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Direct synthesis of pyrroles *via* 1,3-dipolar cycloaddition of azomethine ylides with ynones†

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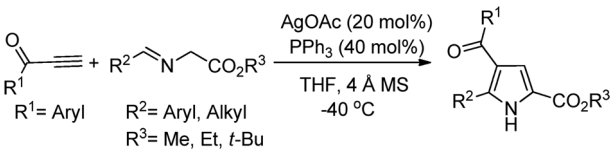
A direct and facile synthesis of multi-substituted pyrroles *via* AgOAc-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with ynones is developed, providing the corresponding adducts in moderate to high yields (up to 89%).

Pyrroles are among the most common and important heteroaromatic compounds, and are found ubiquitously as essential structural motifs in natural products, bioactive compounds, drug molecules and materials.[1,2] For example, Lipitor, as an HMG-CoA reductase inhibitor used to lower LDL cholesterol levels, is the best-selling drug in the past several years, which contains the pyrrole as the core structural unit.[3] The biological importance of pyrroles prompted many research groups to develop new methods for their preparation. The classic synthetic approaches to pyrrole include the Knorr,[4] Paal–Knorr,[5] and Hantzsch[6] syntheses, which routinely involve multistep synthetic operations and suffer from the substrate scope limitation. Recently, many efforts have been devoted to develop novel and highly efficient synthetic protocols for pyrrole synthesis, such as multi-component coupling reactions,[7] transition metal catalyzed cyclizations,[8] cross-metatheses[9] and [3+2] cycloadditions.[10] With regard to the last approach, the cycloaddition of azomethine ylides with both activated alkenes and alkynes has undoubtedly provided the most powerful strategies. Generally, these alkenes should be pre-functionalized with potential leaving groups such as nitro, halogen, sulfone units, which would undergo base-promoted elimination to form pyrroles.[11] As for the reaction with alkynes, in most cases, *in situ* formed azomethine ylides were used for intramolecular 1,3-dipolar cycloaddition, and glycine-derived azomethine ylides have rarely been employed for intermolecular 1,3-dipolar cycloaddition to construct multisubstituted pyrroles.[12]



Scheme 1 AgOAc-catalyzed-1,3-dipolar cycloaddition of azomethine ylides with ynones.

In this context, we would like to report an efficient AgOAc-catalyzed intermolecular 1,3-dipolar cycloaddition of ynones **1** with glycine-derived azomethine ylides **2** to afford a variety of 2,3,5-trisubstituted pyrroles **3** in satisfactory yields (Scheme 1).

Initial study was performed with 1-phenylprop-2-yn-1-one **1a** and iminoester **2a** in the presence of 10 mol% AgOAc in THF at room temperature (Table 1). The reaction proceeded sluggishly and the corresponding product **3aa** was obtained in only 11% yield after 24 h (Table 1, entry 1). The addition of TEA didn't improve the result. Interestingly, when 20 mol% PPh_3 was added as the ligand, the reaction proceeded much faster with a better yield (Table 1, entry 3). The yield of **3aa** was further increased to 41% in the absence of TEA (Table 1, entry 4). Screening both the amount and the ratio of AgOAc and PPh_3 showed that 20 mol% AgOAc and 40 mol% PPh_3 led to the optimal result with 52% yield. It should be noted that the independent use of 1 equivalent of TEA predominantly resulted in the decomposition of **1a** and afforded only trace amounts of the product (Table 1, entry 10).

Next, the variation of crucial reaction parameters, such as metal sources, ligands, solvent, reaction temperature and the catalyst loading, was systematically investigated (Table 2). Screening of various metal salts revealed that AgOAc gave the optimal results and other silver salts were found to be much less active (Table 2, entries 2–4). Copper salts led to moderate to low yield with a prolonged reaction time of 24 h (Table 2, entries 5–7). Iron, zinc, and nickel were inactive under these conditions.

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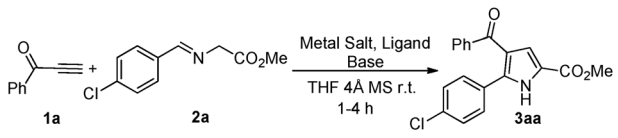
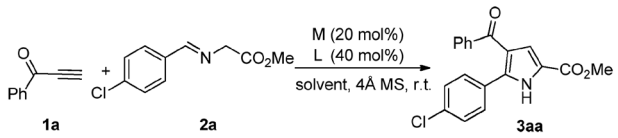
Table 1 1,3-Dipolar cycloaddition of azomethine ylide **2a** with ynone **1a**[a]



Entry	Metal salt (mol%)	Ligand (mol%)	Base (mol%)	Yield[b] (%)
1	AgOAc (10)	—	—	11
2	AgOAc (10)	—	TEA (20)	9
3	AgOAc (10)	PPh_3 (20)	TEA (20)	25
4	AgOAc (10)	PPh_3 (20)	—	41
5	AgOAc (10)	PPh_3 (10)	—	10
6	AgOAc (10)	PPh_3 (30)	—	38
7	AgOAc (10)	PPh_3 (40)	—	38
8	AgOAc (15)	PPh_3 (30)	—	40
9	AgOAc (20)	PPh_3 (40)	—	52
10	—	—	TEA (100)	Trace

[a] All reactions were carried out with 0.30 mmol of **1a** and 0.60 mmol of **2a** in 2 mL of solvent at r.t. [b] Isolated yield.

