Silver-Catalyzed Preparation of Oxazolines from *N*-Propargylamides

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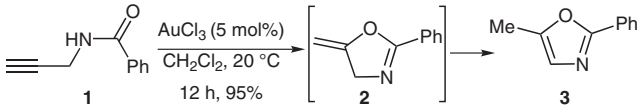
This paper is dedicated to Professor Scott E. Denmark on the occasion of his 55th birthday.

Abstract: Treatment of *N*-propargylamides with 5 mol% of silver hexafluoroantimonate results in the rapid formation of oxazolines in essentially quantitative yield.

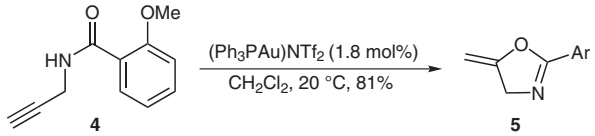
Key words: *N*-propargylamides, silver, oxazolines, catalysis

The reaction of alkynes with metal ions of group 12 has a long-standing and growing history.[1] Copper, silver and gold ions are increasingly of interest for the mild conversion of alkynes into a variety of interesting and useful products. Recently, we reported that the rapid rearrangement of propargylic sulfinate esters to allenic sulfones could be effected by exposure of the former to catalytic amounts of silver cations.[2] As part of our continuing interest in silver ion catalyzed processes, we now report the facile conversion of propargylic amides into alkylidene oxazolines using silver ion catalysis.

The reaction of propargylic amides with electrophilic metal ions is known. Hashmi and co-workers reported the conversion of propargylic amides **1** into the corresponding oxazoles **3**, via the intermediacy of methylidene oxazolines **2**, which could be observed spectroscopically, upon treatment with catalytic amounts of $AuCl_3$ (Scheme 1).[3] A gold(I) catalyst also promoted cyclization of a propargylic amide to a methylene oxazoline, which could be isolated before isomerization to the corresponding oxazole.[4] Alkylidene oxazolidinones have been prepared via the gold(I)-catalyzed cyclization of Boc-protected propargyl amines (Equation 1).[5] A similar route to carbonates using silver ion catalysis has also been published.[6]

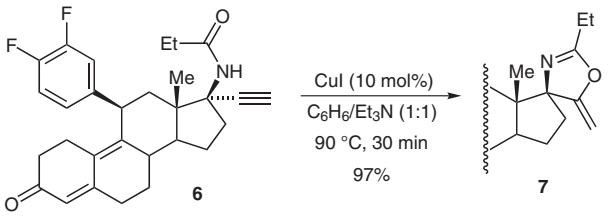


Scheme 1

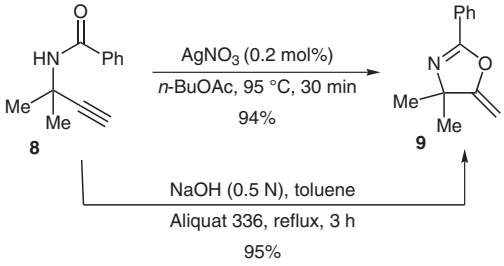


Equation 1

Heating **6** in a 1:1 mixture of benzene and triethylamine in the presence of 10 mol% of CuI afforded **7** in 97% yield (Equation 2).[7] This compound could be obtained with an equivalent in 84% yield upon treatment of **6** with one equivalent of silver nitrate. Interestingly, the reaction of **8** with 0.2 mol% of silver nitrate in *n*-butyl acetate at 95 °C for 30 minutes is reported to afford oxazoline **9** in 94% yield (Scheme 2).[8] Whether the high temperature could have been avoided is not clear. However, many years ago Easton and co-workers reported that several propargylic amides could be converted into methylene oxazolines upon treatment with 20 wt% (ca. 17 mol%) of silver nitrate in anhydrous DMF at room temperature.[9] We assume that such large amounts of silver ion catalyst were really not necessary for the reaction to occur.



