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AN EFFICIENT SILVER TETRAFLUOROBORATE-CATALYZED CYCLOISOMERIZATION OF YNAMIDES

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This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – A silver catalyzed-cycloisomerization of N-Boc protected ynamides has been developed under mild reaction conditions to provide a wide range of oxazol-2(3*H*)-ones in good to excellent yields. Moreover, the acid-promoted Pictet-Spengler cyclization of oxazol-2(3*H*)-ones was described to furnish the corresponding *trans*-oxazolidones in moderate yields.

The heterocycle oxazol-2(3*H*)-ones have emerged as versatile building blocks for synthetic organic chemists and pharmacologists.¹ Some substituted oxazol-2(3*H*)-ones exhibiting herbicidal, antibacterial, antitumor, and neuroleptic activities as well as inhibition against cyclooxygenase-2 have been studied for several decades (Figure 1).² Additionally, the commercially available Linezolid drug (Zyvox®), containing 2-oxazolidone core structure, has been developed against Gram-positive bacteria.³ A number of synthetic routes of various substituted oxazol-2(3*H*)-ones usually involved carbonyl condensation processes to establish the cyclic carbamate moiety.⁴ Alternatively, photochemical promoted chlorination⁵ and electrochemical oxidation⁶ of 2-oxazolidones followed by thermal elimination process have also been studied for the synthesis of various oxazol-2(3*H*)-ones. Further synthetic applications of oxazol-2(3*H*)-one derivatives have been demonstrated for the introduction of additional functionalities, such as, substitution at the nitrogen atom by alkylation or acylation, substitution at the carbonyl oxygen

by halogenation reaction, and electrophilic addition of the reactive olefin moiety.⁷ Therefore, the modifications and transformations for the new types of 0xazol-2(3H)-ones to prepare the valuable N-containing heterocycles still remain a challenge.



Figure 1. Some biologically active compounds containing oxazol-2(3H)-one and 2-oxazolidone skeletons

Recently, we reported the synthesis of the corresponding tetrahydroisoquinoline-oxazol-2(3H)-ones 2 from ynamides 1 via [bis(trifluoroacetoxy)iodo]benzene (PIFA) and BF₃·OEt₂-mediated domino cvclization reaction (Scheme 1).⁸ Interestingly, the obtained tetrahydroisoquinoline-oxazol-2(3H)-ones 2 have attracted our attention for their potent anticancer activities. Therefore, the structural modification of tetrahydroisoquinoline-oxazol-2(3H)-ones 2 was also investigated by hydrogenation of the olefin moiety⁹ to provide the *cis*-oxazolidones 3 and the resulting anticancer activities of these compounds are still promising. For comparing anticancer activities, the *trans*-oxazolidones **3** were contemplated and sought after. Thus, we hypothesized that the *trans*-oxazolidone **3** would be synthesized from an acid-mediated Pictet-Spengler cyclization of oxazol-2(3H)-ones 4 via an N-acyliminium ion 5.¹⁰ So far, the previous procedures for the preparation of 3.5-disubstituted oxazol-2(3H)-ones from ynamides¹¹ were reported by using the expensive gold,¹² palladium,¹³ and rhodium complexes¹⁴ or using copper catalysts.¹⁵ Nevertheless, most of those reaction conditions required relatively high temperatures to affect the reactions. Additionally, Gagosz and coworkers also reported the use of expensive silver triflimide to catalyzed the cycloisomerization of ynamide at ambient temperature only for a few substrates.^{12b,c} During the development of acid-mediated cyclization of a N-acyliminium ion, we required a practical and efficient method to access various substituted oxazol-2(3H)-ones 4 from ynamide 1. Herein, we wish to report our results on the development of such process, namely, the silver-catalyzed cycloisomerization¹⁶ of ynamide and the subsequent acid-mediated Pictet-Spengler cyclization reaction.



