p** can be found online.

Acknowledgments

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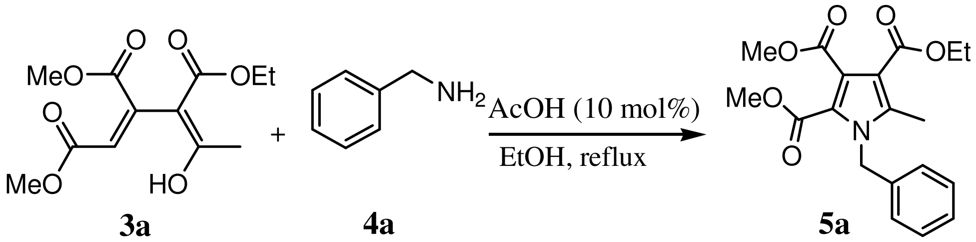
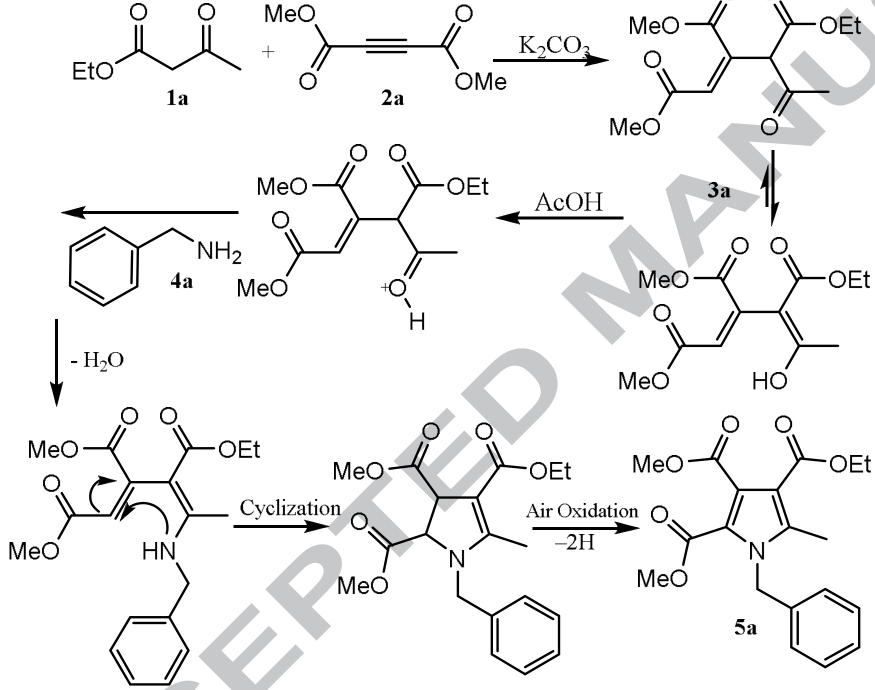
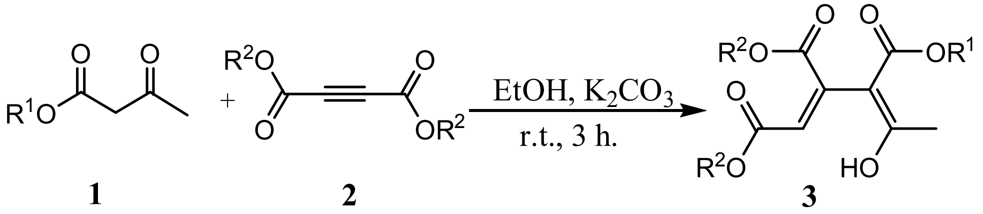


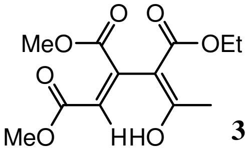
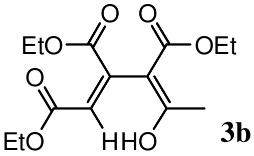
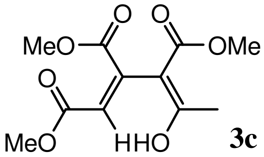
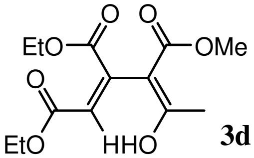
Scheme 1.



Scheme 2.

Table 1. Synthesis of 4-hydroxypenta-1,3-diene-tricarboxylates



Entry	R^1	R^2	Product	Yield (%)[a]
1	Et	Me	 **3a**	98
2	Et	Et	 **3b**	95
3	Me	Me	 **3c**	97
4	Me	Et	 **3d**	95

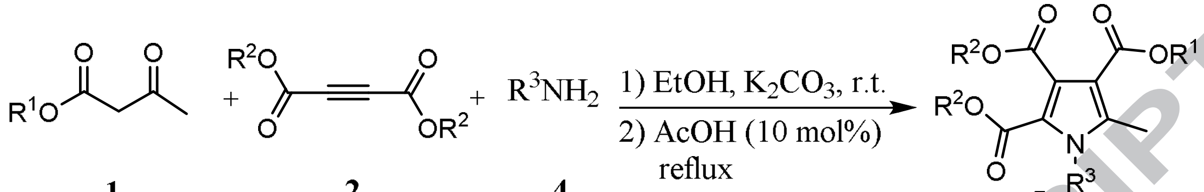
[a] Yields are given for isolated products.