Equation 2



Scheme 2

Palladium-catalyzed cyclizations of propargylic amides have been conducted in the presence of CO and alcohols to afford not simple cyclization products, but compounds that have undergone an additional alkoxycarbonylation (Equation 3).[10]

It should be mentioned that the conversion of propargylic amides into alkylidene oxazolines does not require metal catalysis at all. For example, treatment of **8** with 0.5 N NaOH in toluene in the presence of a phase-transfer catalysis resulted in the formation of **9** in 95% yield after three hours at reflux (Scheme 2).[11]

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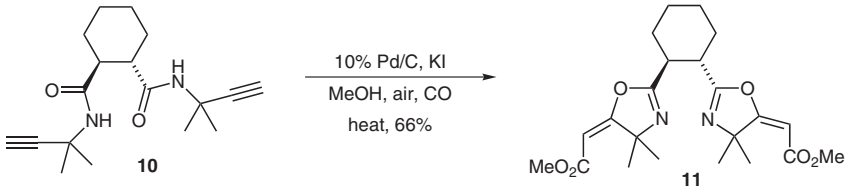
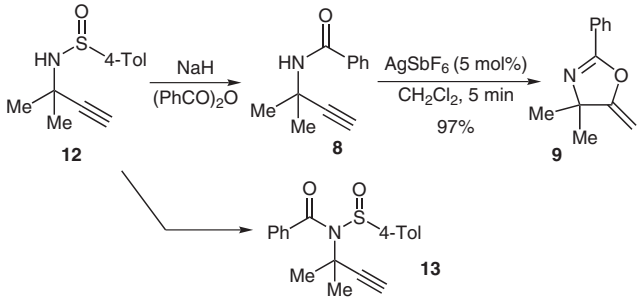


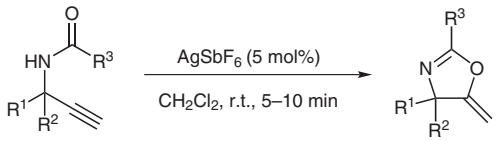
Equation 3

We undertook our studies as a result of a failed attempt to generate an allenic sulfoximine. The reaction of **12** with benzoic anhydride and base afforded not the desired sulfinamide **13** but **8** (Scheme 3), which was treated with silver ion (before we knew we had prepared a simple propargylic amide). This afforded **9** in very high yield. Given that result, we decided to examine the preparation of a number of different 4,4-dialkyl-5-methylene oxazolines. The results are summarized in Table 1.[13]



Scheme 3

Table 1 Oxazolines from Propargylic Amides[12]



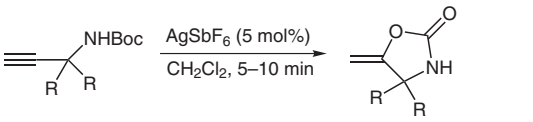
Entry	Amide	R^1	R^2	R^3	Product	Yield (%)
1	**14**	Me	Me	Me	**15**	98
2	**8**	Me	Me	Ph	**9**	97
3	**16**	Me	Me	Bn	**17**	97
4	**18**	Me	Me	Et	**19**	96
5	**20**	Me	Me		**21**	95
6	**22**	Me	Me	$(CH_2)_3Cl$	**23**	89
7	**24**	Me	Me	*t*-Bu	**25**	96
8	**26**	Me	Me	4-$O_2NC_6H_4$	**27**	94
9	**28**	Et	Et	Ph	**29**	96
10	**30**	$(CH_2)_5$		Ph	**31**	97
11	**1**	H	H	Ph	**2**	91[a]

[a] The reaction failed in CH_2Cl_2; $MeNO_2$ was used as solvent.

We found that treatment of a variety of propargylic amides with 5 mol% of silver hexafluoroantimonate in dichloromethane at room temperature afforded excellent to nearly quantitative yields of cyclized product in five to ten minutes.[14] This reaction presumably proceeds through coordination of the silver cation to the alkyne followed by nucleophilic attack by the amide oxygen and proton transfer to afford the product and regenerate the silver cation.

