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Tetrahedron Letters 46 (2005) 2211–2214

Tetrahedron Letters

Benzannulation of heterocyclic ring systems through coupling of Fischer carbene complexes and heterocycle-bridged enynes

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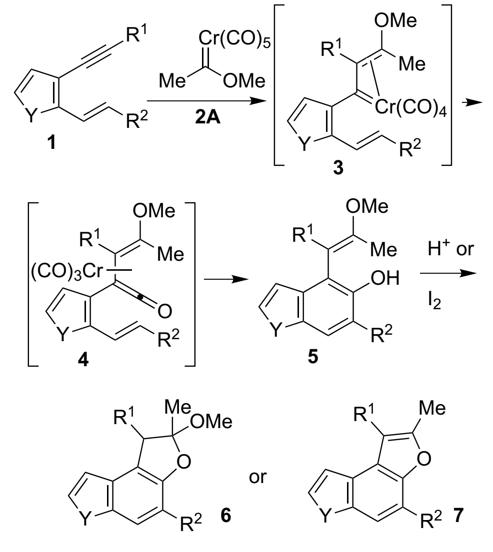
Received 6 August 2004; accepted 7 February 2005

Abstract—An efficient annulation process resulting in heterocyclic rings fused to benzene rings has been discovered. The reaction is highly tolerant of numerous functional groups.

Recently, benzannulation reactions were reported for coupling of conjugated 1,3-hexadien-5-ynes with Fischer carbene complexes.[1] If the central alkene of this system is replaced by a benzene ring, the benzannulation process fails.[2] The focus of this manuscript is to examine the coupling of Fischer carbene complexes with conjugated dienyne systems where the central alkene is contained within a five-membered ring aromatic heterocycle (i.e., furan, thiophene, and imidazole, represented by compound **1** of Scheme 1). Benzannulation is more likely to be successful in these systems (resulting in benzofurans **6** or **7** after acid treatment) due to the lower degree of aromaticity displayed by these ring systems.[3]



Scheme 1.

The reaction in Scheme 1 is a simple method for the synthesis of benzene rings fused to one furan ring and one additional heteroaromatic ring. The benzodifuran ring system is a frequent structural element in antimicrobial,[4] anti-inflammatory,[5] and photobiologically active compounds.[6] Benzofurans can also serve as precursor to biologically important coumarin ring systems.[7] Traditionally these functional groups are most commonly prepared by annulation of a heterocyclic ring onto a pre-existing benzene ring.[8] A less common approach to these ring systems is the annulation of benzene rings onto-preexisting heterocyclic rings. Notable examples of the latter transformation involve coupling of heteroaromatic Fischer carbene complexes with alkynes[9] and thermolysis of 1-heteroarylcyclobutenols.[10] This manuscript focuses on successful execution of the reaction process in Scheme 1 to effect synthesis of these ring systems.

Enyne derivatives used in this investigation were prepared by the general synthetic routes depicted in Scheme 2. Readily available 2,3-dibromofuran,[11] 2,3-dibromothiophene,[12] and N-benzyl-4,5-diiodoimidazole[13] were regioselectively transformed to the corresponding 2-alkenyl-2-alkynylheteroaromatics **1** or 3-alkenyl-2-alkenylheteroaromatics **9**. Since both halogen–metal

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Keywords: Carbene complexes; Alkynes; Benzofurans; Benzannulation.

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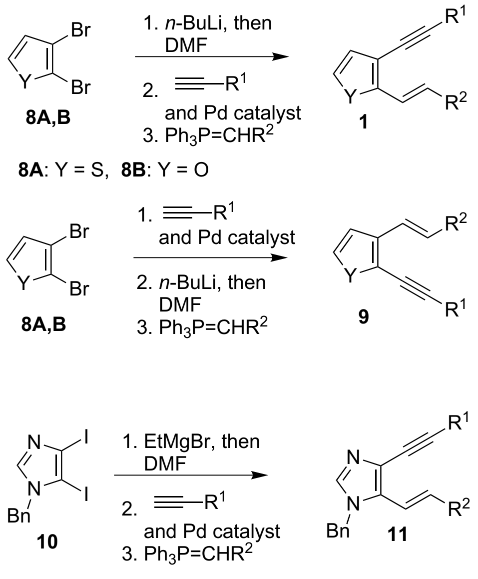
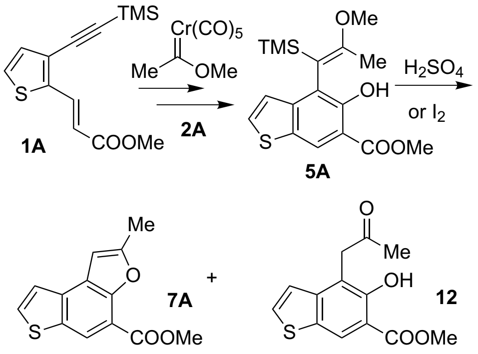
doi:10.1016/j.tetlet.2005.02.037



