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Catalytic Multicomponent Reactions for the Synthesis of *N*-Aryl Trisubstituted Pyrroles

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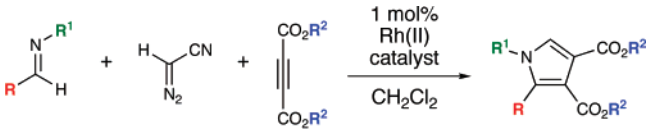

Dirhodium(II) salts efficiently catalyze the three-component assembly reaction of an imine, diazoacetonitrile (DAN), and an activated alkynyl coupling partner to form substituted 1,2-diarylpyrroles in moderate to good yields. The transition-metal-catalyzed decomposition of the diazo compound in the presence of the imine presumably generates a transient azomethine ylide that undergoes cycloaddition with dipolarophiles in a highly convergent manner.

Pyrroles are plentiful structural motifs in natural products,[1] medicinal agents,[2] and materials chemistry.[3] There are many efficient methods for the synthesis of this important class of heterocycle, but all of the various approaches have certain restrictions regarding the scope and placement of the substitution pattern around the heterocycle core. For example, our recently published *N*-heterocyclic carbene-catalyzed, one-pot approach to the synthesis of pyrroles using an acylsilane, α,*β*-unsaturated ketone, and primary amine[4] does not access the 3,4-diester-substituted pyrroles described here. In many instances, specific pyrrole substitution patterns are more important than others for reactivity or biological activity, thus underpinning the need to access a wide variety of pyrrole scaffolds efficiently from straightforward starting materials.[5] In addition to restrictions based on the substitution pattern of the target compound, various methods to synthesize differentially substituted pyrroles can require expensive reagents, prolonged reaction times, or numerous synthetic steps.

We envisaged using our previously reported multicomponent coupling reaction for the synthesis of nitrogen-containing heterocycles for the synthesis of these pyrroles.[6] This interest was initiated by a desire to synthesize *N*-aryl-substituted pyrrole-3,4-dicarboxylic acids for an application in materials/surface attachment chemistry.[7] We were surprised to discover relatively few methods for the synthesis of the desired 3,4-substitution pattern in the literature. For example, **4** has been reported on four previous occasions, but none of the synthetic routes are amenable to accommodate various substitutions efficiently in a single-flask operation. Boyd and Wright have described the preparation and chemistry of a range of unstable mesoionic oxazolium-5-oxide perchlorates, including the dipolar cycloaddition of these compounds with dimethyl acetylene dicarboxylate (DMAD) to yield compound **4**.[8] Yamanaka has reported the synthesis of the related 4-polyfluoroalkylated pyrrole-3-carboxylates through the 1,3-dipolar cycloaddition of a fluoroalkylated acetylenecarboxylate ester with the munchnones described by Boyd.[9] Additionally, phenylsydnonyl-substituted pyrroles have been reported via a related cycloaddition.[10] In this approach, the pyrroles are prepared in five linear steps starting from an *N*-aryl glycine derivative.

In 1984, Reutrakul reported the preparation of phenylsulfinyl aziridines in modest to good yields from benzylidine anilines and α-chloro α-lithio sulfoxides.[11] Pyrolysis of these compounds in the presence of DMAD promoted the thermal ring opening of the aziridine at 90 °C to the corresponding azomethine ylide. Cycloaddition followed by elimination of sulfinic acid afforded the pyrroles in good yield. Similarly, Katritzky has reported the synthesis of the compound **10** from the analogous thermal reaction of 2-benzotriazolylaziridines in the presence of diethyl acetylenedicarboxylate.[12] Although the aziridine precursors are readily accessed in this case, the cycloaddition step requires a prolonged reaction time (48 h at 100 °C) to access the target

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(5) 1,2-Diaryl pyrroles (with adjacent aryl substituents) are common structural motifs in biologically active natural products and medicinal agents, whereas the analogous 1,3-diaryl motif is less common. For an excellent review and discussion of pyrroles containing adjacent aryl groups, see: Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213−7256.