At least three results among those shown are particularly noteworthy. The crotonamide **20** cyclized successfully to give **21** in high yield (Table 1, entry 5). A primary chloride is stable under the reaction conditions (Table 1, entry 6). Finally, blocking aromatization by dialkyl substitution does not appear to be necessary, as evidenced by the isolation of **2** in high yield. As pointed out by Hashmi,[3] structures such as **2** are relatively rare, as they are prone to aromatization except under the mildest of conditions.

Finally, given the reports of the gold-catalyzed synthesis of alkylidene oxazolidinones starting from Boc-protected propargylic amines,[5] we decided to investigate the process using silver ions. To our delight, treatment of **32** and **34** under our standard reaction conditions resulted in the formation of **33** and **35** in 92% and 91% yields, respectively (Equation 4).



32, R = Me, 92%
34, R–R = $(CH_2)_5$, 91%

33, R = Me, 92%
35, R–R = $(CH_2)_5$, 91%

Equation 4

In summary, we have shown that propargylic amides can be rapidly cyclized to 5-methyleneoxazolines in high yields at room temperature upon treatment with catalytic amounts of silver hexafluoroantimonate.[15] It is likely that this chemistry can be extended to the synthesis of highly substituted oxazoles. The investigation of this process and other silver-catalyzed chemistry is in progress. New results will be reported in due course.

Acknowledgment

This work was supported by the National Science Foundation.

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(12) **General Procedure for the Preparation of Methylene Oxazolines from *N*-Propargylamides**:
The amide (1 mmol) was placed in a dry flask with CH_2Cl_2 (2 mL). $AgSbF_6$ (5 mol%) was added in one portion with magnetic stirring. After 5–10 min, TLC showed no starting material. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was evaporated to afford the pure (^{1}H NMR) product.

(13) The starting amides were prepared by the reaction of amines with acid chlorides.

(14) The conversion of **8** into **9** required 15 min with 2% catalyst, 1 h with 1% catalyst and 28 h with 0.1% catalyst, all reactions being conducted at r.t.

