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Silver-catalyzed ring-opening [3+2] annulation of cyclopropenones with amides†

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A ring-opening [3+2] annulation reaction between cyclopropenones and amides was developed to produce 5-amino-2-furanones. Insertion of the carbonyl group of an amide to the C–C single bond of a cyclopropenone occurred efficiently in the presence of a catalytic amount of silver(I) triflate.

Introduction

Cyclopropenones have fascinated organic chemists since the first synthesis of diphenylcyclopropenone in 1959.[1] Since then, a number of ring opening reactions of cyclopropenones have been developed owing to their intrinsic strained three-membered ring structure.[2] Cyclopropenones undergo, upon treatment with an appropriate promoter, various types of ring-opening annulation. In particular, the ring-opening [3+2] annulation of cyclopropenones has been extensively studied, in which C=N, C=C, C=O, C=S, N=N, N=O, and C≡C bonds couple with cyclopropenones to form five-membered rings.[3,4] Indeed, the insertion of a carbonyl group into a cyclopropenone C–C bond is a straightforward method for synthesizing 2-furanones (butenolides),[4] which are important structural motifs found in various bioactive molecules.[5] However, only ring-opening [3+2] annulation reactions utilizing the carbonyl groups of ketones and esters have been reported,[4] with those based on aldehydes and amides remaining unexplored. Moreover, the reported cyclopropenone–carbonyl coupling was conducted under basic conditions using organic bases like DMAP and DBU as catalysts.[4d,e] A reaction employing a Lewis acidic metal has been only limited to dimerization of cyclopropenones.[4b,c]

We recently reported K_2CO_3-catalyzed ring-opening [3+3]-type annulation of cyclopropenones with *N*-(pivaloyloxy)amides forming 1,3-oxazin-6-ones.[6] In the course of our investigation into novel ring-opening annulation reactions of cyclopropenones[6,7] in the presence of catalytic amounts of rhodium(III) and copper(II) salts,[8] we unexpectedly discovered a [3+2] coupling reaction between a cyclopropenone and *N*,*N*-dimethylformamide (DMF), the latter of which has been employed as a solvent. It was later found that copper(II), not rhodium(III), catalyzed the reaction, which produced a 5-(dimethylamino)-2-furanone through a ring-opening [3+2] annulation. Herein, we report our study into the catalytic ring-opening [3+2] annulation of cyclopropenones with amides for the synthesis of 5-amino-2-furanones. A range of formamides, an acetamide, and a thioformamide were employed for attempted coupling with disubstituted cyclopropenones in the presence of a silver(I) triflate catalyst to afford five-membered products.[9]

Results and discussion

We began by exploring the reaction conditions required for the insertion of an amide carbonyl group into a cyclopropenone C–C single bond. Specifically, at 120 °C, diphenylcyclopropenone (**1a**) reacted with DMF (**2a**, **1a**:**2a** = 1:130) in the presence of 10 mol% $Cu(OAc)_2 \cdot H_2O$ to yield 5-(dimethylamino)-3,4-diphenyl-2-furanone (**3a**) in 21% isolated yield after 4 h (Table 1, entry 1). Upon repeating the reaction in the presence of a gold(I) catalyst, **3a** was afforded in 41% yield (entry 2), and a further significant increase in yield was observed when silver(I) salts were employed as catalysts. Among the various silver(I) salts examined, AgOTf exhibited the highest activity (98% yield) toward the ring-opening annulation (entry 3), followed by $AgNTf_2$ (entry 4, 81% yield). Other acetate, nitrate, and tetrafluoroborate salts gave **3a** in yields of 15–51% (entries 5–8), but no reaction was observed in the presence of Ag_2CO_3 (entry 9). Upon lowering the reaction temperature to 100 °C, **3a** was obtained in 90% yield (entry 10), and a considerable decrease in the yield was observed when the reaction temperature was lowered further to 80 °C (entry 11, 48% yield). In addition, no coupling reaction took place in the absence of metal salts (entry 12), and no coupling was observed

