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Regioselective Reversal in the Cyclization of 2-Diazo-3,5-dioxo-6-ynoates (Ynones, Ynamide): Construction of γ-Pyrones and 3(2*H*)-Furanones Starting from Identical Materials

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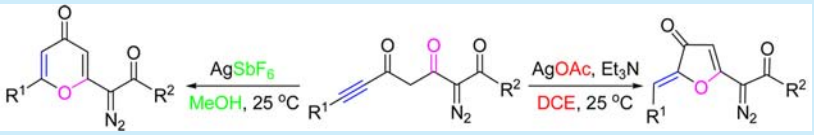
Supporting Information

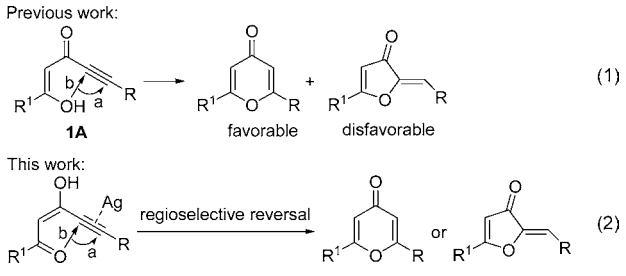


ABSTRACT: The $AgSbF_6$-catalyzed cyclization of 2-diazo-3,5-dioxo-6-ynoates (ynones, ynamide) in alcoholic solvents affords γ-pyrones, whereas the AgOAc-catalyzed cyclization in 1,2-dichloroethane (DCE) produces 3(2*H*)-furanones. The cyclization reactions proceeded cleanly under mild reaction conditions, and the desired γ-pyrones or 3(2*H*)-furanones were obtained in excellent yield. It was observed for the first time that both the catalyst and solvent play key roles in the selective formation. This unique method for the reversal of regioselectivity proved to be highly efficient except for substrates with aliphatic and Me_3Si groups at the triple bond position.

γ-Pyrones and 3(2*H*)-furanones are two types of very important heterocyclic compounds, which have been widely exploited due to their extensive biological and pharmacological activities,[1,2] their existence in many natural products,[3,4] and highly useful building blocks in organic synthesis.[5,6] Synthesis of γ-pyrones and 3(2*H*)-furanones have been widely studied, and many improvements have been made.[7−10] However, they generally suffer from some drawbacks such as nonatom economy, derivation from different raw material, and unusual reaction conditions incompatible with various functional groups. Therefore, the development of their simple and efficient synthesis is an important target in current organic synthesis.

Based on these considerations, a disclosed protocol for the straightforward construction of the two type of compounds starting from identical 1,3-dicarbonyl precursors **1A** may be of interest as described in Scheme 1. However, in general, the internal nucleophilic addition gave a relatively favorable γ-pyrones *via* 6-*endo*-dig cyclization (Scheme 1, eq 1, path a),[9] while a substantial amount of 3(2*H*)-furanones, formed *via* 5-*exo*-dig cyclization (Scheme 1, eq 1, path b), is also observed.[10] In addition, the regioselectivity in the cyclization was moderately to strongly influenced by the substituents R at the acetylenic moiety and R^1 at the carbonyl moiety. Moreover, attempts to mainly prepare 3(2*H*)-furanones in this way have been unsuccessful. Thus, this method faces one fundamental challenge: how to control regioselectivity at the two positions of the carbon−carbon triple bond, such that either a γ-pyrone or 3(2*H*)-furanone unit can be accessed with high fidelity.

Scheme 1. Protocol for the Synthesis of γ-Pyrones and 3(2*H*)-Furanones



On the other hand, the regioselective reversal in cyclization based on subtle catalyst and solvent selection, which creates the two distinct types of important molecules from identical starting materials, is of interest and has become another challenge in modern synthesis. Similar studies have rarely been reported.[11] As a continuation of our interest in exploration of regioselective reversal in organic reactions[12] and the cyclization of 2-diazo-3,5-dioxo-6-ynoates (ynones),[13] herein, we present our recent results on the catalyst and solvent-controlled regioselective reversal in the cyclization of these ynoates (ynones, ynamide) (Scheme 1, eq 2).

