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A Novel Assembly of Substituted Pyrroles by Acid-Catalyzed Sequential Three-Component Reaction of Amines, Alkynoates, and 1,2-Diaza-1,3-dienes

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Abstract: A novel protocol for the assembly of polysubstituted pyrroles has been developed through the acid-catalyzed, sequential three-component reaction of primary aliphatic amines, alkynoates and 1,2-diaza-1,3-dienes (DDs). This methodology proceeds with complete chemo-/regioselectivity involving first formation of an enamino ester intermediate, *in situ* Michael addition with azo-ene compounds and subsequent intramolecular ring closure.

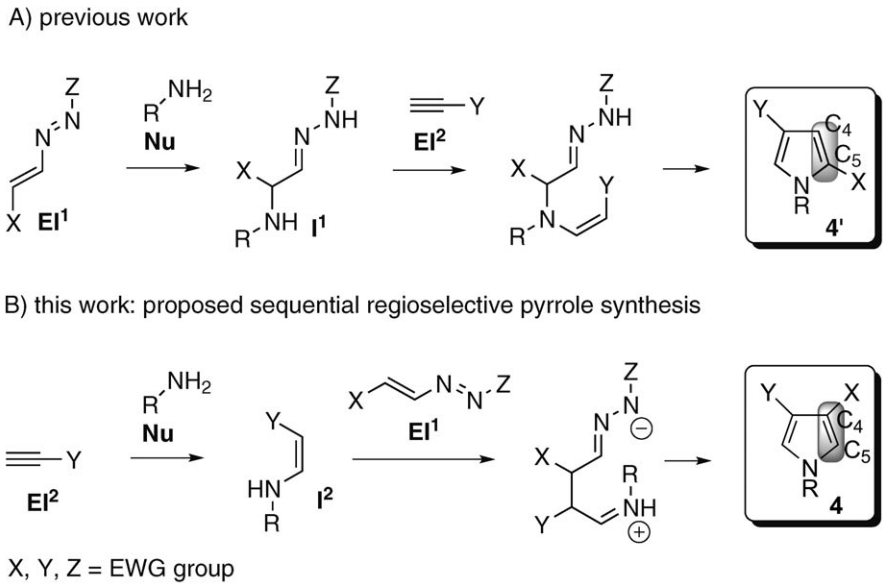
Keywords: 1,2-diaza-1,3-dienes; Michael addition; pyrroles; regioselectivity; sequential reactions

Introduction

By virtue of their productivity, specificity, facile execution and high yields of products avoiding laborious purification techniques, sequential reactions offer significant advantages over classical step-by-step approaches allowing the direct synthesis of complex molecules from simple precursors in a one-pot operation.[1–3] Consequently, over the past decades, numerous reports on sequential transformations have been published.[4] In this context, the concept of combining one set of substrates/reagents for a diverse assembly of functionalized target structures is very attractive, but largely unexplored. Although substantial effort has been directed at the development of diversity-oriented synthesis (DOS)[5] platforms to construct heterocyclic compounds, a "rational" approach able to unite three or more *different* and *independent* components in such a way to divert the regioselectivity in the heterocycle formation is still lacking.

Among compounds containing nitrogen heterocyclic frameworks, regioselectively substituted pyrroles[6] represent an indispensable structural motif of a large number of natural products,[7] synthetic pharmaceuticals,[8] and electrically conducting materials.[9] As a consequence, many new synthetic approaches[10] have been devised and developed as alternatives to the classical methods represented by the Knorr,[11] Paal–Knorr,[12] and Hantzsch[13] protocols. Pursuing our long-standing interest in the chemistry of heterocycles, we have recently reported a novel synthetic route to highly functionalized pyrroles.[14] Specifically, the process was realized by a preliminary addition of a primary amine to a 1,2-diaza-1,3-diene (DD),[15] a hydroamination reaction with an activated alkyne producing an α-(*N*-enamino)-hydrazone and a subsequent Lewis acid-catalyzed ring closure by means of intramolecular C-nucleophilic attack to give the pyrrole heterocycle ($\mathbf{El^1+Nu \rightarrow I^1+El^2 \rightarrow 4'}$; Scheme 1, A).

