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FULL PAPER

Silver-Catalyzed [3+2] Cycloaddition of Azomethine Ylides with Isocyanides for Imidazole Synthesis

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Abstract. A silver-catalyzed aerobic oxidative [3+2]	this cycloaddition was shown by a gram-scale synthesis and
cycloaddition of azomethine ylides with aryl or heteroaryl	a double cycloaddition for the construction of highly
isocyanides was developed. The reaction represents a novel	conjugated polyarylimidazole systems.
protocol for the efficient and practical synthesis of 1,2-diaryl	
imidazoles bearing a broad range of substituents in good to	Keywords: azomethine ylides; [3+2] cycloaddition;
excellent yields under mild conditions. The practicability of	imidazoles; isocyanides; silver catalysis

Introduction

Imidazoles make up an important class of fivemembered azaheterocycles with significant biological activities.^[1] Among their derivatives, 12 diarylimidazoles show a broad range of biological activities. Some of these compounds have been used as antagonists of the cannabinoid CB_1 receptor,^[2] selective inhibitors of COX-2,^[3] clozapine-like mixed activities at dopamine D₂, serotonin and GABA_A receptors.^[4,5] Considerable attention has therefore been focused on the synthesis of these privileged scaffolds.^[2-8] Generally, sequential alkylation/cyclization/dehydration reactions of diarylamidines and 2-halomethylketones (or analogs) are used for the synthesis of 1,2-diarylimidazoles.^{[2-} ^{4,6c-f]} The annulation of *N*-chloro-*N'*-arylbenzamidines and electron-rich alkenes provides an alternative method for synthesizing these frameworks.^[7] Recently, N-arylation of 2-aryl imidazoles^[6a,b,8] and C2-arylation of N-aryl imidazoles^[6a,b,9] have been used to prepare these compounds. However, most of these methods suffer from drawbacks such as lack of readily available precursors, low overall yields or regioselectivity issues. The development of efficient, regiospecific, and general methods for the synthesis of 1,2-diarylimidazoles from readily available starting materials is therefore still needed.

1,3-Dipolar cycloadditions are fundamental organic reactions for the construction of fivemembered heterocycles.^[10] In this context,

azomethine ylides are versatile nitrogen-based 1,3dipoles employed in dipolar cycloadditions.^[10,11] In particular, the reaction of azomethine ylides with alkenes provides a powerful method for both racemic and asymmetric syntheses of pyrrolidines with up to four contiguous stereocenters (Scheme 1, eq 1).^[11,12] Electron-deficient alkenes^[11,12] and alkynes^[11,13] are the most widely used dipolarophiles in such cycloadditions. However, only a few examples involving heteroatom-containing dipolarophiles such as imines^[14] and aldehydes^[15] have been reported (Scheme 1, eq 2). In 2012, Hashmi and co-workers reported the use of Au(I) isocyanide complexes as dipolarophiles in [3+2] cycloaddition with azomethine ylides for the synthesis of saturated NHC-Au(I) complexes (Scheme 1, eq 3).^[16] In addition, a [3+1] cycloaddition of azomethine ylides with isocyanides was developed by Foucaud and coworkers,^[17] and a Lewis acid-catalyzed [3+1+1] cycloaddition involving azomethine ylides and aliphatic isocyanides was reported by Soeta, Ukaji and co-workers.^[18] Although the syntheses of imidazolidines^[14] and saturated NHC-Au(I) complexes^[16] via cycloaddition of azomethine ylides have been documented (Scheme 1, eq 2 and 3), the catalytic synthesis of imidazoles from the cycloaddition of azomethine ylides and isocyanides has not been reported.^[19] During the course of our studies of isocyanide-based annulations^[20] and inspired by Hashmi's work,^[16] we developed a onestep silver-catalyzed aerobic oxidative 1,3-dipolar cycloaddition of azomethine ylides with isocyanides

for the efficient and practical synthesis of 1,2diarylimidazoles (Scheme 1, eq 3). Cyclizations of isocyanides with activated methylene isocyanides^[21] or propargylamines^[22] have recently been reported for the synthesis of 2-unsubstituted imidazoles. This [3+2] cycloaddition not only represents a novel, simple, and general approach for the synthesis of imidazoles with a wide range of substituents at the 2-position, but also considerably expands the scope of azomethine ylidebased 1,3-dipolar cycloadditions.