Scheme 1. Synthetic routes for the preparation of cis- and trans-oxazolidone 3

Our initial experiment of the silver-catalyzed cycloisomerization of ynamide 1a concentrated on the optimization of reaction parameters, such as silver salts, solvent, catalyst loading and reaction time. We found that the use of 5 mol% of silver iodide, silver acetate, silver triflate, silver carbonate or silver oxide in dichloromethane at room temperature (Table 1, entries 1-5) did not result in the formation of the desired product. Treatment of the ynamide 1a with 5 mol% of silver fluoride, silver trifluoroacetate or silver sulfate could furnish the product 4a; however, low conversions of about 10% were observed by ${}^{1}H$ NMR of the crude product (Table 1, entries 6-8). Performing the reaction with 5 mol% of silver triflimide, silver nitrate, silver hexafluoroantimonate (V) or silver nitrite provided the corresponding product 4a after 18 h in the yields of 72-89% (Table 1, entries 9-12). Surprisingly, the reaction of ynamide 1a with 5 mol% of silver tetrafluoroborate provided the corresponding product 4a almost in quantitative yield after 18 h (Table 1, entry 13). Other solvents, such as chloroform, 1,2-dichloroethane, acetonitrile, toluene, diethyl ether, ethyl acetate and acetone, were also investigated but all gave less satisfactory results (0-62% yield). In order to ascertain whether silver tetrafluoroborate served as a true catalyst for this cycloisomerization, a control experiment, whereby 5 mol% of triethylamine was added to capture any in situ formed Brønsted acid, was performed.¹⁷ Under this reaction condition, the product 4a was still generated in 82% yield (Table 1, entry 14); this result thus further supported the role of silver tetrafluoroborate as a true catalyst for this reaction. Additionally, decreasing amount of silver tetrafluoroborate to 1 and 0.5 mol% resulted in complete conversion of 1a after 36 and 48 h, respectively, but yields of oxazol-2(3H)-one 4a were considerably lower (Table 1, entries 15 and 16). In addition, complex mixtures were observed. This could be accounted for by the slow decomposition of the corresponding oxazol-2(3H)-one product under Lewis acid conditions when the reaction time exceeded 18 h. Therefore, we decided to employ the reaction condition in entry 13 to investigate the scope of this transformation.¹⁸

 Table 1. Screening of silver salts

MeO

MeO

Ph

1a



5 mol% Ag⁺ CH₂Cl₂, rt, 18 h

Boc

MeO

MeO

^a Reaction conditions: **1a** (0.05 mmol), Ag salt (0.05 equiv) in CH₂Cl₂ (1 mL) for 18 h. ^b Percent conversions were determined by ¹H NMR analysis of the crude product. ^c Isolated yields after column chromatography.^d nr = no reaction.^e Reaction condition: **1a** (0.10 mmol), AgBF₄ (0.05 equiv), Et₃N (0.05 equiv) in CH₂Cl₂ (2 mL) for 18 h. ^f Reaction condition: 1a (1.0 mmol), AgBF₄ (0.01 equiv) in CH₂Cl₂ (5 mL) for 36 h. ^g Reaction condition: **1a** (1.0 mmol), AgBF₄ (0.005 equiv) in CH₂Cl₂ (5 mL) for 48 h.

Next, various ynamides 1b-1r were investigated and we found that the use of 5 mol% of silver tetrafluoroborate was quite general to transform the substituted ynamides bearing both aromatic groups on Ar¹ and R¹ with the yields ranging from 70 to 99% (Table 2, entries 1-13 and 15-18). If Ar¹ or R¹ of the ynamide substrates bear electron-donating or electron-withdrawing group, the resulting products were formed without significant difference in terms of yields. However, the ynamide 1q with electronically neutral phenyl groups as both Ar^1 and R^1 gave much lower yield of the corresponding product (Table 2, entry 17). Surprisingly, this catalyst could also catalyze the cycloisomerization of the ynamide 1r bearing an N-methylindole moiety as Ar^1 to provide the corresponding product oxazol-2(3H)-one 4r as a sole product in 87% yield (Table 2, entry 18). However, while treating the highly reactive alkene conjugated ynamide 1n with 5 mol% of silver tetrafluoroborate resulted in full conversion, the corresponding oxazol-2(3H)-one 4n was isolated only 32% yield (Table 2, entry 14). The lower yield of oxazol-2(3*H*)-one 4n was probably due to the relatively high reactive conjugated alkene moiety in the product 4n slowly decomposed under this reaction condition.