Table 2. Optimization of the conditions for the synthesis of pentasubstituted pyrroles[a]

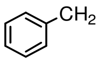
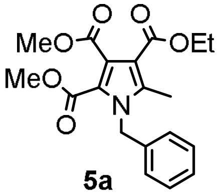
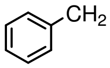
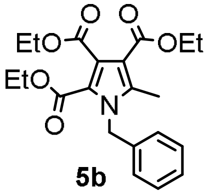
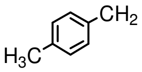
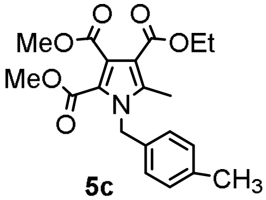
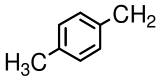
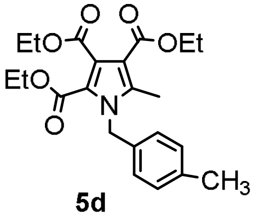
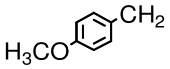
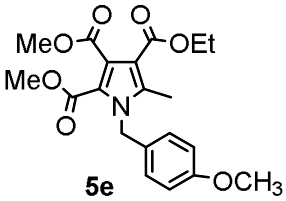
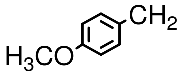
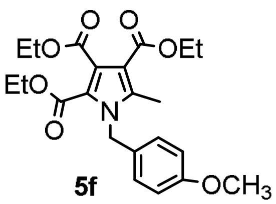
Entry	Solvent	Temp/Time (°C/h)	Yield (%)[b]
1	solvent-free	r.t. / 24	0
2	H_2O	r.t. / 24	45
3	H_2O	reflux / 24	58
4	MeCN	r.t. / 24	trace
5	MeCN	reflux / 24	trace
6	MeOH	r.t. / 24	65
7	MeOH	reflux / 24	77
8	EtOH	r.t. / 12	83
9	EtOH	reflux / 12	90

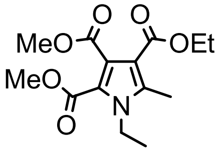
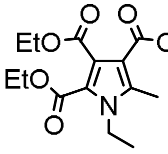
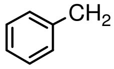
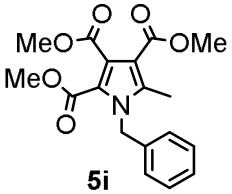
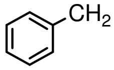
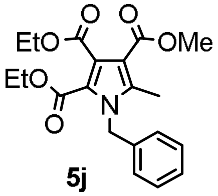
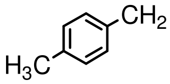
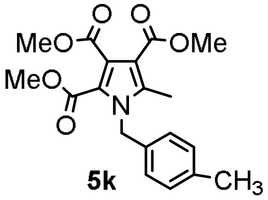
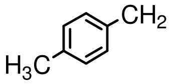
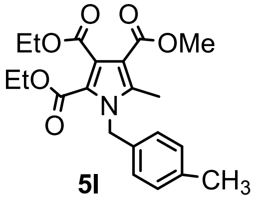
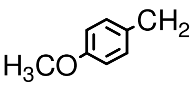
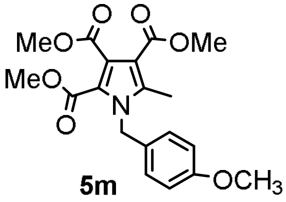
[a] Reaction conditions: **3a** (1.0 mmol), benzylamine (**4a**) (1.0 mmol), AcOH (10 mol%).
[b] Yields are given for isolated products.

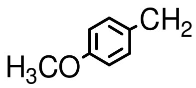
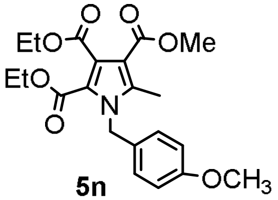
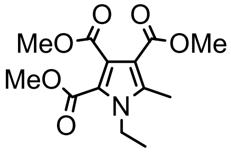
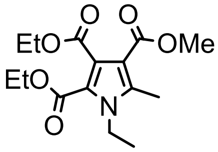
Table 3. One-pot synthesis of pentasubstituted pyrroles



1 **2** **4** **5**

Entry	R^1	R^2	R^3	Product	Yield (%)[a]
1	Et	Me		 **5a**	90
2	Et	Et		 **5b**	87
3	Et	Me		 **5c**	93
4	Et	Et		 **5d**	85
5	Et	Me		 **5e**	95
6	Et	Et		 **5f**	90

7	Et	Me	$H_3C{-}CH_2$	 **5g**	78
8	Et	Et	$H_3C{-}CH_2$	 **5h**	80
9	Me	Me		 **5i**	83
10	Me	Et		 **5j**	90
11	Me	Me		 **5k**	86
12	Me	Et		 **5l**	84
13	Me	Me		 **5m**	93

14	Me	Et		 **5n**	88
15	Me	Me	$H_3C{-}CH_2$	 **5o**	75
16	Me	Et	$H_3C{-}CH_2$	 **5p**	77

[a] Yields are given for isolated products.

Graphical Abstract

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An efficient and convenient synthesis of pentasubstituted pyrroles from alkyl acetoacetates, dialkyl acetylenedicarboxylates and amines

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