Scheme 2.



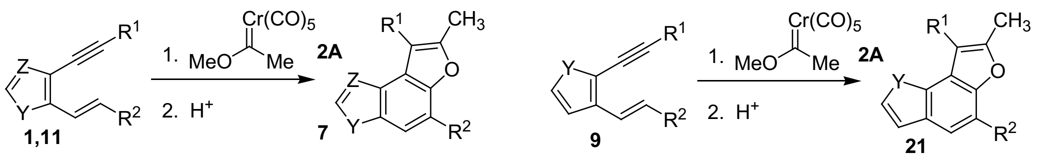
Scheme 3.

exchange and palladium catalyzed couplings[14] are more facile for 2-position of furans and thiophenes, the regiochemistry is set by the order of the formylation and alkynylation steps.

The first reaction tested, coupling of **1A** and **2A** in dioxane at 80 °C, is depicted in Scheme 3. After treatment of the crude reaction mixtures with iodine, a mixture of desilylated benzofuran **7A** and keto-phenol **12** was obtained. Treatment of keto-phenol **12** with catalytic H_2SO_4 effected quantitative conversion to benzofuran **7A**. If the crude reaction mixture from the carbene complex–alkyne coupling was treated with sulfuric acid, benzofuran **7A** was obtained in 79% yield as the only chromatographically mobile product. The coupling of numerous heterocycle-bridged enynes and carbene complexes was tested using optimized reaction conditions (dioxane at 80 °C followed by reaction with sulfuric acid at room temperature) (Table 1). In all cases, benzofuran formation was the exclusive reaction pathway. The reaction proceeds efficiently for regioisomeric compounds of general structure **1** and **9**. Notably lower yields were obtained in the imidazole example (entry J), possibly due to competing coordination of chromium at the imidazole nitrogen.[15] In the reaction in entry H, a slightly higher yield of the product was observed if the pure *trans* isomer was employed. The reaction in entry I is especially interesting. Serious regiochemistry problems were anticipated for this substrate since both sides of the alkyne are of similar steric bulk,[16] however the yield is only slightly lower than for the other examples.

The reaction was also performed in competition with other known chromium carbene–alkyne coupling processes. Reaction of the diyne-ene **13** (Scheme 4) with carbene complex **2A** led exclusively to two-alkyne benzannulation product **14**.[17] Similarly, traditional

Table 1. Coupling of heteroaromatic-bridged enynes with Fischer carbene complex **2A**



Entry	Substrate class	Y	Z	R^1	R^2	Yield **7/21** (%)
A	**1, 11**	S	CH	TMS[a]	COOMe	79
B	**1, 11**	O	CH	TMS[a]	COOMe	89
C	**9**	S	N/A	TMS[a]	COOMe	84
D	**9**	O	N/A	TMS[a]	COOMe	87
E	**1, 11**	S	CH	TMS[a]	H	56
F	**1, 11**	S	CH	TMS[a]	Me	64
G	**1, 11**	S	CH	TMS[a]	Ph	85
H	**1, 11**	S	CH	TMS[a]	CN	74[b,c] (84)[d]
I	**1, 11**	S	CH	Ph	COOMe	51
J	**1, 11**	N-Bn	N	TMS[a]	COOMe	42

[a] In the product, R^1 is H.