Table 2. AgBF4-catalyzed cycloisomerization of ynamide Ta -

Ar ¹	5 mol% AgBF ₄	Ar ¹
R ¹ 1	CH ₂ Cl ₂ , rt, 18 h	R^{1} 4

entry ^a	Ynamide	Ar ¹	R^1	Yield (%) ^b
1	1a	3,4-(MeO) ₂ -C ₆ H ₃	Ph	4a , 98
2	1b		3,4-(MeO) ₂ -C ₆ H ₃	4b , 75
3	1c		3,4-OCH ₂ O-C ₆ H ₃	4c , 78
4	1d		<i>o</i> -(MeO)-C ₆ H ₄	4d , 97
5	1e		<i>m</i> -(MeO)-C ₆ H ₄	4e , 97
6	1f		<i>p</i> -(MeO)-C ₆ H ₄	4f , 98
7	1g		<i>p</i> -F-C ₆ H ₄	4g , 95
8	1h	3,4-OCH ₂ O-C ₆ H ₃	Ph	4h , 96
9	1i		3,4-(MeO) ₂ -C ₆ H ₃	4i , 90
10	1j		3,4-OCH ₂ O-C ₆ H ₃	4j , 97
11	1k		<i>o</i> -(MeO)-C ₆ H ₄	4k , 88
12	11		<i>m</i> -(MeO)-C ₆ H ₄	41 , 89
13	1m		<i>p</i> -(MeO)-C ₆ H ₄	4m , 78
14	1n		1-cyclohexene	4n , 32
15	10	3,4,5-(MeO) ₃ -C ₆ H ₂	Ph	40 , 95
16	1p		3,4-(MeO) ₂ -C ₆ H ₃	4p , 99
17	1q	Ph	Ph	4q , 70
18	1r	3-(N-methyl)indole	Ph	4r , 87

^a Reaction conditions: ynamide **1**, AgBF₄ (0.05 equiv) in CH₂Cl₂ (0.05 M) for 18 h. ^b Isolated yields after chromatography.

To study the generality of this AgBF₄-catalyzed cycloisomerization of the substituted ynamides, we decided to synthesize various substituted ynamides **6a-6k** using CuSO₄·5H₂O catalyzed cross-coupling method^{12b,19} and then employed these ynamides **6a-6k** as substrates under the optimized reaction condition. We found that ynamides **6a-c** substituted with phenyl, 3,4-dimethoxybenzene or benzyl group

as R^2 and substituted with phenyl as R^3 yielded the corresponding oxazol-2(3*H*)-ones **7a-c** in high yields of 70-88% (Table 3, entries 1-3). While ynamides **6d-g** substituted with electron-withdrawing groups, such as *p*-chlorobenzene, *o*-bromobenzene, *p*-trifluoromethylbenzene or ethyl 2-acetate as R^2 and substituted with phenyl as R^3 resulted in oxazol-2(3*H*)-ones **7d-g** in moderate to excellent yields of 43-99% (Table 3, entries 4-7). The substituent effects on R^3 were also investigated and we found that ynamides **6h-i** and **6k**, substituted with silyl ether or ester groups as R^3 , afforded the corresponding oxazol-2(3*H*)-ones **6h-i** and **6k** in good to excellent yields of 72-99% (Table 3, entries 8-9 and 11). However, with ynamide **6j**, substituted with 1-cyclohexene as R^3 , the desired oxazol-2(3*H*)-one **7j** was obtained only 39% yield (Table 3, entry 10).

Table 3. AgBF₄-catalyzed cycloisomerization of ynamide 6a-6k

entry ^a	Ynamide	R ²	R ³	Yield (%) ^b
1	6a	Ph	Ph	7a , 80
2	6b	3,4-(MeO) ₂ -C ₆ H ₃	Ph	7b , 88
3	6c	Bn	Ph	7c , 70
4	6d	<i>p</i> -Cl-C ₆ H ₄	Ph	7d , 99
5	6e	o-Br-C ₆ H ₄	Ph	7e , 43
6	6f	<i>p</i> -CF ₃ -C ₆ H ₄	Ph	7f , 65
7	6g	-CH ₂ CO ₂ Et	Ph	7g , 76
8	6h	Ph	-(CH ₂) ₈ OTIPS	7h , 99
9	6i	Ph	-CH ₂ OAc	7i , 99
10	6j	Ph	1-cyclohexene	7j , 39
11	6k	Bn	-(CH ₂) ₈ OTIPS	7k , 72

^a Reaction conditions: ynamide **6**, AgBF₄ (0.05 equiv) in CH₂Cl₂ (0.05 M) for 18 h. ^b Isolated yields after chromatography.