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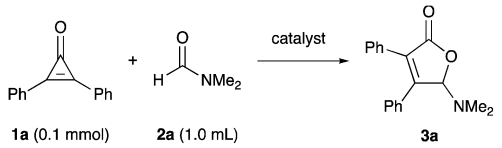
Table 1 Optimization of the reaction conditions

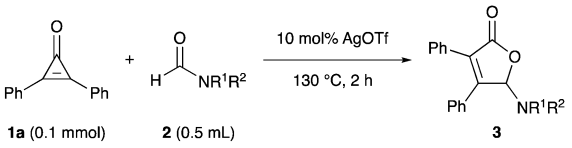


1a (0.1 mmol) 2a (1.0 mL) 3a

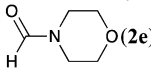
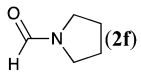
Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield[a] (%)
1	$Cu(OAc)_2{\cdot}H_2O$ (10)	120	4	21
2	$(IPr)AuNTf_2$ (3)	120	3	41
3	AgOTf (10)	120	2	98
4	$AgNTf_2$ (10)	100	2	81
5	$AgOCOCF_3$ (10)	100	2	51
6	AgOAc (10)	100	5.5	29
7	$AgNO_3$ (10)	100	2	28
8	$AgBF_4$ (10)	100	2	15
9	Ag_2CO_3 (5)	100	1	NR
10	AgOTf (10)	100	2	90
11	AgOTf (10)	80	3	48
12	None	120	4	—[b]

[a] Isolated yield. [b] Not detected.

Table 2 Amide scope of the reaction under neat conditions[a]



1a (0.1 mmol) 2 (0.5 mL) 3

Entry	2	3[b] (% yield)
1	$HCONMe_2$ (2a)	3a (95)
2	$HCONEt_2$ (2b)	3b (98)
3	$HCON(i\text{-}Pr)_2$ (2c)	3c (88)
4	HCONMePh (2d)	3d (68)
5	 (2e)	3e (67)
6[c]	 (2f)	3f (12)
7	HCONHMe (2g)	—

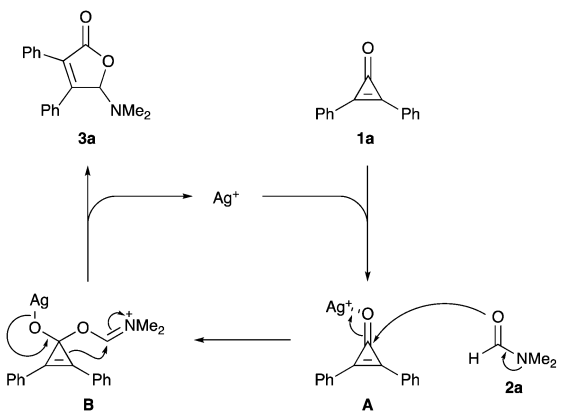
[a] 1a (0.100 mmol) was heated in 2 (0.50 mL) at 130 °C for 2 h in the presence of 10 mol% AgOTf. [b] Isolated yield. [c] 3 h.

at 130 °C in chlorobenzene in the presence of 20 mol% TfOH, thereby indicating that the ring-opening annulation is catalyzed by metal salts rather than by Brønsted acids.[10]

A possible mechanism for the ring-opening [3+2] annulation of cyclopropenone **1a** with amide **2a** was tentatively proposed, as illustrated in Scheme 1. As indicated, following the initial coordination of the carbonyl oxygen atom of **1a** to Ag^+ to generate **A**, the carbonyl oxygen atom of **2a** then attacks the C1 atom of **A** to form intermediate **B**.[11] A final ring expansion step yields the five-membered ring lactone **3a** and concomitantly regenerates Ag^+. Analogous ring expansion step was proposed for other ring-opening reactions of cyclopropenones.[4b,c,12]