The first set of reactions was carried out by using ethyl 2-diazo-3,5-dioxo-7-*p*-tolylhept-6-ynoate **1b** as a model system at 25 °C. Different catalysts were tested in dry 1,2-dichloroethane

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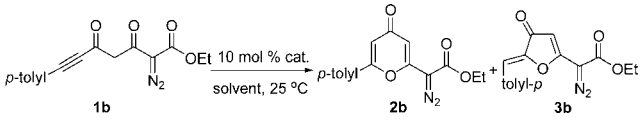
(DCE) (Table 1, entries 1−8). No reaction was observed using AgI (Table 1, entry 1). AgCl, Ag_3PO_4, and Ag_2O gave 52%, 68%, and 87% total yields, respectively, of the desired product γ-pyrone **2b** and 3(2*H*)-furanone **3b** albeit with poor selectivity (Table 1, entries 2−4). Fortunately, Ag_2SO_4, $AgNO_3$, $AgBF_4$, and $AgSbF_6$ afforded predominantly γ-pyrone **2b** (Table 1, entries 5−8). Among the catalysts tested, $AgSbF_6$ was found to be the most effective for this transformation into γ-pyrone **2b** in terms of reactivity and selectivity. Polar solvents, such as DMF and THF, afforded **2b** with relatively higher selection in the presence of $AgSbF_6$ (Table 1, entries 9−10). Encouraged by this result, we performed the reaction in several alcoholic solvents. As expected, alcohols such as MeOH, EtOH, *n*-PrOH, *i*-PrOH, and *t*-BuOH gave excellent results (Table 1, entries 11−15). In the $AgNO_3$−MeOH system, an excellent yield was also obtained (Table 1, entry 16); however, worse selection and activation were observed with the comparison of that in the $AgSbF_6$−MeOH system. Therefore, the optimized reaction conditions for the formation of γ-pyrones are the following: $AgSbF_6$ (10 mol %) in MeOH (Table 1, entry 11).

Interestingly, the treatment of **1b** with AgOAc in DCE provided predominantly five-membered ring product 3(2*H*)-furanone **3b** in 89% total yield (Table 1, entry 17). In the presence of 10 mol % AgOAc, different solvents were screened for this reaction. Both AgOAc and DCE introduced high regioselectivity on the formation of 3(2*H*)-furanone **3b** (Table 1, entry 17), but in contrast polar solvents such as DMF, THF, and especially MeOH were found to be unfavorable for the regioselectivity (Table 1, entries 18−20). With utilization of Et_3N (1 equiv) as an additive, the reaction time was shortened, and the regioselectivity for **3b** was further enhanced (Table 1, entry 21). Investigation of other metal salts in DCE gave worse results based on reactivity (Table 1, entries 22−24). For $Cu(OAc)_2$, **2b** was produced predominately with a longer reaction time, and **3b** was hardly obtained (Table 1, entry 22). A significant amount of byproduct was formed in the presence of a catalytic amount of CuCl (Table 1, entry 23). No reaction was detected using CuI (Table 1, entry 24). The optimal conditions for the formation of 3(2*H*)-furanones were obtained as follows: the use of AgOAc (10 mol %) as catalyst, DCE as solvent, and 1 equiv of Et_3N as base (Table 1, entry 21).

Table 1. Optimization of Reaction Conditions[a]



1b 2b 3b

entry	catalyst	solvent	*t*	yield (%)[b]	ratio[c] (**2b**/**3b**)
1	AgI	DCE	24 h	0[d]	–
2	AgCl	DCE	24 h	52[d]	50:50
3	Ag_3PO_4	DCE	18 h	68[d]	63:37
4	Ag_2O	DCE	15 min	87	40:60
5	Ag_2SO_4	DCE	3.5 h	82	88:12
6	$AgNO_3$	DCE	3.5 h	90	86:14
7	$AgBF_4$	DCE	1 h	88	94:6
8	$AgSbF_6$	DCE	15 min	87	93:7
9	$AgSbF_6$	DMF	8 min	85	97:3
10	$AgSbF_6$	THF	5 min	82[e]	97:3
11	$AgSbF_6$	MeOH	5 min	98	99:1
12	$AgSbF_6$	EtOH	7 min	98	97:3
13	$AgSbF_6$	*n*-PrOH	10 min	97	97:3
14	$AgSbF_6$	*i*-PrOH	9 min	97	96:4
15	$AgSbF_6$	*t*-BuOH	10 min	93	96:4
16	$AgNO_3$	MeOH	10 min	94	96:4
17	AgOAc	DCE	1.2 h	89	18:82
18	AgOAc	DMF	0.5 h	87	80:20
19	AgOAc	THF	0.5 h	93	75:25
20	AgOAc	MeOH	6 min	98	87:13
21	AgOAc/1 equiv Et_3N	DCE	1 h	95	6:94
22	$Cu(OAc)_2$	DCE	24 h	90	90:10
23	CuCl	DCE	36 h	40[e]	100:0
24	CuI	DCE	24 h	0[d]	–

