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One-Pot AgOAc-Mediated Synthesis of Polysubstituted Pyrroles from Primary Amines and Aldehydes: Application to the Total Synthesis of Purpurone

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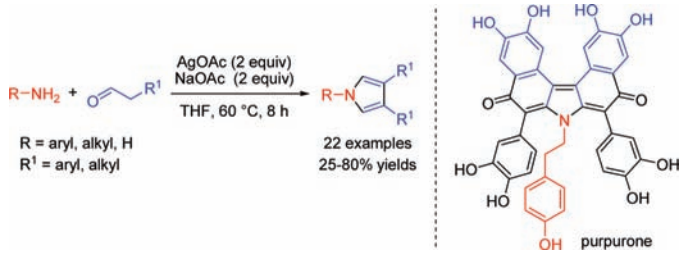
ABSTRACT



A simple and efficient method for the synthesis of 1,3,4-trisubstituted or 3,4-disubstituted pyrroles has been developed. The reaction represents the first time that pyrroles are synthesized directly from readily available aldehydes and amines (anilines) as starting materials. This method has been successfully applied to the rapid synthesis of purpurone.

The pyrrole nucleus is one of the most important heterocycles since it is not only found in many natural products[1] and bioactive molecules[2] but also broadly used in material science and supramolecular chemistry.[3] Accordingly, a variety of well-documented traditional and modern methods have been developed for the construction of pyrroles and their derivatives.[4,5] However, there are very few general approaches that convert commercially available or readily accessible materials in one step to polysubstituted pyrroles. Therefore, a more flexible and general approach from simple and easily accessible starting materials is still of critical importance. It is also noteworthy that the 3,4-disubstituted pyrrole system is probably the most difficult to obtain since selective substitutions at one or more of the β-positions have been a challenging goal in many synthetic programs. Functionalizations of pyrrole−N systems also suffered from a lack of selectivity and significant polymerization.[6]

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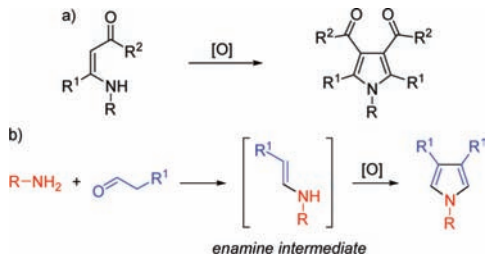
Oxidative homodimerization of enamino ketones or esters for the synthesis of pyrrole has been described in the literature under electrochemical conditions[7] or by using $Pb(OAc)_4$,[8] Ce(IV),[9] and $PhI(OAc)_2$[10] as the oxidants (Scheme 1a). However, the substrates are limited to enamino ketones or esters, and these must be prepared before use.[7−10] The oxidative homodimerization of aldehyde enamine has never been reported.[11] In fact, pure aldehyde enamines are rarely employed in organic synthesis due to the limitations of their preparation and the isolation restrictions.[12]

Scheme 1. (a) Homodimerization of the Enamino Ketones or Esters and (b) Homodimerization of Enamines Formed in Situ Drectly from Simple Amines and Aldehydes



Recently, oxidative coupling reactions have proven to be excellent and efficient methods for formation of C−C bonds.[13,14] In connection with our work for preparation of indole using *o*-halo-aniline with aldehyde via an enamine intermediate,[15] we recently questioned whether the pyrrole product could be obtained via oxidative homodimerization of the enamine intermediate, formed in situ by reaction of amine (aniline) and aldehyde, with an appropriate oxidant (Scheme 1b). Herein, we demonstrate the first efficient and direct approach to polysubstituted pyrroles from simple and readily available amine (aniline) and aldehyde by using AgOAc as the oxidant in a one-pot manner.

To test this activation concept, reaction of 4-methoxyaniline **1a** with butylaldehyde **2a** was initially attempted under oxidative conditions [$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2 equiv), AgOAc (2 equiv)]. Gratifyingly, the pyrrole product **3a** was obtained in 24% yield as the only detectable product.

A condition survey quickly revealed that $Pd(OAc)_2$ and $Cu(OAc)_2$ were not necessary, and AgOAc (2 equiv) alone could promote this reaction well (see Supporting Information). In addition, the use of equivalent amounts of amine and aldehyde was crucial for obtaining good yield (see Scheme 2). A wide variety of reaction conditions (silver source oxidants, solvents, and additives) were also examined, and some of the representative results are shown in Table 1. AgOAc turned out to be the oxidant of choice, albeit Ag_2CO_3 was also capable of promoting the reaction but with lower yield (entries 1−4). The solvent also played a very important role in this reaction (entries 1 and 6−8). Further studies indicated that the addition of a base such as pyridine or NaOAc dramatically increased the yield of **3a** (entries

