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Silica-supported zinc bromide (ZnBr₂/SiO₂): a highly efficient heterogeneous catalyst for coupling acid chlorides with terminal alkynes

vent-free conditions at room temperature.

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ABSTRACT

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1. Introduction

Ynones are compounds of considerable synthetic interest because of their occurrence in a wide variety of biologically active molecules and as key synthetic intermediates.¹ Their role as synthetic intermediates is important for the preparation of numerous biologically active heterocyclic compounds.²

The preparation of ynones typically involves the reaction of alkynyl organometallic reagents of silver,³ copper,⁴ sodium,⁵ lithium,⁶ cadmium,⁷ zinc,⁸ silicon,⁹ or tin¹⁰ with acid chlorides. The combination of copper(I) salts with a tertiary amine is also widely used.¹¹ However, these methods require anhydrous solvents, inert atmospheres, and the use of toxic triethylamine as a solvent or base.^{11a,1c} Most of the reported methods have disadvantages such as low yields, use toxic or expensive reagents, and require long reaction times.

Heterogeneous catalysts have gained significant attraction due to economic and environmental considerations. The catalysts used are generally inexpensive and readily available. They can be handled conveniently and removed from the reaction mixture, thus making experimental procedures simple.

As part of our continuing interest in palladium-catalyzed carbon-carbon cross-coupling reactions, we recently reported the use of heterogeneous and homogeneous Pd-catalysts for coupling reactions at ambient temperature under copper-free conditions.¹² We have extended our studies to the synthesis of ynones by cross-coupling acid chlorides with terminal alkynes in the pres-



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Silica-supported zinc bromide (ZnBr₂/SiO₂) is an efficient heterogeneous catalyst for the rapid synthesis

of ynones by cross-coupling of acid chlorides with terminal alkynes in good to excellent yields under sol-

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Scheme 1. Silica-supported zinc bromide coupling reaction of acyl chlorides with terminal alkynes.

ence of silica-supported zinc bromide (ZnBr₂/SiO₂) under solvent-free conditions (Scheme 1).

Previously, Lee et al. reported the alkynylation of *N*-tosylimines and quinolinium salts with aryl acetylenes promoted by $ZnBr_2$ and *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base) in acetonitrile.¹³ They have also reported the coupling of acid chlorides with terminal alkynes employing $ZnBr_2$ as the catalyst, but utilized an excess of the catalyst (1.2 equiv) in the presence of an organic solvent and a base.¹⁴

Initially, we screened a variety of combinations of solvents and bases as shown in Table 1 using *p*-chlorobenzoyl chloride (**1b**) ($R^1 = 4$ -Cl-C₆H₄-) and phenylacetylene (**2a**) ($R^2 = C_6H_5$ -) as representative examples. *N*,*N*-Dimethylformamide and acetonitrile proved to be good solvents, and among the bases tested, pyridine was the most efficient for this coupling reaction (entries 3 and 8).

To our surprise, the highest yield of product was obtained when the reaction was performed under solvent-free conditions. As shown in Table 1, when the reaction was performed with DIPEA as base, an excellent yield of 98% of the expected product was obtained (entry 11). Consequently, all subsequent reactions were performed neat under anhydrous conditions.



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Table 1

Silica-supported zinc bromide coupling reaction of *p*-chlorobenzoyl chloride (**1b**) with phenylacetylene (**2a**) in the presence of different bases and solvents^a

Entry	Solvent	Base	Yield ^b (%)
1	CH ₃ CN	DIPEA ^c	56
2	CH ₃ CN	Et ₃ N	90
3	CH ₃ CN	Pyridine	92
4	THF	DIPEA	35
5	THF	Et ₃ N	40
6	DMF	DIPEA	73
7	DMF	Et ₃ N	69
8	DMF	Pyridine	89
9	1,4-Dioxane	DIPEA	83
10	1,4-Dioxane	Et₃N	80
11	d	DIPEA	98
12	d	Et₃N	89
13	d	Pyridine	93

^a Reaction conditions: *p*-chlorobenzoyl chloride (1.2 mmol), phenylacetylene (1.0 mmol), base (1.2 mmol), solvent (1 mL), ZnBr₂/SiO₂ (0.1 g), rt.

^b GC vield.

^c Diisopropylethylamine.

^d Solvent-free.

Table 2

Solvent-free coupling reaction of *p*-chlorobenzoyl chloride with phenylacetylene (2a) in the presence of varying amounts of catalyst and over different reaction times^a

Entry	ZnBr ₂ (mmol)	Time (min)	Yield ^b (%)
1	0.24	30	38
2	0.24	60	56
3	0.24	90	91
4	0.24	100	98
5	0.12	120	98
6	0.06	120	65
7	0.03	120	30
8	0.12	150	98

^a Reaction conditions: *p*-chlorobenzoyl chloride (1.2 mmol), phenylacetylene (1.0 mmol), DIPEA (1.2 mmol), catalyst, rt.

^b GC yield.