[a]Reaction conditions: ethyl 2-diazo-3,5-dioxo-7-*p*-tolylhept-6-ynoate (0.2 mmol), catalyst (10 mol %), solvent (4 mL). [b]Total yield of isolated products (**2b** + **3b**). [c]The ratio was determined by ^{1}H NMR spectroscopic analysis (500 MHz) and was confirmed by separation by column chromatography. [d]Starting material was recovered. [e]Byproduct was formed.

The generality of Method A was proven by applying the optimized reaction conditions to various substrates **1**. The results are summarized in Table 2, Method A. We were pleased to find that all examined 2-diazo-3,5-dioxo-6-ynoates (ynones, ynamide) were suitable substrates for this transformation. The desired γ-pyrones **2** were obtained in almost quantitative yield (Table 2, Method A, entries a−v). For example, the compounds **1d**, **1q**, and **1t**−**1v** gave the corresponding γ-pyrones **2d**, **2q**, and **2t**−**2v** in up to 98% yield without forming 5-*exo* cyclized 3(2*H*)-furanone derivatives (Table 2, Method A, d, q, and t−v).

With the optimized reaction conditions for reversal of regioselectivity, we next studied another reaction of substrates **1** to determine the scope of this transformation to 3(2*H*)-furanones **3**, and the results are listed in Table 2, Method B. In the case of R^1 = aryl or vinyl groups, the corresponding 3(2*H*)-furanones **3a**−**3q** were obtained in 88−98% yield and with high regioselectivity regardless of the substituents attached to both the aryl ring at the triple bond position (R^1) and the carbonylic carbon (R^2) (Table 2, Method B, entries a−q). The regioselective reversal also exists in the case of R^1 being an aromatic heterocycle (Table 2, entry r). Interestingly, in the case of a cyclopropyl group as R^1, the expected product **3s** was also obtained (Table 2, Method B, entry s). Notably, when R^1 is the *n*-butyl or Me_3Si group, γ-pyrones **2t**−**v** were formed predominantly rather than the expected 3(2*H*)-furanones (Table 2, Method B, entries t−v).

Several points are noteworthy: (1) except for the substituents attached to the triple bond position (R^1) such as aliphatic and Me_3Si groups, the regioselective reversal in the cyclization reaction is quite successful, and γ-pyrones and 3(2*H*)-furanones could be easily synthesized from the same starting materials in excellent yields and with excellent regioselectivity based on the subtle catalyst and solvent selection (Table 2, entries a−s); (2) the substituents attached to both the aryl ring at the triple bond position (R^1) and the carbonylic carbon (R^2) have no obvious impact on the activation of the substrates **1** (Table 2, Method A and Method B, entries a−v); (3) a single *Z*-type isomer was generated in Method B, and the structures of γ-pyrones and 3(2*H*)-furanones were finally established by single-crystal X-ray diffraction analysis of products **2n** (CCDC1059899) and **3e** (CCDC1059949) (see Supporting Information (SI)).