Scheme 2. Proposed Mechanism for the Transformations

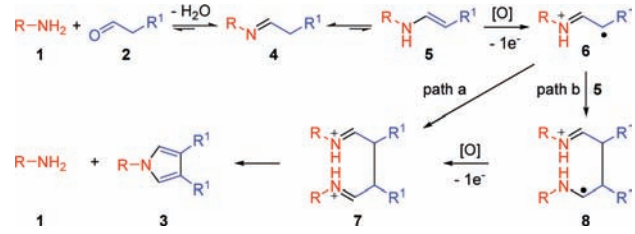


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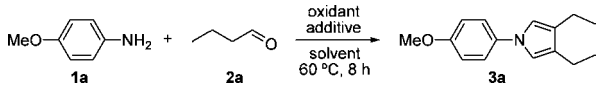
Table 1. Optimization of the Reaction Conditions[a]



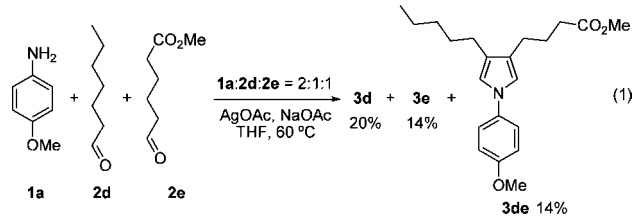
entry	oxidant	solvent	additive	yield (%)[b]
1	AgOAc	THF	–	49
2	$AgBF_4$	THF	–	0
3[c]	Ag_2CO_3	THF	–	21
4	$AgCO_2CF_3$	THF	–	0
5	$Mn(OAc)_3{\cdot}2H_2O$	THF	–	12
6	AgOAc	1,4-dioxane	–	20
7	AgOAc	$ClCH_2CH_2Cl$	–	19
8	AgOAc	DMF	–	10
9	AgOAc	THF	L-proline	35
10[d]	AgOAc	THF	pyridine	66
11	AgOAc	THF	NaOAc	72
12[e]	**AgOAc**	**THF**	**NaOAc**	**74**

[a] General reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), oxidant (1.0 mmol), additive (1.0 mmol), solvent (2.5 mL), 60 °C, 8 h. [b] Yields determined by GC analysis. [c] Ag_2CO_3 (1.0 equiv) was employed. [d] Pyridine (0.25 mL) was employed. [e] rt for 0.5 h, then 60 °C for 8 h.

10−12), and it was proposed that the base would neutralize the acid formed during the reaction (see Scheme 2).

Having established the optimal reaction conditions, the scope of this reaction was examined with respect to the aldehydes and amines. As illustrated in Figure 1, the transformation was found to be very general. A diverse set of aldehydes are suitable reaction partners (**3a**−**3g**). However, the reaction is quite sensitive to the electronic contribution of substituents on the benzene ring of anilines. Only anilines with electron-donating and electron-neutral substituents provide the desired pyrroles in reasonable yield (**3h**−**3o**). Steric hindrance at the 2-position of anilines is tolerated well (**3j**, **3l**, and **3m**). In addition, all the tested aliphatic amines, including sterically hindered cases, prove to be suitable partners (**3p**−**3u**). Most notably, the desired pyrrole is also formed by using NH_3 as a reaction partner, albeit in lower yield (25%) (**3v**).

With the successful synthesis of symmetric pyrroles, attempts were next made to prepare asymmetric pyrroles by reaction of amine with two different aldehydes. However, no selectivity was observed. For example, reaction of 4-methoxyaniline **1a** with heptanal **2d** and methyl 6-oxohexanoate **2e** gave pyrroles **3d**, **3e**, and **3de** in the yield of 20%, 14%, and 14%, respectively [eq 1].



A plausible mechanism for this multicomponent oxidative coupling reaction was hypothesized as shown in Scheme 2.