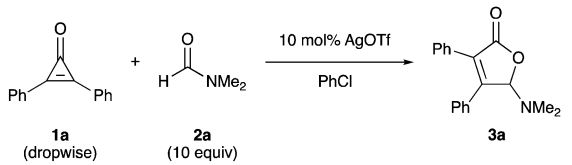
We then examined the reaction of various formamides (**2a–g**) with cyclopropenone **1a** at 130 °C under neat conditions where the amides themselves were present as solvents (Table 2). Thus, the coupling of **1a** with *N*,*N*-dimethyl-, *N*,*N*-diethyl-, and *N*,*N*-diisopropylformamides (**2a–c**) proceeded efficiently to give the corresponding 5-amino-2-furanones (**3a–c**) in excellent yields (entries 1–3). In addition, the reactions of **1a** with *N*-methyl-*N*-phenylformamide (**2d**) and *N*-formylmorpholine (**2e**) delivered **3d** and **3e**, respectively, in acceptable yields (entries 4 and 5), while *N*-formylpyrrolidine (**1f**) gave a low yield (entry 6), and the reaction with secondary formamide **2g** was unsuccessful (entry 7).

As the use of reactants as solvents is not ideal in terms of purification and from an economical view point, we sought to optimize the reaction conditions to incorporate a solvent (Table 3). Thus, the reaction of **1a** and 10 equiv. **2a** at 120 °C in chlorobenzene over 2 h was attempted, and an inseparable mixture of the desired product **3a** and the cyclopropenone dimer, 1,2,6,7-tetraphenyl-4-oxaspiro[2.4]hepta-1,6-dien-5-one was obtained, the latter of which was formed through a pathway involving a radical anion of **1a** (entry 1).[4b,c] However, the dropwise addition of a chlorobenzene solution of **1a** to a chlorobenzene solution of **2a** (10 equiv.) over 3 h followed by additional stirring for 1 h afforded **3a** alone in 37% yield (entry 2). Following a thorough



Scheme 1 Proposed mechanism.

Table 3 Optimization of the reaction conditions in the presence of a solvent[a]

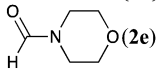
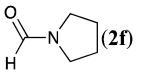


1a (dropwise) 2a (10 equiv) 3a

Entry	Concentration of 1a in PhCl (M)	Temp. (°C)	Dropping time of 1a (min)	Additional reaction time (min)	Yield[b] (%)
1	—	120	0	120	—[c]
2	0.5	120	180	60	37
3	0.25	120	80	40	74
4	0.25	120	40	80	55
5	0.25	130	80	40	97

[a] A solution of 1a (0.100 mmol) in PhCl (0.20 or 0.40 mL) was added to a solution of 2a (1.00 mmol) in PhCl (0.20 mL). [b] Isolated yield. [c] Formation of an inseparable mixture of 3a and 1,2,6,7-tetraphenyl-4-oxaspiro[2.4]hepta-1,6-dien-5-one.

Table 4 Amide scope of reaction in the presence of a solvent[a]

Entry	2	3 (% yield with 10/20 equiv. of 2)[b]
1	$HCONMe_2$ (**2a**)	**3a** (97/98)
2	$HCONEt_2$ (**2b**)	**3b** (76/79)
3	$HCON(i\text{-}Pr)_2$ (**2c**)	**3c** (59/56)
4	HCONMePh (**2d**)	**3d** (32/55)
5	 (**2e**)	**3e** (59/73)
6	 (**2f**)	**3f** (92/96)
7	HCONHMe (**2g**)	**3g** (31/34)
8	$HCONBn_2$ (**2h**)	**3h** (50/68)

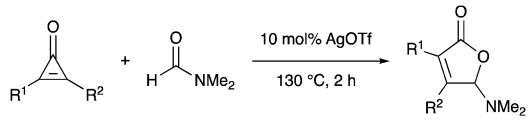
[a] A solution of **1a** (0.100 mmol) in PhCl (0.40 mL) was added dropwise to a solution of **2** (1.00 or 2.0 mmol) in PhCl (0.20 mL) over 80 min and the mixture was stirred for 40 min at this same temperature. [b] Isolated yield.

optimization of the reaction conditions, **3a** was obtained in 97% yield by the dropwise addition of a 0.25 M chlorobenzene solution of **1** to a chlorobenzene solution of **2a** over 80 min at 130 °C followed by stirring for 40 min at 130 °C (entry 5).