In connection with these findings, and considering the mutual reactivity of the reagents, we envisage that an intriguing modified three-component process involving first the combination of an amine with an alkyne and then the reaction with an azo-ene compound could also be worthy of interest. Thus, we postulate that the amine-alkyne adduct (enamino ester)[16] $\mathbf{I^2}$ could be suitable for a sequential Michael addition and ring closure, directly providing the regioisomerically substituted pyrrole. The key step would involve a reactive zwitterionic intermediate that could cyclize through N-nucleophilic attack upon 1,3-hydrogen shift (in essence a tautomerization) furnishing the corresponding pyrrole derivative ($\mathbf{El^2+Nu \rightarrow I^2+El^1 \rightarrow 4}$; Scheme 1, B).



Scheme 1. Divergent regioselective synthesis of pyrroles from amines, alkynoates and DDs.

Importantly, it is noteworthy that, with this sequence, it is possible to divert the regioselective behaviour of the reaction from the formation of pyrroles towards that of their regioisomers simply by changing the addition order of the two electrophilic components (**4′** *vs.* **4**; Scheme 1). Here, we describe a novel and flexible one-pot strategy towards pyrroles by way of a sequential enamino ester formation/Michael addition reaction/azaheterocyclization process starting from primary amines, alkynoates[17] and DDs.

To the best of our knowledge, the use of one set of substrates/reagents in sequential reactions to produce regioisomers, specifically heterocyclic isomers, has not been reported previously. Recently, Zhu's group has reported a palladium-catalyzed three-component synthesis of 3-(diarylmethylene)oxindoles in a stereocontrolled manner.[18] Both *E*- and *Z*-isomers of the oxoindoles can be prepared through *identical* domino Sonogashira/carbopalladation/C–H activation/C–C bond forming sequences from the same starting materials simply by changing the addition order of the two aryl halides.

Results and Discussion

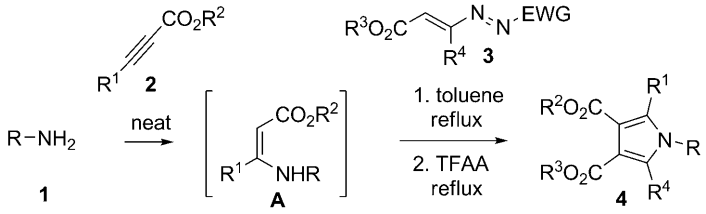
With this hypothesis in mind, we planned to explore the feasibility of this strategy. In order to realize a one-pot process by subsequent addition of reagents, we first developed the desired formation of the enamino ester by reaction of primary aliphatic amines and alkynoates. This aza-Michael reaction has been reported under the following conditions: in EtOH, MeOH, AcOH, DMF, THF, H_2O MeOH/AcOH, DMF/MeOH, DMF/AcOH, DMF/H_2O, DMSO/H_2O, EtOAc, etc.[16] Since these conditions cannot be combined with the subsequent Michael addition/heterocyclization step in a single flask because of the natural incompatibility of the starting DD with these solvents (scarce solubility and/or degradability) we found that the synthesis of the desired enamino compound also proceeds at room temperature under solvent-free conditions[19] and in the absence of a Brønsted or Lewis acid.

Thus, a preliminary study of the sequential reactions was conducted using benzylamine (**1a**) (1 mmol), diethyl acetylenedicarboxylate (**2a**) (1 mmol), followed by addition of 1,2-diaza-1,3-diene (**3a**) (1 mmol) under the above-mentioned conditions.

A careful examination of the reaction progress over time revealed that even when the reaction was stopped after consumption of the starting DD at room temperature or heating up to 80 °C no transformation to a pyrrole compound was observed. To our delight, the formation of pyrrole was detected (34%) when the reaction was performed in refluxing toluene after addition of the azo-ene compound. Gratifically, increasing the DD from 1 equivalent to 1.5 equivalents and adding a catalytic amount of triflouroacetic acid (TFAA) after the disappearance of the starting **3a** enhanced the product yield (83%) (Table 1, entry 1). Other catalysts (Lewis/Brønsted acids), such as AcOH, PTSA, $ZnCl_2$, $Zn(TfO)_2$, $InCl_3$, $InBr_3$, $In(TfO)_3$ and $Cu(TfO)_2$ also promoted the transformation albeit in lower yields. Furthermore, a change of the solvent (CH_3CN) did not improve the yields (35%).