The reaction mechanism is not clear at present. On the basis of these investigations, a possible catalytic cycle for these transformations is outlined in Scheme 3. First, the acetylenic

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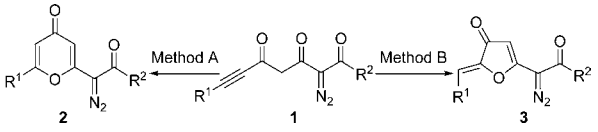
Table 2. Regioselective Synthesis of 3(2*H*)-furanones 2 and γ-Pyrones 3 from Various 2-Diazo-3,5-dioxo-6-ynoates (Ynones, Ynamide)[a]

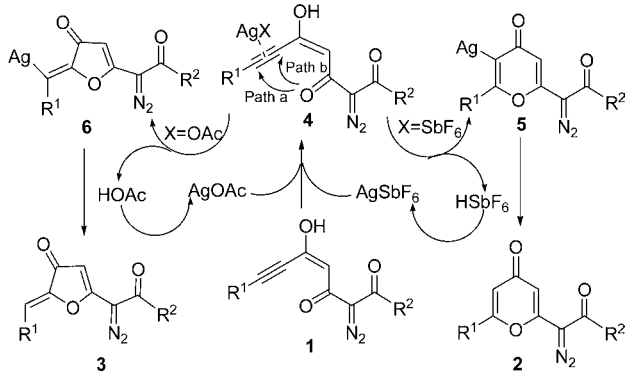


entry	substrate **1** R^1/R^2	Method A (*t* min, yield %[b], **2**/**3**[c])	Method B (yield %[b], **2**/**3**[c])
a	Ph/OEt (**1a**)	5, 98, 97:3	89, 3:97
b	*p*-MeC_6H_4/OEt (**1b**)	5, 98, 99:1	95, 6:94
c	*p*-^{n}PrC_6H_4/OEt (**1c**)	5, 97, 98:2	94, 6:94
d	3,5-^{t}Bu$_2C_6H_3$/OEt (**1d**)	15, 98, 100:0	98, 0:100
e	*p*-$MeOC_6H_4$/OEt (**1e**)	5, 97, 96:4	95, 5:95
f	*p*-ClC_6H_4/OEt (**1f**)	6, 98, 94:6	88, 1:99
g	*p*-FC_6H_4/OEt (**1g**)	4, 95, 96:4	92, 2:98
h	Ph/Ph (**1h**)	5, 95, 98:2	95, 4:96
i	*p*-MeC_6H_4/Ph (**1i**)	5, 94, 98:2	97, 7:93
j	*p*-^{n}PrC_6H_4/Ph (**1j**)	7, 93, 98:2	96, 6:94
k	*p*-$MeOC_6H_4$/Ph (**1k**)	5, 94, 98:2	96, 5:95
l	*p*-ClC_6H_4/Ph (**1l**)	6, 97, 96:4	96, 3:97
m	*p*-FC_6H_4/Ph (**1m**)	5, 97, 94:6	95, 3:97
n	 (**1n**)	5, 98 98:2	97, 2:98
o	(*E*)-PhCH=CH/OEt (**1o**)	5, 92, 97:3	95, 0:100
p	(*E*)-Me$(CH_2)_6$CH=CH/OEt (**1p**)	5, 97, 99:1	95, 5:95
q	Me_2C=CH/OEt (**1q**)	5, 93, 100:0	87, 11:89
r	 /OEt (**1r**)	5, 91, 97:3	97, 5:95
s	 /OEt (**1s**)	15, 96, 99:1	94, 17:83
t	*n*-Bu/OEt (**1t**)	3, 98, 100:0	98, 85:15
u	*n*-Bu/Ph (**1u**)	8, 98, 100:0	97, 87:13
v	Me_3Si/OEt (**1v**)	15, 98, 100:0	98, 100:0

[a]Method A: The reaction was carried out by using **1** (0.2 mmol) and $AgSbF_6$ (10 mol %) in MeOH (4 mL) at 25 °C. Method B: The reaction was carried out by using **1** (0.2 mmol), Et_3N (0.2 mmol), and AgOAc (10 mol %) in DCE (4 mL) at 25 °C for 1 h. [b]Isolated total yield (**2** + **3**). [c]The ratio was determined by ^{1}H NMR spectroscopic analysis (500 MHz) and was confirmed by separation by column chromatography.