Table 2 Screening studies of the reaction[a]



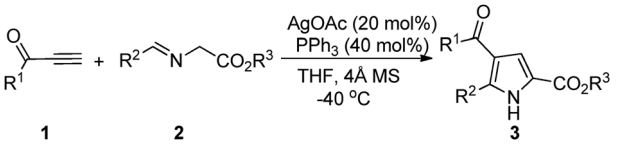
Entry	Metal salt	Ligand	Solvent	Yield[b] (%)
1	AgOAc	PPh_3	THF	52
2	$AgClO_4·H_2O$	PPh_3	THF	27
3	AgOTf	PPh_3	THF	33
4	$AgBF_4$	PPh_3	THF	29
5	CuBr	PPh_3	THF	21
6	$Cu(ClO_4)_2·6H_2O$	PPh_3	THF	25
7	$Cu(acac)_2$	PPh_3	THF	41
8	$CuCl_2·H_2O$	PPh_3	THF	Trace
9	$FeCl_3$	PPh_3	THF	N.P.
10	$Zn(ClO_4)_2·6H_2O$	PPh_3	THF	Trace
11	$Zn(OAc)_2·2H_2O$	PPh_3	THF	N.P.
12	$Ni(OAc)_2·2H_2O$	PPh_3	THF	Trace
13	AgOAc	P(*o*-Tol)$_3$	THF	35
14	AgOAc	PCy_3	THF	24
15	AgOAc	P(*t*-Bu)$_3$	THF	34
16[c]	AgOAc	dppb	THF	47
17[c]	AgOAc	dppf	THF	46
18[c]	AgOAc	2,2′-bpy[e]	THF	30
19[c]	AgOAc	1,10-phen[f]	THF	14
20[c]	AgOAc	(*S*,*S*)-*i*Pr-phosferrox	THF	39
21	AgOAc	PPh_3	CH_3CN	35
22	AgOAc	PPh_3	Toluene	30
23	AgOAc	PPh_3	CH_2Cl_2	17
24	AgOAc	PPh_3	Et_2O	44
25	AgOAc	PPh_3	DMF	10
26	AgOAc	PPh_3	EtOAc	27
27[d]	AgOAc	PPh_3	THF	73
28[d,g]	AgOAc	PPh_3	THF	47

[a] See Table 1. [b] Isolated yields, N.P. means no product observed (TLC analysis). [c] 20 mol% ligand is added. [d] The reaction was carried out at −40 °C. [e] 2,2′-bpy = 2,2′-bipyridine. [f] 1,10-phen = 1,10-phenathroline. [g] 10 mol% AgOAc and 20 mol% PPh_3 were used.

Other ligands, including monophosphine ligands, bisphosphine ligands, diamine ligands and *N,P*-ligands, were found to be inferior to PPh_3 in terms of the yield of **3aa** (Table 2, entries 13–20). The solvent effect was also investigated for this reaction, and THF was found to be optimal for those tried (Table 2, entries 22–26). Lowering the temperature to −20 °C had no positive effect on yield albeit with prolonged reaction time. Pleasingly, when the reaction was conducted at −40 °C, a remarkable improvement in the yield of **3aa** could be obtained (73% yield, Table 2, entry 28). Further lowering the temperature to −78 °C led to lower yield.

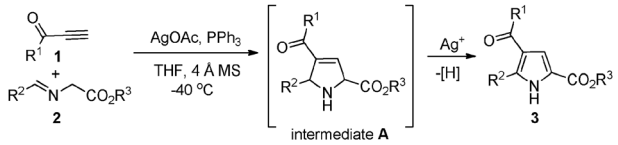
The above optimization led to AgOAc (20 mol%)/PPh_3 (40 mol%)/THF/4 Å molecular sieve (MS)/−40 °C as the optimal reaction conditions for this 1,3-dipolar cycloaddition reaction, and the scope and generality of substrates were then examined. As shown in Table 3, a wide array of ynones **1**, bearing both electron-rich and -deficient groups, reacted smoothly with iminoester **2a** affording the corresponding pyrrole adducts exclusively in good yields (Table 3, entries 1–10). Notably, heteroaromatic substrate **1j** was also tolerated in this reaction (Table 3, entry 11). Various iminoesters were also evaluated as viable substrates for this reaction. It appeared that the position and the electronic property of the substituents on the aromatic rings of the iminoesters had a very minor effect on the yields. What's more, the variation in the ester moiety of iminoesters from the methyl group to the ethyl or the more hindered *t*-butyl group had no influence on the yield (Table 3, entries 12 and 13). However, when the iminoester **2j** derived from aliphatic aldehyde was employed, the yield of the corresponding product **3aj** dropped dramatically to 31% (Table 3, entry 23). It is noteworthy that comparable results were still