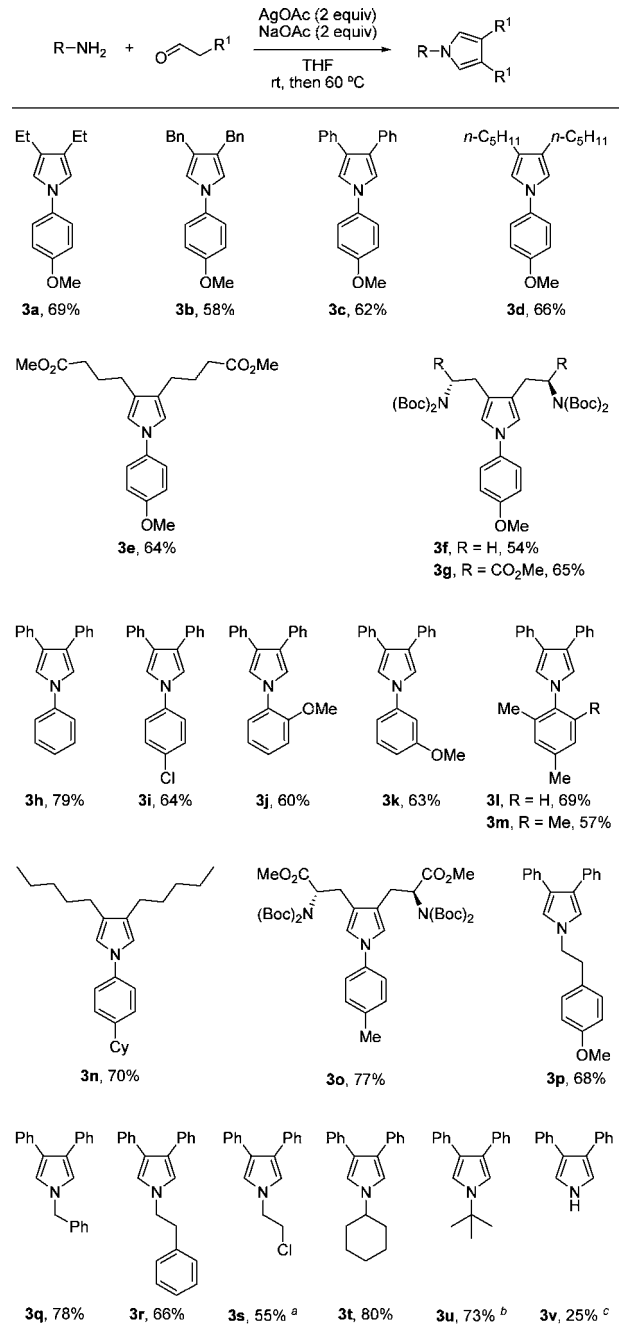


Figure 1. Scope of the AgOAc-mediated oxidative coupling of amine **1** and aldehyde **2**. [a]2-Chloroethylamine hydrochloride was used; AgOAc (3 equiv) and NaOAc (3 equiv) were employed. [b]A condenser was needed. [c]An NH_3 balloon was used.

Reaction of amine **1** with aldehyde **2** rapidly produces imine **4**, which equilibrates to enamine **5**. A one-electron oxidation of a transient enamine species **5** with AgOAc generates an α-imine radical cation **6**. At this stage, **6** can undergo self-coupling to give the diimine **7** (path a).[7,8,11,16] Alternatively, **6** can also suffer attack by another enamine **5** resulting in a

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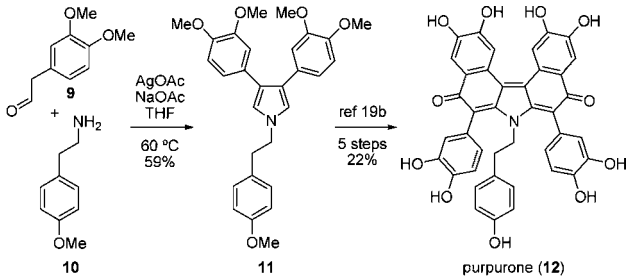
radical cation **8**, which is then further oxidized by AgOAc to produce **7** (path b).[13] Finally, aromatization of **7** affords pyrrole **3** and one mole of amine **1**.

Shi recently reported that phenethylamines could be converted to pyrroles under oxidation conditions.[5h] Since it is known that diphenethylamine can be produced by deamination of phenethylamine, we believe that this transformation takes the same reaction pathway with us.

The utility of this new process is demonstrated by a rapid total synthesis of purpurone, a potent ATP-citrate lyase (ACL) inhibitor,[17] which belongs to a group of biologically very important marine natural products (Scheme 3).[18,19]

Scheme 3. Synthesis of Purpurone



Treatment of aldehyde **9** with amine **10** under our optimized conditions provided the desired pyrrole **11** in 59% yield, which was then transformed to purpurone **12** following a literature protocol reported by Steglich.[19b]

In summary, we have developed a simple and efficient method for the synthesis of 1,3,4-trisubstituted or 3,4-disubstituted pyrroles using a AgOAc-mediated oxidative coupling reaction in a one-pot manner. The reaction represents the first time that pyrroles are synthesized directly from simple, readily available aldehydes and amines (anilines) as starting materials. Its utility can be seen in the rapid total synthesis of purpurone. Broadening of the scope of this reaction and the synthesis of biologically important lamellarin derivatives and related compounds[20] are in progress in our laboratory and will be reported in due course.

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Supporting Information Available: Detailed experimental procedures, compound characterization, and copies of spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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