Synthesis of Highly Substituted Pyrroles via a Multimetal-Catalyzed Rearrangement—Condensation—Cyclization Domino Approach

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ABSTRACT



In a convenient one-pot process, easily accessed propargyl vinyl ethers and aromatic amines are effectively converted into tetra- and pentasubstituted 5-methylpyrroles which can further be transformed into 5-formylpyrroles via IBX-mediated oxidation. The cascade reaction proceeds through a silver(I)-catalyzed propargyl–Claisen rearrangement, an amine condensation, and a gold(I)-catalyzed 5-*exo-dig* heterocyclization.

Highly substituted pyrroles are important structural elements of many natural products¹ and pharmaceutically active substances (e.g., lipitor).² Moreover, they are widely used in materials science.³ The construction of multiple substituted pyrrole rings typically relies on classical condensation methods such as the Paal–Knorr synthesis,⁴ although catalytic multicomponent coupling approaches⁵ are particularly attractive due to their rapid access to structural diversity. Despite numerous strategies for pyrrole synthesis through cyclization,⁶ access to pentasubstituted pyrroles^{5e,6b} is somewhat limited. In the context of ongoing efforts to develop cascade reactions initiated by transition-metal-catalyzed π -activation, we recently reported that acceptor substituted propargyl vinyl ethers can be effectively transformed into furans by a gold(I)-catalyzed cascade reaction.⁷ Herein, we report a conceptually new synthetic approach to tetra- and pentasubstituted pyrroles utilizing a transition-metal-catalyzed domino reaction of a formal [3,3]-sigmatropic rearrangement, an amine condensation, and a heterocyclization. In this simple one-pot assembly,

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readily obtained acceptor substituted propargyl vinyl ethers 1 and aromatic amines 2 are used as starting materials to produce pyrrole products 3 with high diversity (Scheme 1).



During the envisioned process, three independent reactions should occur sequentially: a catalytic version of a propargyl-Claisen rearrangement^{8,9} to generate allenic ketones, a condensation with a primary amine,10 and a transition-metalcatalyzed 5-exo-dig cyclization.⁷ To realize a single-step process by subsequent addition of reactants and catalysts,¹¹ we first developed the silver(I)-catalyzed rearrangement route to the intermediary occurring allenylcarbonyl compounds. Treatment of propargyl vinyl ethers 1 with several silver(I) salts at room temperature produced an isomeric mixture of the corresponding allenes in a remarkably clean reaction. By far, the best catalyst was AgSbF₆, which provided the rearrangement products rapidly in CH₂Cl₂. The reaction takes place at room temperature without the formation of significant amounts of any byproducts. Of primary importance, the corresponding furans7 were not seen by 1H NMR analysis of crude reaction mixtures. Low catalyst loadings (1-5 mol)%) are sufficient to effect rearrangement in almost quantitative yield.

As the next step, we attempted to combine the Ag(I)catalyzed propargyl-Claisen rearrangement with condensation and heterocyclization.¹² After formation of the corresponding allenylcarbonyl compound from propargyl vinyl ether **1a** (R¹ = Ph, R² = Me, R³ = H, Y = OEt), using 5 mol % of AgSbF₆ in CH₂Cl₂, 1.5 equiv of aniline was added directly to the reaction mixture followed by 5 mol % of (PPh₃)AuCl to provide pyrrole **3aa** in 71% yield after 30 min at 38 °C (Table 1, entry 1).^{13,14} The Au(I)-catalyzed cyclization was Table 1. Survey of Amines for Pyrrole Synthesis^a

P 	h 1) AgSbF ₆ 2) R ⁴ –NH ₂ 3) (Ph ₃ P)A	(5 mol %), 23 (2) uCl (5 mol % CH ₂ Cl ₂	3 °C), 38 °C Me	R ⁴ Ph 3a
entry	R^4	3	time [min] ^b	yield [%] ^c
1	Ph	aa	30	71
2	p-MeO(C ₆ H ₄)	ab	60	75
3	$p-i\Pr(C_6H_4)$	ac	60	73
4	$p-HO(C_6H_4)$	ad	120	41
5	p-Br(C ₆ H ₄)	ae	75	74
6	$m-Cl(C_6H_4)$	af	60	83
7	$o-i\Pr(C_6H_4)$	ag	60	67
8	$m-O_2N(C_6H_4)$	ah	120	55
9	MeO ₂ C	ai	60	52
10	1-naphthyl	aj	30	72
11 ^d	Ph Eto N Me	^O ak	105	31

^{*a*} Conditions: (1) 0.2 mmol of **1a**, 5 mol % of AgSbF₆, 23 °C, CH₂Cl₂ (0.4 M), 30 min; (2) R⁴-NH₂ (1.5 equiv), 23 °C; (3) 5 mol % (PPh₃)AuCl, 38 °C. ^{*b*} Reaction time for the cyclization (step 3). ^{*c*} Yield of pure product after column chromatography. ^{*d*} Reaction of **1a** with 0.5 equiv of 1,4-phenylenediamine (**2k**).

slowed markedly when carried out at room temperature. In the absence of the catalyst, pyrrole formation was not observed under these conditions. While (PPh₃)AuCl was unreactive, the presence of AgSbF₆ in the reaction mixture led to activation of the Au(I) catalyst by changing the counterion from chloride to hexafluoroantimonate. With optimized reaction conditions in hand [(1) substrate **1**, 5 mol % of AgSbF₆, 23 °C, 30 min, CH₂Cl₂ (0.4 M); (2) R⁴-NH₂, 23 °C; (3) 5 mol % of (PPh₃)AuCl, 38 °C], pentasubstituted pyrroles **3a** were formed in a one-pot reaction in good yields from propargyl vinyl ether **1a** with R⁴ being aryl and heteroaryl substituents (Table 1).¹⁵ Unfortunately, reaction with aliphatic amines (R⁴ = Me, *i*Pr, Bn) did not provide the corresponding pyrroles.