After having developed an efficient silver-catalyzed cycloisomerization of ynamides, we then considered whether it would be possible to extend the obtained 0xazol-2(3H)-one **4a** to the more valuable tetrahydroisoquinoline-oxazolidone **3a** via an acid-mediated Pictet-Spengler cyclization process. Several reaction conditions were screened and the best reaction condition was found to be the use of 2.5

 $R^{3} = \frac{R^{2}}{6} R^{3} = \frac{5 \text{ mol}\% \text{ AgBF}_{4}}{CH_{2}CI_{2}, \text{ rt, 18 h}} R^{2} = \frac{R^{2}}{0} R^{3} = \frac{R^{2}}{7} R$

equivalents of TsOH·H₂O in acetonitrile under microwave irradiation at 200 W, 50 psi and 100 °C for 3 h to provide oxazolidone **3a** in 75% yield as a 10:1 mixture (*trans:cis*) (Table 4, entry 1).²⁰ Unfortunately, oxazol-2(3*H*)-ones **4b** and **4c**, substituted with 3,4-dimethoxybenzene and 3,4-methylenedioxybenzene as the aryl ring C, resulted only in the decomposition of the starting material and oxazolidones **3b** and **3c** were not detected under this optimized reaction condition (Table 4, entries 2-3). The decomposition of **4b** and **4c** was probably due to the high electron density of the aryl ring C which rendered the oxazol-2(3*H*)-one ring unstable under this strongly acidic condition. Finally, oxazol-2(3*H*)-ones **4h** and **4o** were also employed under this optimized reaction condition and *trans*-oxazolidones **3d** and **3e** were obtained as sole geometrical products in 58 and 50% yields, respectively (Table 4, entries 4-5).

Table 4. An acid-mediated Pictet-Spengler cyclization under microwave irradiation

R ⁴	2.5 equiv TsOH·H ₂ O MeCN	R ⁴ A B N
R^{5} R^{6} O Ar 4	microwave, 100 °C 200 W, 50 psi, 3 h	$ \begin{array}{c} R^{3} \\ R^{6} \\ Ar \\ H Ar $

Entry ^a	4	R	Ar	Yield (%) ^b	trans:cis ^c
1	4a	$R^4 = R^5 = MeO, R^6 = H$	Ph	3a , 75	10:1
2	4b	$R^4 = R^5 = MeO, R^6 = H$	3,4-(MeO) ₂ -C ₆ H ₃	3b , nd ^d	_
3	4c	$R^4 = R^5 = MeO, R^6 = H$	3,4-OCH ₂ O-C ₆ H ₃	$3c$, nd^d	_
4	4h	$R^4 - R^5 = OCH_2O, R^6 = H$	Ph	3d , 58	only trans
5	40	$R^4 = R^5 = R^6 = MeO$	Ph	3e , 50	only trans

^aReaction conditions: **4** (0.05 mmol), TsOH·H₂O (2.5 equiv) in MeCN (1 mL); microwave condition: 200W, 50 psi, 100 °C. ^b Isolated yield after chromatography. ^c Diastereomeric ratio was determined by ¹H NMR analysis of the crude product. ^d nd = not detected

In summary, we have developed an efficient silver-catalyzed cycloisomerization of a wide range of ynamides to provide the corresponding oxazol-2(3H)-one derivatives in good to excellent yields. The operational simplicity and practicability and the mild reaction conditions, as well as the low catalyst loading and low cost of silver tetrafluoroborate, as compared to gold, palladium and rhodium salts, render this transformation an attractive approach to various oxazol-2(3H)-one heterocycles. Additionally, we were able to demonstrate that the acid-mediated Pictet-Spengler cyclization of oxazol-2(3H)-ones could furnish to the corresponding *trans*-oxazolidones as major products in moderate yields.