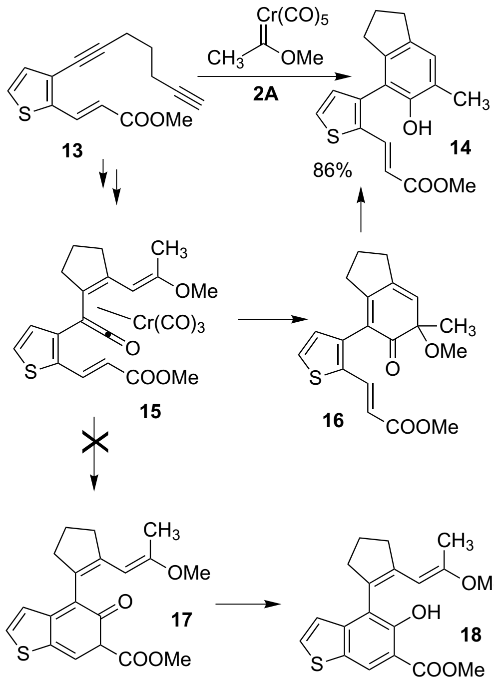
[b] The yield is from using the purified *cis* isomer as the starting material.

[c] For a procedure see Ref. 19.

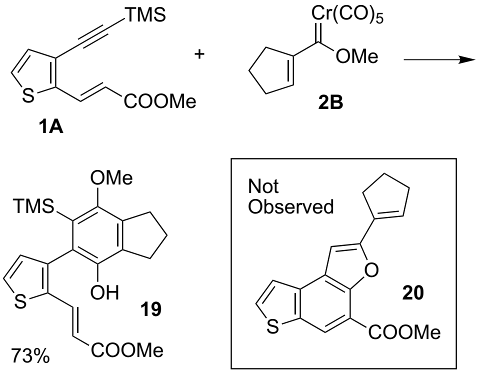
[d] The number in parentheses is the yield using the purified *trans* isomer as the starting material.

benzannulation product **19** (Scheme 5) was the exclusive product from reaction of **1A** with alkenylcarbene complex **2B**.[18] In these cases the intermediate dienylketene (e.g., **15**) can undergo electrocyclic ring closure through either the simple dienylketene system or through the system featuring the heterocyclic ring. Cyclization through the simple dienylketene system was observed, which does not interrupt the aromatic character within the heterocyclic ring system.

In conclusion, benzofuran rings are easily annulated onto furan, thiophene, and imidazole ring systems in a reaction process involving the coupling of Fischer carbene complexes with either 2-alkenyl-3-alkynylheteroaromatic systems 3-alkenyl-2-alkynylheteroaromatic systems. Further studies in additional heterocyclic ring systems are presently under investigation.



Scheme 4.



Scheme 5.

Acknowledgements

This research was supported by the SCORE and RISE programs of NIH.

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19. Experimental for the reaction in entry H: A solution of alkene **1H** (R^1 = TMS, R^2 = CN, *cis* isomer) (161 mg, 0.70 mmol) and carbene complex **2A** (210 mg, 0.84 mmol) in (dioxane 20 mL) was heated at 80 °C under nitrogen for 20 h. The solution was cooled to room temperature and the solvent was removed on a rotary evaporator. The residue was dissolved in 2:1 hexane:ethyl acetate (10 mL) and filtered through Celite to remove chromium residue. After removal of the solvent on a rotary evaporator, dichloromethane (10 mL) and sulfuric acid (0.05 mL) were added and the solution was stirred at room temperature for 3 h. Additional dichloromethane (30 mL) was added and the solution was washed with saturated aqueous sodium bicarbonate solution. The solution was dried over sodium sulfate and the solvent was removed on a rotary evaporator. The residue was purified by flash chromatography on silica gel using 9:1 hexane:ethyl acetate as eluent; a single fraction was isolated. After solvent removal, a white solid (110 mg, 74%) was obtained and identified as compound **7H** (R^1 = H, R^2 = CN). ^{1}H NMR ($CDCl_3$): δ 7.92 (s, 1H), 7.75 (d, 1H, $J = 5.5$), 7.49 (d, 1H, $J = 5.5$), 6.69 (s, 1H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 157.0, 150.8, 135.3, 133.9, 131.6, 124.1, 121.5, 121.3, 115.6, 101.8, 92.9, 14.0, IR (neat): 2222 (m) cm^{-1}; Anal. Calcd for $C_{12}H_7NSO$: C, 67.58; H, 3.32; N, 6.57. Found: C, 67.34; H, 3.71; N, 6.39.