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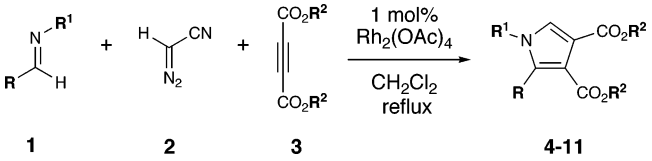
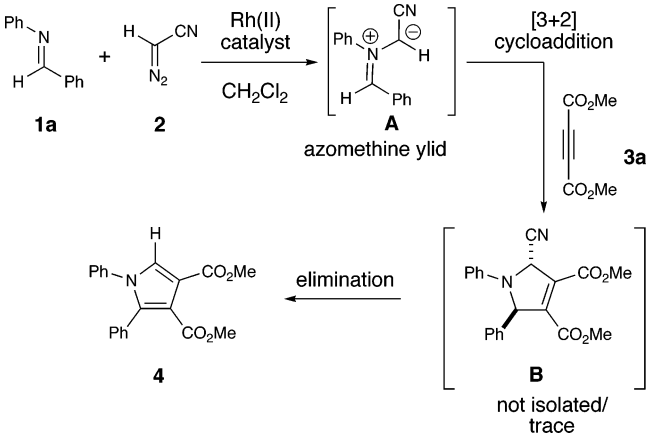
SCHEME 1. Multicomponent Assembly Reaction for the Synthesis of Pyrroles



SCHEME 2. Proposed Reaction Pathway

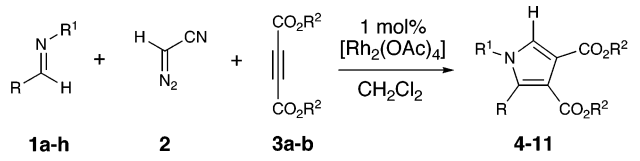


pyrroles. Here we report a concise approach to 1,2-diarylpyrroles using a multicomponent assembly reaction of an imine, diazoacetonitrile, and an activated alkyne dipolarophile (Scheme 1).

The combination of rhodium(II) salt and a diazo compound produces the corresponding metallocarbenoid.[13] The presence of an imine during this process generates an azomethine ylide intermediate, which is trapped via a Huisgen [3 + 2] cycloaddition onto an alkynyl dipolarophile.[14] The resultant adduct then undergoes elimination in situ to form the aromatic pyrrole (Scheme 2).[15]

After examining a number of possible transition metal salts for this reaction, we determined that rhodium acetate is the catalyst of choice for this transformation, proving to be superior to 10 mol % of copper triflate (as in our previous work),[6] which surprisingly yielded no product in this case. Other rhodium salts also promoted the transformation (dirhodium tetraoctanoate and dirhodium tetrahexafluorobutyrate), albeit in lower yields (27% and 12%, respectively). We were pleased to discover that as little as 1 mol % of catalyst smoothly effected the transformation.

TABLE 1. Scope of the Multicomponent Reaction[a]



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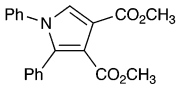
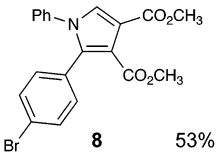
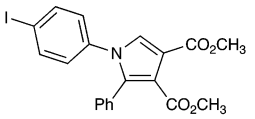
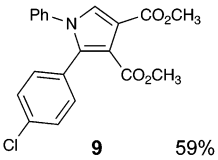
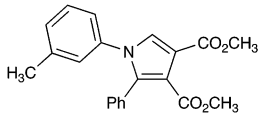
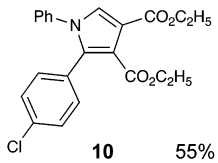
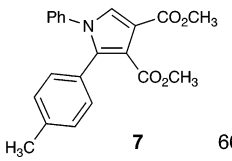
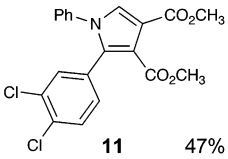
1		4 71%	5		8 53%
2		5 61%	6		9 59%
3		6 63%	7		10 55%
4		7 66%	8		11 47%

[a] Reaction conditions: a solution of DAN (**2**, 4.5 equiv) in CH_2Cl_2 (4 mL) was added via syringe pump over 3 h to a solution of imine (**1a**−**h**, 3 equiv), acetylene dicarboxylate (**3a** or **3b**, 1 equiv), and $Rh_2(OAc)_4$ (1 mol %) in CH_2Cl_2 (3 mL), heating at gentle reflux.