The amide scope of the reaction was then investigated, with formamides **2a–h** being subjected to the coupling reaction with **1a** in the presence of chlorobenzene at 130 °C (Table 4). In general, 10 equiv. of each formamide was sufficient to achieve yields comparable to those obtained under neat conditions, although reaction with **2d**, **2e**, and **2h**, required the use of 20 equiv. of the corresponding formamides (entries 4, 5, and 8). These solvent-based conditions were found to be more sensitive to the bulkiness of the *N*-substituents of **2** compared to the neat conditions (entries 1–3). While the reaction of **1a** with pyrrolidine **2f** under neat conditions gave **3f** in a poor yield of 12%, in the presence of chlorobenzene, **3f** was obtained in yields of 92 and 96% (10 and 20 equiv., entry 6). In addition, the reaction using secondary amide **2g**, which was unsuccessful under neat conditions, afforded the desired product **3g** in yields of 31 and 34% (10 and 20 equiv., entry 7). We also found that solid *N*,*N*-dibenzylformamide (**2h**) participated in the coupling reaction (entry 8), but no such coupling was observed with *N*,*N*-diphenylformamide.

The cyclopropenone scope for the ring-opening annulation was also examined under both the neat and solvent-based conditions (Table 5). As indicated, cyclopropenones **1b**, **1c**, and **1d** bearing 4-methylphenyl, 4-methoxyphenyl, and 3-nitrophenyl groups, respectively, provided the corresponding annulation products **3i–k** (entries 1–3), and the use of di(2-thienyl)cyclopropenone **1e** was also tolerated (entry 4). For the reaction of unsymmetrical cyclopropenone **1f**, a regioselective reaction took place to furnish a single isomer **3m** (entry 5).

Table 5 Cyclopropenone scope for the reaction[a]



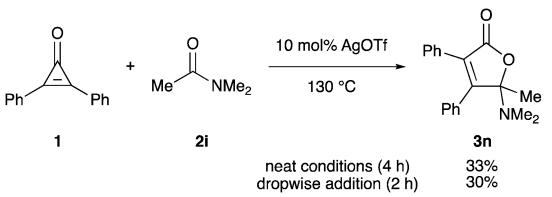
Entry	1	3	% yield[b] under neat conditions	% yield[b] in the presence of solvent
1	**1b** ($R^1 = R^2 = 4\text{-}MeC_6H_4$)	**3i**	81	81
2	**1c** ($R^1 = R^2 = 4\text{-}MeOC_6H_4$)	**3j**	77	67[c]
3	**1d** ($R^1 = R^2 = 3\text{-}(O_2N)C_6H_4$)	**3k**	69	—[d]
4	**1e** ($R^1 = R^2$ = 2-thienyl)	**3l**	87	93
5	**1f** (R^1 = Me, R^2 = Ph)	**3m**	77	87[e]

[a] Neat conditions: **1** (0.10 mmol) and **2a** (0.50 mL); solvent-based conditions: **1** (0.10 mmol) and **2a** (20 equiv.) in PhCl, unless otherwise noted. [b] Isolated yield. [c] A 1,1,2,2-tetrachloroethane solution of **1c** was added to a PhCl solution of **2a**. [d] Not examined due to the low solubility of **1d** in PhCl. [e] 10 equiv. of **2a** was used.

To expand the scope of the silver(I)-catalyzed [3+2] annulation of **1**, various coupling partners bearing a carbonyl group were screened. Specifically, *N*,*N*-dimethylacetamide (**2i**) was found to be a viable but less reactive coupling partner, with the reaction affording the desired annulation product **3n** in yields of 33 and 30% (neat and solvent-based conditions, Scheme 2). All attempts to improve the yield of **3n** failed.