Scheme 1. Cycloadditions of azomethine ylides.

Results and Discussion

Initially, the reaction of imino ester 1a with 4benzoyl phenyl isocyanide 2a was used as a model reaction to optimize the reaction conditions (Table 1). Under catalysis with Ag₂CO₃ (30 mol%), the reaction of 1a (0.36 mmol) and 2a (0.3 mmol) gave imidazole **3aa** in 34% yield after stirring for 26 h at room temperature in 1,4-dioxane (Table 1, entry 1). When the reaction temperature was elevated to 40 °C, the yield of 3aa increased to 85% (Table 1, entry 2). However, when the temperature was further elevated to 60 °C, silver mirror was observed and 3aa was obtained in 38% yield even when the reaction time was prolonged to 12 h (Table 1, entry 3). This result is consistent with Bi's finding that one equivalent of Ag_2CO_3 was needed when the reaction was performed at higher temperatures.^[19] Decreasing the amount of Ag₂CO₃ to 20 mol% led to a lower yield (Table 1, entry 4). Selected solvents, i.e., THF, acetonitrile, 1,2-dichloroethane and toluene were examined, but all gave 3aa in lower yields (Table 1, entries 5-8). AgOAc (Table 1, entry 9), AgNO₃ (Table 1, entry 10), AgF (Table 1, entry 11), Ag₂O (Table 1, entry 12), Cu₂O (Table 1, entry 13) and CuCl (Table 1, entry 14), were less effective catalysts than Ag_2CO_3 . Gold catalysts such as [IPrAu]Cl (IPr = 1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene), AuCl(PPh₃) and Au₂O₃ were also screened (Table 1, entries 15–17); imidazole **3aa** was not detected, and hydrolysis of both isocyanide **2a** and imino ester **1a** was observed.

Table 1. Optimization of Reaction Conditions^[a].

Ph	N CO ₂ Et +	C catalyst P (30 mol %) solvent temperature time		t Ph	N CO ₂ Et
En	Cat Za	Sol	Temn	4 Time	Vield
Liii.	Cut.	501.	(°C)	(h)	(%) ^[b]
1	Ag ₂ CO ₃	1,4-dioxane	25	26	34
2	Ag ₂ CO ₃	1,4-dioxane	40	8	85
3	Ag ₂ CO ₃	1,4-dioxane	60	12	38
4	Ag ₂ CO ₃	1,4-dioxane	40	18	78 ^[c]
5	Ag ₂ CO ₃	THF	40	6	70
6	Ag ₂ CO ₃	CH ₃ CN	40	6	73
7	Ag ₂ CO ₃	DCE	40	3	61
8	Ag ₂ CO ₃	toluene	40	7	60
9	AgOAc	1,4-dioxane	40	13	74
10	AgNO ₃	1,4-dioxane	40	5	8
11	AgF	1,4-dioxane	40	24	48
12	Ag ₂ O	1,4-dioxane	40	24	13 ^[d]
13	Cu ₂ O	1,4-dioxane	40	60	24 ^[e]
14	CuCl	1,4-dioxane	40	48	ND ^[f]
15	[IPrAu]Cl	1,4-dioxane	40	12	ND ^[g]
16	AuCl(PPh ₃)	1,4-dioxane	40	12	ND ^[h]
17	Au ₂ O ₃	1,4-dioxane	40	12	ND ^[i]

^[a] Reaction conditions: 1a (0.36 mmol), 2a (0.3 mmol), Ag₂CO₃ (0.09 mmol), solvent (2 mL), air atmosphere.
^[b] Yield of isolated product.

 $^{[c]}$ Ag₂CO₃ (20 mol%) was used.

^[d] **1a** was recovered in 78% yield.

^[e] **4aa** was obtained in 45% yield.

^[f] ND = not detected.

^[g] [IPrAu]Cl (5 mol%) was used, IPr = 1,3-bis(2,6-

diisopropylphenyl) imidazol-2-ylidene.

