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A New Pyrrole Synthesis via Silver(I)-Catalyzed Cycloaddition of Vinylogous Diazoester and Nitrile

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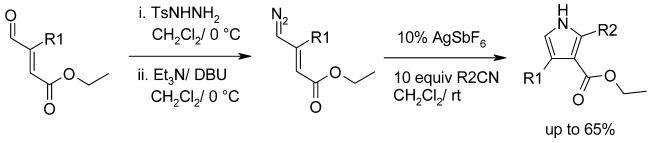
ABSTRACT

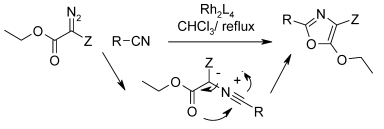


A new synthesis of di- and trisubstituted pyrroles was achieved by treating in situ generated vinylogous diazoesters and readily available nitriles with a catalytic amount of silver(I) antimony hexafluoride at room temperature. This method showcased the potential of utilizing silver(I) carbenoids in preparing heterocyclic compounds.

Pyrroles are an essential structural component of many biologically active natural products and medicines.[1] Since the first reported synthesis of pyrroles,[2] much effort has been devoted to the development of new synthetic methods to prepare functionalized pyrroles with well-defined substitution patterns under mild conditions,[3] some of which were facilitated by metal catalysis.[4]

Inspired by Moody's synthesis of oxazoles using rhodium(II) catalyzed cycloaddition of diazoesters and nitriles (Scheme 1),[5] we conceived a synthetic route to pyrroles via cycloaddition of vinylogous diazoesters and nitriles. (Scheme 2)

Scheme 1. Moody's Oxazole Synthesis via Possible 1,5-Cyclization of Nitrile Ylide



Surprisingly, we found few literature reports on the synthesis, properties, and reactivity of simple vinylogous diazoesters.[6] Therefore, we performed a proof-of-concept

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(1) (a) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilcrist, T. L., Eds; Pergamon: Oxford, 2003; Vol. 15, p 167. (b) Boger, D. L.; Boyce, C. W.; Labrili, M. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (c) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109.

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(5) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761. For selected general reviews of diazo compounds: (a) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.

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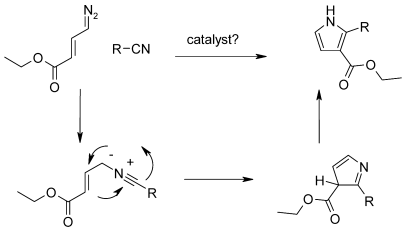
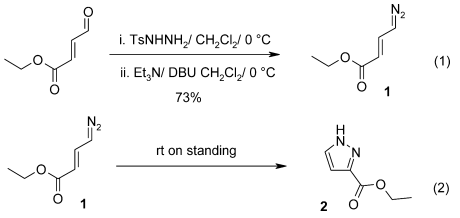
Scheme 2. Proposed Pyrrole Synthesis via 1,5-Cyclization of Vinylogous Nitrile Ylide



experiment to examine whether vinylogous diazoesters could undergo [3 + 2] cycloaddition with a nitrile. For simplicity, (*E*)-5-diazo-pent-3-enoic acid ethyl ester (**1**) was chosen. Diazoester **1** was prepared in one pot by treating (*E*)-4-oxo-but-2-enoic acid ethyl ester with tosyl hydrazine followed by exposure to triethyl amine and DBU (eq 1).[7] After purification, diazoester **1** was found to be stable for weeks when stored below −10 °C either neat or as solution in dichloromethane. However, at room temperature, **1** slowly and cleanly rearranges over days to 1*H*-pyrazole-3-carboxylic acid ethyl ester (**2**) (eq 2).



With diazoester **1** in hand, a variety of Lewis acid catalysts were screened to catalyze its reaction with benzonitrile to form pyrrole **3a**. As can be seen from the results in Table 1, $Rh_2(OAc)_4$ did not promote the desired reaction at room temperature or at reflux in chloroform or toluene. AgOBz was the first catalyst to give a trace amount of the desired product (entry 6). When the more Lewis acidic AgOTf was used, the desired pyrrole product **3a** was obtained in 10% yield at room temperature. When $AgSbF_6$ was used, the yield improved to 62% (entry 9). Interestingly, during our investigation, the use of Ag(I) catalysts was reported by others for cycloaddition reactions with stable diazo compounds and shown to be more effective than Rh(II) catalysts in cyclopropanation[8] and cyclopropenation[9] reactions with donor-/acceptor-substituted diazo compounds. Our results further support the hypothesis[8] that silver carbenoids can provide differerentiated reactivity from more commonly used rhodium carbenoids.

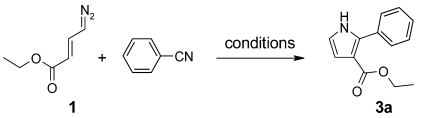
The substrate scope of the reaction catalyzed by $AgSbF_6$ appeared to be quite broad. The reaction worked with both alkyl and aryl nitriles, giving desired pyrroles **3a**−**k** in about 40−60% yields (Table 2). The reaction was tolerant of both electron-rich (entry 4) and electron-deficient aryl nitriles (entry 7). Steric hindrance did not seem to adversely affect the yield as 2,6-dimethyl benzonitrile (entry 8) and *tert*-butyl nitrile (entry 10) gave 64% and 45% of the desired products, respectively, within the general range of this reaction under standard conditions. Further improvement of the yield might be possible with more vigorously anhydrous conditions, assessment of the catalyst loading, and screening of other Ag salts.