Other amides, including propanamide and 2-pyrrolidinone, failed to couple with **1** under our conditions (Chart 1). Moreover, as indicated, a 2-oxazolidone, a carbamoyl chloride, a urea, a formate, and an aldehyde were all also unreactive in the [3+2] annulation, thereby indicating that the present reaction was only applicable to a narrow range of acyclic amides.

Continuing our investigation into possible coupling partners for the annulation reaction revealed that *N*,*N*-dimethylthioformamide (**2j**) reacts with **1a** under similar conditions (Scheme 3).[13] The reaction of **1a** with **2j** at 130 °C in chlorobenzene in the presence of a catalytic amount of AgOTf resulted in the formation of the expected [3+2] annulation product **3o**, accompanied by the same



Scheme 2 [3+2] Annulation of **1** with *N*,*N*-dimethylacetamide (**2i**).

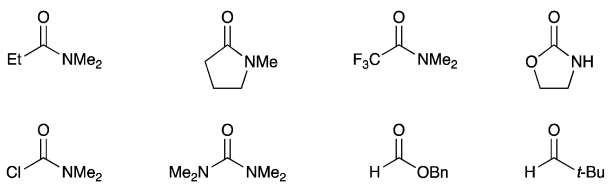
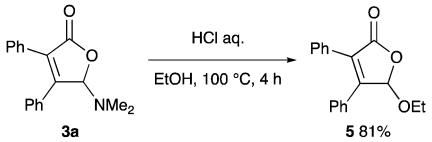


Chart 1 Unsuccessful substrates.

Scheme 3 [3+2] Annulation of **1** with *N*,*N*-dimethylthioformamide (**2j**).



Scheme 4 Reaction of **3a** with HCl.

amount of **4**, which lacked the dimethylamino group.[14] Details regarding the observed reductive deamination remain unclear.

Finally, we demonstrated a derivatization of the [3+2] annulation products. Upon heating 5-amino-2-furanone **3a** at 100 °C in ethanol in the presence of HCl, clean conversion to 5-ethoxy-2-furanone **5** was achieved in 81% isolated yield (Scheme 4).[15]

Conclusions

We successfully developed a silver(I)-catalyzed ring-opening [3+2] annulation of cyclopropenones with amides to afford 5-amino-2-furanones. This reaction was based on insertion of the carbonyl group of an amide into the C–C single bond of a cyclopropenone. The present work adds to the synthetic repertoire of 2-furanones as well as to the organic transformations of *N*,*N*-dimethylformamide.[16]

Experimental

General procedure for the silver(I)-catalyzed ring-opening annulation of cyclopropenones 1 with amides 2: neat conditions

A Schlenk tube was charged with AgOTf (0.010 mmol) and cyclopropenone **1** (0.10 mmol), and the tube was evacuated and backfilled with nitrogen. Amide **2** (0.50 mL) was added *via* a syringe through the septum, and the mixture was heated at 130 °C for 2 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica gel eluting with hexane–AcOEt, and the filtrate was concentrated. The residue was purified by preparative TLC or column chromatography on silica gel to afford furan-2(5*H*)-one **3**.

Dropwise addition

A Schlenk tube was charged with AgOTf (0.010 mmol), and the tube was evacuated and backfilled with nitrogen. Amide **2** (1.00 or 2.00 mmol) and chlorobenzene (0.20 mL) were added successively *via* a syringe through the septum, and the mixture was heated at 130 °C. To the mixture was added dropwise a solution of cyclopropenone **1** (0.10 mmol) in chlorobenzene (0.40 mL) over 80 min, and the resulting solution was further heated for 40 min. After cooling to room temperature, the reaction mixture was filtered through a plug of silica gel eluting with hexane–AcOEt, and the filtrate was concentrated. The residue was purified by preparative TLC or column chromatography on silica gel to afford furan-2(5*H*)-one **3**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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