The scope of this domino approach to substituted pyrroles is summarized in Table 2. A broad variety of propargyl vinyl ethers **1** with different substituents R^1 and R^2 was effectively converted into the corresponding pyrroles. The reaction tolerated substitution of the substrate with R^1 and R^2 being both phenyl and alkyl groups.

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⁽¹⁵⁾ General Procedure. Synthesis of **3af**: AgSbF₆ (3.4 mg, 5 mol %) was added to a solution of 1a (50 mg, 0.20 mmol) in CH₂Cl₂ (0.5 mL), and the reaction vial was sealed, protected from light, and stirred at room temperature for 10 min. Then, 3-chloroaniline (39.2 mg, 0.31 mmol, 1.5 equiv) and (Ph_3P)AuCl (5.1 mg, 5 mol %) were added subsequently. The dark reaction mixture was stirred at 38 $^\circ C$ for 1 h (until TLC analysis indicated complete conversion). The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on neutral Al_2O_3 (P/EtOAc = 98/2) gave pyrrole **3af** as a colorless solid (59.0 mg, 0.17 mmol, 83%). $R_f 0.73$ (P/EtOAc = 80/20); ¹H NMR (360 MHz, CDCl₃) δ 1.04 (t, J = 7.2 Hz, 3 H), 2.01 (s, 3 H), 2.31 (s, 3 H), 4.08 (q, J = 7.2Hz, 2 H), 6.88–6.90 (m, 1 H), 7.05–7.06 (m, 1 H), 7.09–7.12 (m, 2 H), 7.15-7.24 (m, 5 H); ¹³C NMR (90.6 MHz, CDCl₃) δ 10.7, 11.1, 14.1, 59.4, 113.4, 117.2, 127.1, 127.2, 127.5, 127.6, 128.2, 129.1, 129.8, 131.2, 132.5, 134.4, 137.9, 139.6, 165.8; IR (cm⁻¹) 2924 (m), 1700 (vs), 1592 (m), 1481 (s), 1380 (m), 1259 (m), 1147 (s), 1069 (m); LRMS (EI) 353 (100%) [M⁺], 324 (26%), 308 (26%), 280 (8%), 244 (15%), 152 (12%); HRMS 353.1182 [353.1183 calcd for C₂₁H₂₀NO₂Cl (M⁺)].





^{*a*} Conditions: (1) 0.2 mmol of **1**, 5 mol % of AgSbF₆, 23 °C, CH₂Cl₂ (0.4 M), 30 min; (2) R⁴-NH₂ (1.5 equiv), 23 °C; (3) 5 mol % (PPh₃)AuCl, 38 °C, 30–240 min. ^{*b*} Yield of pure product after column chromatography. ^{*c*} The methyl ester was used. ^{*d*} With 1.3 mmol of **1e**.

Unfortunately, only pyrroles in which the 5-position bears a methyl group ($\mathbb{R}^3 = \mathbb{H}$) are easily accessible. Although substrate **1k** derived from a secondary propargyl alcohol reacted to pyrrol **3ka** ($\mathbb{R}^3 = \mathbb{M}e$) in 38% yield (eq 1), flexibility at this position remains limited. Surprisingly, the reaction of substrates with $\mathbb{R}^3 = \mathbb{E}t$ and $\mathbb{R}^3 = \mathbb{P}h$ failed to give pyrrole formation, providing instead six-membered heterocycles **4** in moderate yields through 6-*endo* cyclization of the condensation products (eq 2).



The method described above is particularly attractive for assembling 5-methylpyrrole-3-carboxylates **3**, as subsequent functionalization of the methyl group in the 5-position has the potential to access further synthetic applications. Examples to modify the C5-Me include halogenations, alkylations, and Mannich reactions as well as partially practical oxidations to aldehydes.¹⁶ Gratifyingly, we found that 2-iodoxybenzoic acid (IBX)¹⁷ is an excellent reagent for the selective oxidation¹⁸ to generate synthetically useful 5-formyl-pyrroles. Though the IBX oxidation of benzylic positions has been intensively studied with aromatic systems,^{18c} the method is not well established for heteroaromatic systems. For example, oxidation of the 5-methylpyrroles **3ea**, **3ha**, **3af**, and **3gj** with 4 equiv of IBX in DMSO at 110 °C produced the corresponding aldehydes **5** (eq 3).



In summary, a new and simple method for the synthesis of pentasubstituted *N*-aryl pyrroles has been described. The use of acceptor substituted propargyl vinyl ethers as starting materials is particularly convenient as these intermediates can be prepared in high yield by simple PMe₃-catalyzed addition of propargyl alcohols to 2-propynoic acid derivatives.¹⁹ The overall process is useful to generate pharmaceutically interesting pyrroles rapidly and with high diversity. Moreover, the products of the domino reaction can easily be transformed into valuable 5-formylpyrroles by IBX oxidation. We anticipate applications of this concept for the synthesis of further five-membered heterocycles, and applications in total synthesis are currently underway.

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Supporting Information Available: Representative experimental procedures for catalytic pyrrole formation, and copies of ¹H and ¹³C NMR of **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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