Based on the success of the model system, a series of products **4a–r** was constructed in order to evaluate the applicability of this reaction sequence (Table 1).

Table 1. Acid-catalyzed sequential three-component reaction of primary amines **1a–e**, alkynoates **2a–d** and DDs **3a–f**; synthesis of *N*-alkylpyrroles **4a–r**.[a]



Entry	**1** (R)	**2** (R^1; R^2)	**3** (R^3; R^4; EWG)	**4** [%][b]
1	**1a** (Bn)	**2a** (CO_2Et; Et)	**3a** (Me; Me; CO_2Me)	**4a** (83)
2	**1a** (Bn)	**2b** (CO_2Me; Me)	**3a** (Me; Me; CO_2Me)	**4b** (68)
3	**1a** (Bn)	**2b** (CO_2Me; Me)	**3e** (Et; Pr; CO_2Et)	**4c** (59)
4	**1a** (Bn)	**2d** (Ph; Et)	**3a** (Me; Me; CO_2Me)	**4d** (37)
5	**1a** (Bn)	**2b** (CO_2Me; Me)	**3b** (Et; Me; Ts)	**4e** (66)
6	**1a** (Bn)	**2a** (CO_2Et; Et)	**3c** (Bn; Me; CO_2-*t*-Bu)	**4f** (61)
7	**1a** (Bn)	**2c** (H; Et)	**3d** (Me; Et; CO_2Me)	**4g** (42)
8	**1a** (Bn)	**2d** (Ph; Et)	**3f** (All; Me; CO_2Me)	**4h** (47)
9	**1a** (Bn)	**2c** (H; Et)	**3a** (Me; Me; CO_2Me)	**4i** (56)
10	**1b** (*n*-Pr)	**2a** (CO_2Et; Et)	**3c** (Bn; Me; CO_2-*t*-Bu)	**4j** (57)
11	**1b** (*n*-Pr)	**2a** (CO_2Et; Et)	**3f** (All; Me; CO_2Me)	**4k** (55)
12	**1b** (*n*-Pr)	**2b** (CO_2Me; Me)	**3a** (Me; Me; CO_2Me)	**4l** (67)
13	**1c** (*n*-Bu)	**2a** (CO_2Et; Et)	**3a** (Me; Me; CO_2Me)	**4m** (59)
14	**1c** (*n*-Bu)	**2b** (CO_2Me; Me)	**3d** (Me; Et; CO_2Me)	**4n** (65)
15	**1d** (*sec*-Bu)	**2a** (CO_2Et; Et)	**3a** (Me; Me; CO_2Me)	**4o** (47)
16	**1e** (*c*-Hex)	**2b** (CO_2Me; Me)	**3a** (Me; Me; CO_2Me)	**4p** (73)
17	**1e** (*c*-Hex)	**2b** (CO_2Me; Me)	**3d** (Me; Et; CO_2Me)	**4q** (54)
18	**1e** (*c*-Hex)	**2c** (H; Et)	**3a** (Me; Me; CO_2Me)	**4r** (49)

[a] *Reaction conditions:* all the reactions were run by mixing amine **1** (1 mmol), and alkynoate **2** (1.1 mmol) under solvent-free conditions at room temperature. After 5–10 min (12 h when **2d** was used), DD **3** (1.5 mmol) in toluene (10 mL) was added and the reaction was refluxed for 2-4 h. A catalytic amount of TFAA was added once the DD had been consumed completely (TLC check) and the reaction was refluxed for additional 2-4 h.

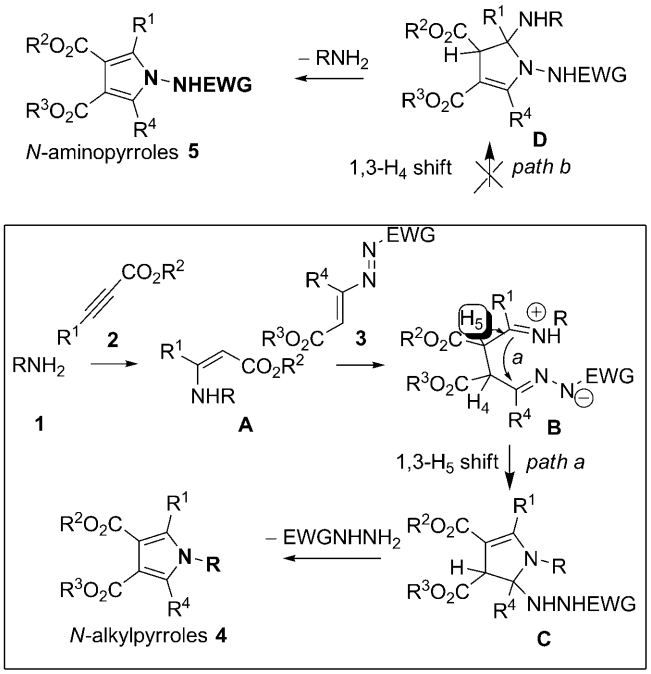
[b] Yield of pure product **4** after column chromatography.