^[h] AuCl(PPh₃) (5 mol%) was used.

^[i] Au_2O_3 (5 mol%) was used.

With the optimal conditions in hand (Table 1, entry 2), the scope of viable imino ester substrates 1 was examined; the results are summarized in Scheme 2. A wide range of substrates 1 were tolerated in this reaction, and a series of 2-substituted imidazoles (**3ba-ta**) were produced in good to high yields from the reactions of isocyanide **2a** with a wide range of imino esters 1 bearing various R¹ groups, e.g., *para*-(**1b-e**),^[23] *ortho-* (**1f**), and *meta-* (**1g**) substituted aryls, di- (**1h** and **1i**) and tri- (**1j**) substituted phenyls, 2-naphthyl (**1k**), heteroaryl groups (**1h** and **1n**), 2-ferrocenyl (**1o**), and alkyl groups (**1p** and **1q**). Alkoxycarbonyl-substituted substrates (**1a-r**) and the

cyano-substituted imine 1s were also tolerated in this [3+2] cycloaddition, but the yield of 3sa was low. Reactions of CF₃-substituted imine 1t with isocyanide 2a did not give the corresponding trifluoromethylated imidazole 3ta. This is probably because it is more difficult to form the corresponding azomethine ylide from cyano-substituted imine 1s and CF₃-substituted imine 1t than from ester-substituted imines under these conditions.



Scheme 2. Scope of imino esters 1.

The scope of the reaction was then evaluated with respect to isocyanides 2 (Scheme 3). The reaction tolerated a wide range of aryl and heteroaryl isocyanides 2. Aryl isocyanides 2 with electronwithdrawing, -donating and -neutral groups at the para position gave 2-substituted imidazoles 3ab-af in good to high yields. Aryl isocyanides 2 bearing substituents at the *meta* position, such as PhCO (2g), CO₂Et (2h) and Br (2i) afforded the corresponding imidazoles 3ag-ai in good yields. The orthosubstituted 2-benzoyl- (2j), 2-chloro- (2k), and 2methoxy- (21) aryl isocyanides gave the 2-substituted imidazoles 3aj-al in moderate yields. In the cycloaddition of 1a with 2j, as well as the imidazole product **3aj**, the intermediate (Z)-ethyl 3-[(2benzoylphenyl)amino]-2-[(E)-benzylideneamino]acrylate 4aj was isolated in 35% yield. The structure of **4aj** was determined using X-ray diffraction.^[23] The disubstituted aryl isocyanides 2m and 2n and trisubstituted aryl isocyanides 20 and 2p produced the corresponding 2-substituted imidazoles 3am-ap in good to high yields. In addition, the reactions of α and β -naphthyl isocyanides **2q** and **2r** gave imidazoles **3aq** and **3ar** in high yields. Heteroaryl isocyanides **2s–v** also afforded the corresponding imidazoles **3as–av** in moderate yields. When *tert*-butyl isocyanide and cyclohexyl isocyanide were used in this [3+2] cycloaddition, the desired imidazole products were not detected.



Scheme 3. Scope of isocyanides 2.

Control experiments were performed to clarify the reaction mechanism. The reaction of imino ester **1a** with isocyanide **2a** in a nitrogen atmosphere for 2 h at 40 °C gave intermediate **4aa** in 82% yield (Scheme 4, eq 1); **4aa** was converted to imidazole **3aa** in 92% yield under the standard conditions (Scheme 4, eq 2). These results show that **4aa** is probably the reactive intermediate in this [3+2] cycloaddition reaction. Furthermore, when 2.0 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy or 2,6-di-*tert*-butyl-4-methylphenol were added to the standard reaction, **3aa** was obtained in 55% and 65% yields, respectively (Scheme 4, eq 3), indicating that this transformation probably does not proceed via a radical pathway.