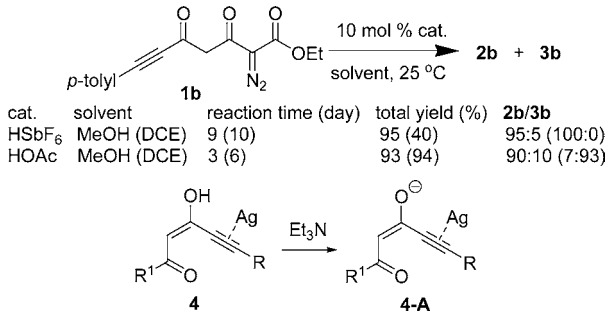
carbon−carbon triple bond is activated by the coordination of species **1** with Ag(I) ion.[14] The nucleophilic attack of carbonyl oxygen to the silver coordinated alkyne **4** then occurs to give vinyl silver(I) species **5** *via* 6-*endo*-dig cyclization (Path a, Mehtod A) or vinyl silver(I) species **6** *via* 5-*exo*-dig cyclization (Path b, Method B).[15] Protonation of **5** with $HSbF_6$ or **6** with HOAc releases the product **2** or **3** and regenerates the $AgSbF_6$ or AgOAc for next cycle (Scheme 2).

Scheme 2. Plausible Reaction Mechanism



Furthermore, we speculate that Brönsted−Lowry acidity of $HSbF_6$ and HOAc generated in the process could play an important role in determining the regioselectivity. Control experiments were carried out (Scheme 3). The treatment of **1b**

Scheme 3. Control Experiments



with $HSbF_6$ (10 mol %) in EtOH or DCE at 25 °C afforded **2b**. The use of HOAc (10 mol %) in MeOH also provided **2b**; however, **3b** was produced predominately using HOAc (10 mol %) in DCE at 25 °C. The results are in agreement with our speculation. However, the effect of solvent on the reaction is not clear.

In the case of R^1 as an aryl or a vinyl group, AgOAc in DCE induced the formation of 3(2*H*)-furanones (Method B); we speculated that the interaction of the π orbital of these groups with the π orbital of the carbon−carbon triple bond is favorable in 5-*exo*-dig cyclization. In the case of R^1 = cyclopropyl group, an interaction of the cyclopropyl bonding orbitals with the π orbital of carbon−carbon triple bond exists.[16] We concluded that this interaction imposes a preference for 5-*exo*-dig cyclization in Method B. When R^1 is an aliphatic or Me_3Si group, 6-*endo*-dig cyclization is prioritized compared to 5-*exo*-dig cyclization perhaps due to the lack of π orbital for this interaction. For Et_3N (1 equiv) as an additive, the reaction velocity increased. It can be rationalized by the conversion of Ag(I)-complex **4** of enol **1** into the corresponding enolate ion **4-A** with higher activity.

Since the nucleophilic addition products bear diazo functionality, perhaps both 6-*endo*-dig and 5-*exo*-dig cyclization products can be subjected to synthetically useful transformations.[17] For example, when **2b** was treated with *p*-

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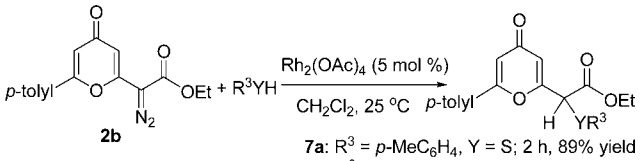
MeC_6H_4SH or $PhNH_2$ in the presence of $Rh_2(OAc)_4$ (5 mol %) in DCM, highly efficient chemoselective intermolecular insertion into the Y−H bond (Y = S, N) occurred to afford novel α-heteroatom substituted γ-pyrone derivatives **7** in good yields (Scheme 4).

Scheme 4. $Rh_2(OAc)_4$-Mediated Intermolecular Y−H Insertion



7a: R^3 = *p*-MeC_6H_4, Y = S; 2 h, 89% yield
7b: R^3 = Ph, Y = NH; 25 h, 76% yield

In summary, we describe herein the first regioselective synthesis of α-diazo functionalized γ-pyrones and 3(2*H*)-furanones from the same starting materials based on subtle catalyst and solvent selection. The mild reaction conditions, simple procedure, excellent yields, and a unique reversal of regioselectivity make the method attractive. Similar control of selectivity may be possible for other types of substrates. Detailed mechanistic studies and investigations along this line are underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02973.

Experimental details, compound characterization, crystallographic abstracts of product **2n** and **3e**, NMR spectra of all new products (PDF)

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Notes

The authors declare no competing financial interest.

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