Various amines **1a–e**, alkynoates **2a–d**, and DDs[20] **3a–f** were explored and the results are summarized in Table 1. In general, primary aliphatic amines such as benzylamine, *n*-propylamine, *n*-butylamine, *sec*-butylamine, and cyclohexylamine (R = Bn, *n*-Pr, *n*-Bu, *sec*-Bu, *c*-Hex) worked well to give the substituted pyrroles. Although aromatic primary amines (R = Ph, *p*-Me-C_6H_5, *p*-MeO-C_6H_5, *p*-Br-C_6H_5) were well tolerated in the coupling with alkynoates, unfortunately the subsequent acid-promoted enamine-azoene annulation failed, probably because of the reduced nucleophilicity of the amine nitrogen atom.

Moderate to excellent yields were achieved with several types of activated alkynes such as dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate, ethyl propiolate and ethyl 3-phenylprop-2-ynoate (R^1 = H, Ph, CO_2Et, CO_2Me). If R^2 was changed from ethyl to methyl, the yields were almost the same even when different amine/DD partners were used. Additionally, these reactions were compatible with a variety of DD compounds possessing different functional CO_2R^3, R^4, and EWG groups (R^3 = Me, Et, Bn, All; R^4 = Me, Et, Pr, Ph, CO_2Et; EWG = Ts, CO_2Me, CO_2Et, CO_2-*t*-Bu).

The structures of the *N*-alkylpyrrole-3-carboxylic acid derivatives **4a–r** were supported by spectroscopic evidence and unequivocally confirmed by comparison of the 4,5-dimethoxycarbonyl-2-methylpyrrole derivative **4e** with the same pyrrole previously reported by Chuang and Wu.[21]

Although the behaviour of DDs with various enamines has been extensively investigated so far, no examples of alkylpyrroles **4** using *N*-monosubstituted enamines/enaminones are known. In fact, even if a large number of modifications of the enamine reagent have been explored, the studies were restricted to the use of secondary amine-derived enamines.[22] For these reactions, the accepted mechanism of generation of aminopyrrole derivative **5** has been hypothesized to involve as a key step the formation of a zwitterionic transient species of type **B** (Scheme 2).



Scheme 2. Plausible mechanism for the formation of pyrrole derivatives.

On the basis of all these results, a plausible mechanism for the sequential three component reaction is described in Scheme 2. In the first step, the formation of enamino ester **A** occurs through addition of amine **1** with alkynoate **2**. Next, 1,4-nucleophilic addition of **A** to the azo-ene system of DD **3** produces the zwitterionic hydrazone adduct intermediate **B**, which is not isolable, that promptly afforded 5-alkylhydrazinopyrroline-3-carboxylic acid derivatives **C** by an intramolecular azacyclization (promoted by TFAA) *via* CH/NH tautomerization or 1,3-hydrogen shift. In turn, **C** aromatizes into the *N*-alkylpyrrole **4** by loss of the hydrazine residue (path *a*, Scheme 2).

The exclusive formation of 1-alkylpyrrole **4** rather than 1-aminopyrrole **5** may be explained by the nature of the enamine component. In fact, as expected, the use of **A** by introduction of a primary amine, has a strong influence on the position of the iminium/enamine equilibrium in **B** favouring the intramolecular nucleophilic attack of the NH bond of the enamine (derived from a 1,3-hydrogen shift of H-5) across the unsaturated C=N bond of the hydrazone function (path *a*) to give the stable aromatic compound **4**. This occurrence would be assisted by the presence of the CO_2R^2 group in the α-position to the iminium functionality (intermediate **B**).