A possible mechanistic pathway based on the present and previously reported results^[21,22] is shown in Scheme 5. Initially, the azomethine ylide dipole **A** is formed by coordination to silver and deprotonation.^[24] Intermediate **A** attacks silver-activated isocyanides **B**, giving the imidoyl-silver intermediate \mathbf{C} .^[22,25] Protonation of **C** generates dipole **D**, which resonates with structure **E**. Two pathways are then possible. In pathway a, intramolecular nucleophilic addition occurs to give dihydroimidazole-silver complex **F**, and protonolysis by AgHCO₃ regenerates the catalyst Ag₂CO₃ and delivers dihydroimidazole **G**,^[26] which produces the final imidazole **3** by aerobic oxidative aromatization.

Alternatively, intermediate E can be reversibly protonated by AgHCO₃ to afford the diamino acrylate intermediate **4** (pathway b).



Scheme 4. Control experiments.



Scheme 5. Proposed mechanism.

To evaluate the practicability of the present [3+2] cycloaddition, a gram-scale synthesis of ethyl 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-4-

imidazole carboxylate **3cw** was performed (Scheme 6, top). Imidazole **3cw** has an enhanced ability to potentiate γ -aminobutyric acid (GABA)-evoked currents in *Xenopus laevis* oocytes expressing recombinant human GABA_A receptors with potency (EC₅₀ = 0.19 µM) and efficacy (388%).^[5] In addition,

double cycloadditions of imino esters **1** with biisocyanides **2x** and **2y** were performed to construct polyarylbiimidazoles **6**, which have extended conjugated systems (Scheme 6, bottom). Biimidazoles **6ax**, **6bx**, **6ex** and **6ay** were obtained in moderate yields under the optimal conditions.



Scheme 6. Gram-scale synthesis and double cycloaddition.

Conclusion

In summary, a silver-catalyzed [3+2] cycloaddition of azomethine ylides with aryl or heteroaryl isocyanides was developed. This new reaction provides a general and efficient strategy for the synthesis of 1,2-diaryl imidazoles in a single operation from readily available starting materials. Unusual reactivity profiles of isocyanides, which acted as dipolarophiles, observed. The practicability were of this cycloaddition was shown by a gram-scale synthesis and double cycloaddition for the construction of polyarylimidazole highly conjugated systems. Investigation of [3+2] cycloaddition of other 1,3dipoles with isocyanides is ongoing.

Experimental Section

Typical Procedure for Synthesis of Imidazole 3aa

Ag₂CO₃ (24.7 mg, 0.09 mmol) was added to a solution of (*E*)-ethyl 2-(benzylideneamino)acetate (**1a**) (68.7 mg, 0.36 mmol) and (4-isocyanophenyl)(phenyl)methanone (**2a**) (62.1 mg, 0.3 mmol) in 1,4-dioxane (2.0 mL) in a sealed tube. The mixture was heated at 40 °C under stirring. TLC indicated that substrate **2a** was consumed in 8 h. The resulting mixture was concentrated in vacuo. Purification of the crude product using flash column chromatography (silica gel; petroleum ether:ethyl acetate = 8:1(v/v)) gave **3aa** (101 mg, 85% yield) as a white solid. m. p. 145–146 °C; ¹H NMR (600 MHz, CDCl₃) δ 1.40 (t, *J* = 7.2 Hz, 3H), 4.42 (q, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.31–7.34 (m, 3H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 2H), 7.89 (s, 1H); ¹³C NMR (CDCl₃, 151 MHz) δ 14.4, 60.7, 125.3, 127.8, 128.3, 128.4,

128.9, 129.1, 129.3, 129.8, 131.3, 132.8, 134.0, 136.7, 137.5, 140.6, 147.7, 162.7, 195.0; HRMS (ESI-TOF) m/z calculated for $C_{25}H_{21}N_2O_3^+$ ([M+H]+) 397.1547, found 397.1564.

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FULL PAPER

Silver-Catalyzed [3+2] Cycloaddition of Azomethine Ylides with Isocyanides for Imidazole Synthesis

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R ¹ N EWG + R ² -NC	[3+2] cycloaddition	EWG	
	Ag ₂ CO ₃ (30 mol %) 1,4-dioxane, air, 40 °C	$R^1 \xrightarrow{N} R^2$	
EWG = electron-withdrawing group		40 examples up to 98% yield	