Gratifyingly, several imines can be employed in this reaction manifold (Table 1). Substitution on the starting imine is tolerated, especially on the benzylidene aryl ring (compounds **6**−**11**, entries 4−8). Compound **8** required a longer reaction time after the syringe pump addition was complete (12 h). Most likely, this is due to a destabilizing effect on the putative azomethine ylide. Diethyl acetylenedicarboxylate (**3b**) is readily used in place of DMAD to yield the 3,4-diethyl ester in good yield (compound **10**, entry 7). Alternative activated acetylenes, such as methyl propiolate, yielded no product. In addition to our proposed mechanism, we could not discount the possibility of a pathway involving initial formation of an aziridine that undergoes ring opening (similar to that of Katritzky). Doyle has shown that the analogous Rh(II)-catalyzed aziridination of imines by carbene transfer of ethyl diazoacetate shows a strong structure dependency on the imine substituents, with respect to the reaction's product distribution (the azomethine ylide can undergo ring closure to yield aziridines or cycloaddition to afford alternative products).[16] In our case, this may suggest competing pathways leading to the same product, with a strong dependency

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on the imine structure being a prerequisite for this second pathway to be substantial.

Under our optimized reaction conditions, we did not isolate any aziridine products. However, other side products are known to form with diazoacetonitrile.[17] The pyrrole-3,4-diester products are known to undergo other side reactions with acetylene dicarboxylates,[18] and optimization efforts were therefore primarily directed at the minimization of these side products. Diazoacetonitrile was conveniently prepared by the diazotization of the commercially available aminoacetonitrile bisulfate according to the procedure of Witiak and Lu and handled only as a solution in methylene chloride.[19] It is important to note that explosions caused by concentrating diazoacetonitrile solutions have been reported,[20] but solutions (approximately 0.4−0.5 M in CH_2Cl_2) could be safely prepared in our laboratory and handled without incident.

In summary, the combination of a diazoacetonitrile and an imine in the presence of a rhodium(II) catalyst generates a reactive, transient azomethine ylide. This 1,3-dipole undergoes a [3 + 2] cycloaddition with activated alkynyl dipolarophiles to afford 1,2-diaryl-substituted pyrroles in a convergent three-component assembly reaction. Notably, this process works efficiently at low catalyst loadings.

Experimental

Sample Procedures for Pyrrole Synthesis. To a flame-dried, two-necked, round-bottom flask fitted with a reflux condenser containing a magnetic stirring bar was added 1 mol % of $Rh_2(OAc)_4$ catalyst, imine, and acetylene diester in CH_2Cl_2 (3 mL). The mixture was heated to a gentle reflux, and the diazoacetonitrile solution was added via syringe pump (1.5 mL per hour). After complete addition, the mixture was heated for a further 1−2 h (12 h in the case of compounds **5** and **8**) and then allowed to cool to 25 °C. The unpurified reaction mixture was filtered through a silica plug with CH_2Cl_2 (50 mL). The solvent was evaporated, and purification by flash chromatography on silica gel provided the title compounds.

Dimethyl 1,2-Diphenyl-1*H*-pyrrole-3,4-dicarboxylate (4). Prepared according to the general procedure using imine **1a** (213 mg, 1.2 mmol), DMAD **3a** (49 mL, 0.4 mmol), and a solution of DAN **2** in methylene chloride (4.0 mL, 0.45 M). Flash column chromatography using gradient elution mixtures of EtOAc/toluene (6−12%) afforded 94 mg (71%) of **4** as a viscous white foam. Analytical data for **4**: R_f 0.24 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 2947.9, 2860.2, 1722.7, 1560.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.36−7.08 (m, 10H), 3.84 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 163.6, 138.7, 135.1, 130.4, 129.9, 129.0, 128.1, 127.9, 127.7, 125.9, 117.0, 115.7; LRMS (electrospray) exact mass calcd for $C_{20}H_{17}NO_4$ $[M]^+$, 335.12; found [M + H], 336.5.

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Supporting Information Available: Characterization data and details of experimental techniques and procedures used in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Diazoacetonitrile **2** slowly undergoes dipolar cycloaddition with benzylidene anilines as the dipolarophile to yield triazolines as the major product. Enamines and aziridines are also formed in this reaction: Roelants, F.; Bruylants, A. *Tetrahedron* **1978**, *34*, 2229−2232.

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