Table 3 Substrate scope of 1,3-dipolar cycloaddition of various azomethine ylides **2** with ynones **1a**[a]



Entry	R^1	R^2/R^3	Yield[b] (%)	*t* (h)
1	C_6H_5 (**1a**)	4-ClC_6H_4/Me (**2a**)	73	30
2	4-ClC_6H_4 (**1b**)	4-ClC_6H_4/Me (**2a**)	63	20
3	4-$NO_2C_6H_4$ (**1c**)	4-ClC_6H_4/Me (**2a**)	71	20
4	3-BrC_6H_4 (**1d**)	4-ClC_6H_4/Me (**2a**)	69	20
5	2-FC_6H_4 (**1e**)	4-ClC_6H_4/Me (**2a**)	67	20
6	2-MeC_6H_4 (**1f**)	4-ClC_6H_4/Me (**2a**)	62	48
7	2,4-MeC_6H_3 (**1g**)	4-ClC_6H_4/Me (**2a**)	53	48
8	4-$MeOC_6H_4$ (**1h**)	4-ClC_6H_4/Me (**2a**)	80	48
9[c]	4-$MeOC_6H_4$ (**1h**)	4-ClC_6H_4/Me (**2a**)	51	48
10	4-MeC_6H_4 (**1i**)	4-ClC_6H_4/Me (**2a**)	65	48
11	2-Furyl (**1j**)	4-ClC_6H_4/Me (**2a**)	68	20
12	C_6H_5 (**1a**)	4-ClC_6H_4/Et (**2b**)	69	12
13	C_6H_5 (**1a**)	4-ClC_6H_4/*t*-Bu (**2c**)	69	12
14	C_6H_5 (**1a**)	C_6H_5/Me (**2d**)	82	20
15[c]	C_6H_5 (**1a**)	C_6H_5/Me (**2d**)	61	20
16	C_6H_5 (**1a**)	4-BrC_6H_4/Me (**2e**)	79	20
17	C_6H_5 (**1a**)	2-ClC_6H_4/Me (**2f**)	89	20
18[c]	C_6H_5 (**1a**)	2-ClC_6H_4/Me (**2f**)	79	20
19	C_6H_5 (**1a**)	3-BrC_6H_4/Me (**2g**)	72	20
20	C_6H_5 (**1a**)	4-MeC_6H_4/Me (**2h**)	76	30
21	C_6H_5 (**1a**)	2-MeC_6H_4/Me (**2i**)	82	30
22[c]	C_6H_5 (**1a**)	2-MeC_6H_4/Me (**2i**)	63	30
23	C_6H_5 (**1a**)	Cy/Me (**2j**)	31	30

[a] Conditions: AgOAc (20 mol%), PPh_3 (40 mol%), THF, 4 Å MS, −40 °C. [b] Isolated yields. [c] 10 mol% AgOAc and 20 mol% PPh_3 were used.



Scheme 2 A plausible mechanism of the synthesis of pyrroles *via* 1,3-dipolar cycloaddition of azomethine ylides with ynones.

achieved for some substrates when the catalyst loading was decreased to 10 mol% (Table 3, entries 9, 15, 18, and 22).

Due to the fact that silver mirror was found after the completion of the reaction, we speculate the possible pathway for this transformation although we failed to isolate the key intermediate dihydropyrrole **A**. The dihydropyrrole molecules **A** were formed first *via* AgOAc-catalyzed 1,3-dipolar cycloaddition followed by a fast silver-catalyzed dehydrogenation process to afford the corresponding pyrrole products (Scheme 2).[12,13]

Conclusions

In summary, we have developed an efficient protocol for the synthesis of 2,3,5-trisubstituted pyrroles *via* AgOAc-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with ynones in good yields (up to 89%). A possible reaction pathway for this one-pot pyrroles preparation was proposed. Further application of this novel method is still ongoing in our laboratory.

General procedure for AgOAc catalyzed 1,3-dipolar cycloaddition of azomethine ylides with ynones

Under a N_2 atmosphere, AgOAc (10 mg, 0.06 mmol), PPh_3 (31.5 mg, 0.12 mmol) and activated 4 Å MS were dissolved in 2 mL anhydrous THF and stirred at room temperature for about 1 h. Iminoesters **2** (0.6 mmol) were added and after the reaction temperature was reduced to −40 °C, ynones **1** (0.3 mmol) were added. Once starting material was consumed (monitored by TLC), the mixture was concentrated to dryness and then the residue was purified by column chromatography to give the corresponding products **3**.

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