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- 18. General procedure for the preparation of oxazol-2(*3H*)-one derivatives: To a 10 mL screw-cap test-tube was charged with ynamides 1a (38.2 mg, 0.10 mmol) and AgBF₄ (1.0 mg, 5.0 µmol) in dry CH₂Cl₂ (2 mL). The reaction mixture was stirred at room temperature for 18 h and directly purified by using column chromatography on silica gel (2:1, hexane:EtOAc as eluent) to afford the product 4a (32.0 mg, 98%) as a pale yellow solid (mp 136-138 °C). ¹H NMR (300 MHz, CDCl₃) δ: 7.44-7.30 (m, 4H), 7.27 (dd, *J* = 7.1, 7.0 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.78-6.69 (m, 2H), 6.50 (s, 1H), 3.86 (s, 3H), 3.85 (t, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.97 (t, *J* = 7.1 Hz, 2H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ: 154.8, 149.0, 147.9, 138.7, 129.8, 128.8, 128.0, 127.3, 122.8, 120.8, 111.8, 111.4, 109.7, 55.9, 55.8, 45.7, 34.8 ppm; IR (neat): v_{max} = 2937, 2833, 1745, 1592, 1516, 1452, 1400, 1263, 1237, 1189, 1154, 1025, 806, 764, 741, 691 cm⁻¹; EI-MS: *m/z* (relative intensity) = 325 (3, M⁺), 178 (8), 164 (38), 149 (17), 129 (8), 111 (16), 97 (31), 83 (38), 71 (42), 69 (59), 57 (100); TOF–HRMS calcd. for C₁₉H₂₀NO4 (M + H)⁺ 326.1387, found 326.1385.
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- 20. General procedure for the preparation of oxazolidone derivatives: in a 10 mL microwave vessel, a suspension of oxazol-2(3H)-one 4a (16.3 mg, 0.05 mmol) and TsOH·H₂O (23.8 mg, 0.13 mmol) in MeCN (1 mL) was irradiated using microwave. The microwave run time was set to 2 min, with power at 200 Watt, temperature at 100 °C, and pressure at 50 psi, and the conditions held for 3 h. The resulting solution was diluted with EtOAc (3 mL) and neutralized with sat.aq. NaHCO₃. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over anh. Na₂SO₄ and concentrated in *vacuo*. The crude product was purified by preparative thin-layer chromatography on silica gel (2:1, hexane:EtOAc) to obtain product 3a (12.2 mg, 75% with *trans:cis* ratio of 10:1). *trans-*3a as a white solid (mp 168-169 °C). ¹H NMR (300 MHz, CDCl₃) δ : 7.62-7.35 (m, 5H), 6.66 (s, 1H), 6.32 (s, 1H), 5.16 (d, J = 7.5 Hz, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 4.20 (dd, *J* = 12.7, 5.6 Hz, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 3.25-3.11 (m, 1H), 3.11-2.96 (m, 1H), 2.68 (d, J = 15.5 Hz, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ : 156.7, 148.5, 148.1, 137.8, 129.5, 129.1, 127.1, 125.8, 125.1, 112.0, 107.4, 84.0, 61.6, 55.9, 55.8, 38.6, 27.7 ppm; IR (neat): $v_{\text{max}} = 2936$, 2840, 1751, 1612, 1515, 1454, 1420, 1365, 1310, 1256, 1228, 1173, 1117, 1086, 1033, 997, 961, 872, 854, 767, 702 cm⁻¹; EI-MS: m/z (relative intensity) = 325 (2, M⁺), 313 (10), 296 (67), 284 (22), 268 (33), 256 (19), 236 (12), 213 (18), 207 (14), 185 (28), 171 (21), 149 (18), 135 (24), 129 (53), 111 (35), 97 (78), 84 (61), 73 (77), 69 (100), 57 (89); TOF-HRMS

calcd. for C₁₉H₂₀NO₄ (M + H)⁺ 326.1387, found 326.1385. *cis*-**3a** as a white solid (mp 163-165 °C). ¹H NMR (400 MHz, CDCl₃) δ : 7.23-7.17 (m, 3H), 7.12-7.06 (m, 2H), 6.47 (s, 1H), 5.88 (d, *J* = 8.5 Hz, 1H), 5.79 (s, 1H), 5.31 (d, *J* = 8.5 Hz, 1H), 4.19 (dd, *J* = 13.1, 5.1 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 3H), 3.15 (ddd, *J* = 12.9, 12.6, 3.6 Hz, 1H), 2.98 (ddd, *J* = 15.9, 12.2, 5.5 Hz, 1H), 2.56 (dd, *J* = 15.8, 3.2 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ : 157.8, 147.7, 146.8, 135.2, 128.8, 128.2, 127.4, 127.0, 122.3, 111.4, 110.2, 80.6, 59.5, 55.6, 55.5, 39.7, 27.4 ppm; IR (neat): *v*_{max} = 2925, 2853, 1747, 1611, 1516, 1456, 1420, 1360, 1331, 1256, 1231, 1209, 1173, 1120, 1088, 1030, 1009, 765, 736, 700 cm⁻¹; EI-MS: *m/z* (relative intensity) = 325 (8, M⁺), 207 (8), 191 (100), 176 (32), 149 (11), 133 (7), 121 (9), 111 (15), 105 (34), 97 (25), 85 (17), 83 (27), 77 (24), 69 (24), 57 (30); TOF-HRMS calcd. for C₁₉H₂₀NO₄ (M + H)⁺ 326.1387, found 326.1398.