The conditions with respect to the amount of catalyst and the reaction times, were optimized as shown in Table 2. It was found

Table 3

Solvent-free coupling reactions of various acyl chlorides with terminal alkynes^a

that 0.1 g of $ZnBr_2/SiO_2$ (0.12 mmol $ZnBr_2$) and 120 min (entry 5) were the optimum. Increasing the amount of catalyst shortened the reaction time but did not increase the yield (entry 4). A low concentration of zinc bromide resulted in a decreased yield (entry 7). Increasing the reaction time (entry 8) did not increase the yield of product further.

To examine the scope of this coupling reaction, various benzoyl chlorides **1** containing either electron-withdrawing or electron-donating groups were coupled with different terminal alkynes **2** (Table 3). The results show that this reaction is equally facile with both electron-donating and electron-withdrawing substituents present on the aroyl chloride and affords excellent yields of the corresponding ynones.

In summary, we have developed an efficient method for the synthesis of ynones from the reaction of acid chlorides with 1-alkynes in the presence of DIPEA using ZnBr₂/SiO₂ as catalyst under solvent-free conditions. We believe that the present procedure provides a useful method for the synthesis of ynones which are key intermediates for the preparation of several important biologically active molecules. The simple procedure, short reaction time and excellent isolated yields make this method well-suited for the generation of a combinatorial library of ynones.

2. Preparation of silica-supported zinc bromide

Silica gel (Wakogel C-100, 3.65 g) was added to a solution of $ZnBr_2$ (6 mmol, 1.35 g) in MeOH (20 ml), and the mixture was heated at reflux for 1 h. The solvent was removed on a rotary evaporator and the product was dried under vacuum at 150 °C for 10 h. Inductively coupled plasma atomic absorption spectrometry (ICP) indicated that 1.2 mmol of $ZnBr_2$ was supported on 1 g of $ZnBr_2/SiO_2$.

3. General procedure for the synthesis of ynones

A test-tube was charged with the acyl chloride (1.2 mmol), a terminal alkyne (1.0 mmol), $\text{ZnBr}_2/\text{SiO}_2$ (0.1 g, 0.12 mmol), and DI-PEA (1.2 mmol). The mixture was stirred at room temperature for 2 h under anhydrous conditions. Upon completion of the reaction



(continued on next page)

Table 3 (continued)





Table 3 (continued)

^a Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), DIPEA (1.2 mmol), catalyst (0.12 mmol), rt.

^b GC yield. Isolated yields in parentheses.

(monitored by TLC), the mixture was extracted with EtOAc (3×5 mL). The organic layers were combined and washed with H₂O (2×5 mL) to remove the amine hydrochloride formed during the reaction. The organic layer was separated, dried over anhydrous MgSO₄, filtered, and concentrated under vacuum to give the product which was further purified by column chromatography using hexane/EtOAc (20:1) as eluent.

Compounds **3a**,^{15a} **3b**,^{15b} **3c**,^{15b} **3d**,^{15a} **3e**,^{12c} **3f**,^{15c} **3g**,^{15c} **3h**,^{15c} **3i**,^{15b} **3j**,^{15b} **3h**,^{15b} **3m**,^{15b} **3p**,^{15c} and **3q**,^{15a} are known. Characterization data for ynones **3k**, **3n**, and **3o** are given below.

3.1. 1-(2-Iodophenyl)-3-phenylprop-2-yn-1-one (3k)

IR (KBr): 2198, 1651; ¹H NMR (500 MHz, CDCl₃): δ 7.10–7.52 (m, 7H), 7.70–8.10 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 87.2, 91.4, 119.9, 127.7, 128.8, 130.3, 130.5, 130.7, 132.4, 133.2, 135.5, 144.4, 178.2; Anal. Calcd for C₁₅H₉IO: C, 54.24; H, 2.73; found: C, 54.21; H, 2.82.

3.2. 1-(4-Bromophenyl)-3-phenylprop-2-yn-1-one (3n)

IR (KBr): 2199, 1653; ¹H NMR (500 MHz, CDCl₃): δ 7.43–7.52 (m, 3H), 7.66–7.70 (m, 4H), 8.10–8.13 (m, 2H); ¹³C NMR

(125 MHz, CDCl₃): δ 86.74, 93.79, 119.96, 128.90, 129.68, 131.02, 131.07, 132.08, 133.25, 135.81, 176.85; Anal. Calcd for C₁₅H₉BrO: C, 63.18; H, 3.18; found: C, 63.20; H, 3.15.

3.3. 1-(2,4-Dichlorophenyl)-3-phenylprop-2-yn-1-one (3o)

IR (KBr): 2200, 1663; ¹H NMR (500 MHz, CDCl₃): δ 7.15–7.58 (m, 7H), 8.2 (d, *J* = 8.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 88.2, 92.5, 120.2, 128.9, 130.8, 131.2, 133.1, 135.4, 137.8, 138.2, 139.4, 143.2, 177.5; Anal. Calcd for C₁₅H₈Cl₂O: C, 65.48; H, 2.93; found: C, 65.45; H, 2.91.

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