Alternatively, the tautomerization of intermediate **B** *via* CH/NH prototropism of the hydrazono/hydrazino form (derived from H_4) before the cyclization process (path *b*, Scheme 2) still remains the generally accepted mechanism when a simple *N,N*-disubstituted enamine and DD **3** are used.[22]

Taken together, the previous and present results, including the impact of the nature of the substitutents of the enamine moiety, suggest that the ability to reverse the regiochemistry in the *N*-alkylpyrrole formation using the one and the same set of substrates/reagents (amines, alkynoates and DDs) simply depends on the addition order of the two electrophilic components. Notably, the present synthetic protocol was performed by combining two steps in the same reaction vessel; overall, this sequential methodology builds up two carbon-nitrogen bonds, one carbon-carbon bond, and an aromatic heterocycle ring in a chemo-, regioselective and efficient manner.

Experiments to perform a one-pot three-component reaction by putting all the substrates in one flask showed that both the competitive Michael additions (Nu = amine on El^1 = DD[14b] and Nu = amine on El^2 = alkynoate) proceed to give complex reaction mixtures of both pyrrole heterocycle derivatives.

Conclusions

In conclusion, we have discovered a novel, simple (metal-free), two-step, three-component process for the union of readily available primary amines, alkynoates and DDs. The synthetic route itself is completely different from the previous one and provides an orthogonal approach for easy access of regioselectively polysubstituted pyrroles (that are regioisomers at C-4 and C-5). Thus, a formal reversal of regioselectivity in the pyrrole ring formation can be obtained through sequential *non-identical* reactions with respect to those previously published simply by changing the addition order of the two electrophilic components (**4′** *vs.* **4**; Scheme 1).

Compared with the related enamine-DD [3+2] cycloaddition,[22] the complete control of pathway selectivity of these reactions is strictly dictated by the use of the primary amine-derived enamino ester as nucleophilic partner for heterocycle annulation. Further work to expand and apply these findings is ongoing, and the results will be reported in due course.

Experimental Section

General Procedure for the Acid-Catalyzed Sequential Three-Component Reaction of Primary Amines 1a–e, Alkynoates 2a–d and DDs 3a–f; Synthesis of *N*-Alkylpyrroles 4a–r

A mixture of amine **1a–e** (1 mmol), and alkynoate **2a–d** (1.1 mmol) was stirred under solvent-free conditions at room temperature. After 5–10 min (12 h when **2d** was used),

DD **3a–f**[20] (1.5 mmol) in toluene (10 mL) was added and the reaction mixture was refluxed for 2–4 h. A catalytic amount of TFAA (2 drops) was added once the DD had been consumed completely (TLC check) and the reaction was refluxed for additional 2–4 h. After removal of the solvent, the crude mixture was purified by column chromatography on silica gel (elution mixture: ethyl acetate/cyclohexane) to afford products **4a–r**.

2,3-Diethyl 4-methyl 1-benzyl-5-methyl-1*H*-pyrrole-2,3,4-tricarboxylate (4a): *N*-Alkylpyrrole **4a** was isolated by column chromatography (ethyl acetate/cyclohexane = 15:85) as a yellow oil; yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, J = 7.2 Hz, 3H), 1.38 (t, J = 7.2 Hz, 3H), 2.46 (s, 3H), 3.78 (s, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 5.61 (s, 2H), 6.94 (d, J = 7.6 Hz, 2H), 7.20–7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.3 (q), 13.8 (q), 14.1 (q), 48.3 (t), 60.6 (t), 61.3 (t), 110.9 (s), 119.0 (s), 125.7 (d), 126.3 (s), 127.3 (d), 128.7 (d), 136.2 (s), 141.4 (s), 159.5 (s), 163.6 (s), 166.2 (s); IR (nujol): ν_{max} = 1722, 1516, 1452, 1267, 1217, 1146, 1097, 1033, 876 cm^{-1}; MS: *m/z* (%) = 373 (M^+) (16), 341 (10), 327 (77), 281 (100), 267 (19), 192 (24); anal. calcd. for $C_{20}H_{23}NO_6$ (373.40): C 64.33, H 6.21, N 3.75; found: C 64.52, H 6.29, N 3.66.

Supporting Information

Experimental details, spectroscopic characterization of all compounds and copies of NMR spectra are given in the Supporting Information.

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