(7) Note: in order to minimize decomposition during purification, vacuum concentration of the crude mixture was performed at 0 °C.

(8) Thompson, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090.

(9) Briones, J. F.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 3984.

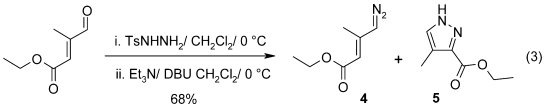
Table 1. Screened Catalytic Conditions To Form Pyrrole **3a** with Diazoester **1** and Benzonitrile[a]



entry	catalyst	solvent	temperature	yield[b] of **3a**
1	$Rh_2(OAc)_4$	$CHCl_3$	rt to reflux	none
2	$Cu(OTf)_2$	$CHCl_3$	reflux	none
3	TMSOTf	$ClCH_2CH_2Cl$	reflux	none
4	$In(OTf)_3$	$CHCl_3$	reflux	none
5	$(Ph_3P)AuOTf$	$CHCl_3$	reflux	none
6	AgOBz	$CHCl_3$	reflux	trace
7	AgOTf	$CHCl_3$	reflux	3%
8	AgOTf	$CHCl_3$	rt	10%
9	$AgSbF_6$	CH_2Cl_2	rt	62%

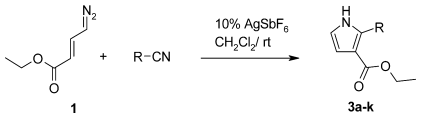
[a] All reactions were carried out by adding 0.1 mmol of diazoester **1** via syringe pump over 1 h into a solution of 1 mmol of benzonitrile and 0.01 mmol of catalyst in 5 mL of respective solvent. [b] Isolated yield.

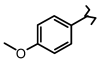
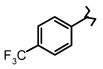
Encouraged by the general reaction scope with diazoester **1** to prepare disubstituted pyrroles, we decided to explore a possible extension to more substituted diazos such as diazoester **4** to make more heavily substituted pyrroles. Though diazoester **4** could be prepared in an analogous fashion as diazoester **1**, it seemed to be much less stable and the isolated product usually contained ~20% of the corresponding cyclized pyrazole **5**.



$AgSbF_6$ was found to be capable of catalyzing similar cycloaddition reactions with diazoester **4** and various nitriles to form trisubstituted pyrroles **6a**−**e**, albeit at lower yields (Table 3). There are multiple factors that could contribute to the lower yields with diazoester **4**: the suboptimal reactivity of the corresponding silver carbenoid, the comparably lower stability of diazoester **4**, and the likelihood of interference by impurity **5**. However, further studies are warranted to fully evaluate the electronic and steric impact of different substituents on the stability and reactivity of these vinylogous diazoesters.

Table 2. $AgSbF_6$ Catalyzed Pyrrole Formation with Diazoester **1** and Various Nitriles[a]

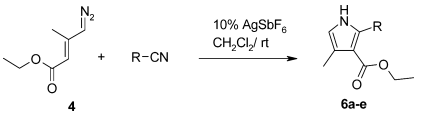


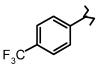
entry	R	product	yield[b] (%)
1		**3a**	62
2		**3b**	53
3		**3c**	57
4		**3d**	42
5		**3e**	42
6		**3f**	36
7		**3g**	54
8		**3h**	64
9		**3i**	46
10		**3j**	45
11		**3k**	46

[a] All reactions were carried out by adding 0.1 mmol of diazoester **1** in 1.25 mL of CH_2Cl_2 via syringe pump over 1 h into a solution of 1 mmol of corresponding nitrile and 0.01 mmol of $AgSbF_6$ in 5 mL of CH_2Cl_2. [b] Isolated yield.

In summary, we have discovered that $AgSbF_6$ can effectively catalyze cycloaddition reactions of vinylogous diazo compounds and readily available nitriles to provide a new synthetic approach to di- and trisubstituted pyrroles. This new reactivity of silver carbenoids may find wider application in preparing other types of pyrroles and other heterocyclic compounds.

Table 3. $AgSbF_6$ Catalyzed Pyrrole Formation with Diazoester **4** and Various Nitriles[a]



entry	R	product	yield[b] (%)
1		**6a**	15
2		**6b**	12
3		**6c**	19
4		**6d**	24
5		**6e**	9

[a] All reactions were carried out by adding 0.1 mmol of diazoester **4** in 1.25 mL of CH_2Cl_2 via syringe pump over 1 h into a solution of 1 mmol of corresponding nitrile and 0.01 mmol of $AgSbF_6$ in 5 mL of CH_2Cl_2. [b] Isolated yield.

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Supporting Information Available. Detailed experimental procedures and full characterization including ^1H NMR, ^{13}C NMR, FTIR, and HRMS for new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.