(15) Data of selected compounds: **16**: solid; mp 138–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.37 (m, 5 H), 5.55 (s, 1 H), 3.54 (s, 2 H), 2.31 (s, 1 H), 1.57 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 169.9, 134.8, 129.2, 128.9, 127.2, 87.5, 69.1, 47.6, 44.4, 28.7. IR (CH_2Cl_2): 3309, 3215, 2099, 1642, 1540, 1221, 722 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{15}NONa^+$: 224.1043; found: 224.1043. **17**: solid; mp 192–193 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.34 (m, 5 H), 4.57 (d, *J* = 3.0 Hz, 1 H), 4.14 (d, *J* = 3.0 Hz, 1 H), 3.69 (s, 2 H), 1.35 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 167.7, 134.2, 128.8, 128.7, 127.1, 82.3, 68.5, 34.8, 29.4. IR (CH_2Cl_2): 2974, 2921, 1662, 1454, 1180, 1123 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{15}NONa^+$: 224.1043; found: 224.1044. **18**: solid; mp 96–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.65 (s, 1 H), 2.33 (s, 1 H), 2.17 (q, *J* = 12.5 Hz, 2 H), 1.64 (s, 6 H), 1.14 (t, *J* = 12.5 Hz, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 177.8, 87.3, 68.9, 47.4, 30.1, 28.9, 9.4. IR (CH_2Cl_2): 3309, 3223, 2982, 2238, 2099, 1658, 1540, 898, 718 cm^{-1}. HRMS: *m/z* calcd for $C_8H_{13}NONa^+$: 162.0889; found: 162.0887. **19**: solid; mp 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.81 (d, *J* = 3.5 Hz, 1 H), 4.38 (d, *J* = 3.5 Hz, 1 H), 2.50 (q, *J* = 3.0 Hz, 2 H), 1.45 (s, 6 H), 1.32 (t, *J* = 3.0 Hz, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 171.6, 164.6, 86.0, 68.0, 30.1, 22.9, 9.7. IR (CH_2Cl_2): 3624, 3411, 2986, 1654, 1180, 665 cm^{-1}. HRMS: *m/z* calcd for $C_8H_{13}NOH^+$: 140.1070; found: 140.1068. **20**: solid; mp 96–98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.84 (dt, *J* = 9.0, 14.5 Hz, 1 H), 5.92 (s, 1 H), 5.81 (d, *J* = 14.5 Hz, 1 H), 2.34 (s, 1 H), 1.83 (d, *J* = 9.0 Hz, 3 H), 1.67 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 165.0, 139.9, 125.3, 87.2, 68.9, 47.3, 28.9, 17.5. IR (CH_2Cl_2): 3293, 3239, 2974, 2108, 1634, 1540, 1233, 967 cm^{-1}. HRMS: *m/z* calcd for $C_9H_{13}NONa^+$: 174.0890; found: 174.0889. **21**: oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.84 (dt, *J* = 6.0, 15.5 Hz, 1 H), 6.07 (d, *J* = 15.5 Hz, 1 H), 4.72 (d, *J* = 3.0 Hz, 1 H), 4.27 (d, *J* = 3.0 Hz, 1 H), 1.94 (d, *J* = 6.0 Hz, 3 H), 1.41 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 165.9, 161.3, 143.3, 117.6, 83.5, 68.1, 29.8, 18.5. IR (CH_2Cl_2): 2970, 1674, 1307, 1184, 972, 661 cm^{-1}. HRMS: *m/z* calcd for $C_9H_{13}NONa^+$: 174.0889; found: 174.0886. **22**: solid; mp 48–49 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.81 (s, 1 H), 3.61 (t, *J* = 6.0 Hz, 2 H), 2.34 (t, *J* = 6.0 Hz, 2 H), 2.11 (tt, *J* = 6.0, 6.0 Hz, 2 H), 1.64 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 170.8, 86.9, 67.1, 47.5, 44.4, 33.5, 28.9, 27.9. IR (CH_2Cl_2): 3350, 3239, 2994, 2108, 1646, 1540, 1221 cm^{-1}. HRMS: *m/z* calcd for $C_9H_{14}ClNONa^+$: 210.0656; found: 210.0651. **23**: oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.60 (d, *J* = 3.0 Hz, 1 H), 4.10 (d, *J* = 3.0 Hz, 1 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 2.56 (t, *J* = 7.0 Hz, 2 H), 2.17 (tt, *J* = 6.0, 7.0 Hz, 2 H), 1.35 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 167.5, 162.9, 82.2, 68.3, 43.8, 29.5, 28.2, 25.2. IR (CH_2Cl_2): 2974, 2929, 1679, 1192, 1127, 963 cm^{-1}. HRMS: *m/z* calcd for $C_9H_{14}ClNOH^+$: 188.0837; found: 188.1277. **24**: solid; mp 106–107 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.67 (s, 1 H), 2.32 (s, 1 H), 1.66 (s, 6 H), 1.20 (s, 9 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 177.4, 87.4, 68.8, 47.4, 38.9, 28.7, 27.4. IR (CH_2Cl_2): 3362, 3288, 2998, 1650, 1523, 1356, 1209 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_{17}NONa^+$: 190.1202; found: 190.1200. **25**: oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.56 (d, *J* = 2.5 Hz, 1 H), 4.10 (d, *J* = 2.5 Hz, 1 H), 1.33 (s, 6 H), 1.27 (s, 9 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 169.6, 168.5, 80.9, 68.2, 32.9, 29.5, 27.4. IR (CH_2Cl_2): 3419, 2974, 1646, 1180, 1094 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_{17}NONa^+$: 190.1202; found: 190.1042. **26**: solid; mp 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 9.0 Hz, 2 H), 7.93 (d, *J* = 9.0 Hz, 2 H), 5.57 (s, 1 H), 2.43 (s, 1 H), 1.78 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 164.5, 149.4, 140.3, 128.1, 123.6, 86.4, 69.8, 49.3, 28.8. IR (CH_2Cl_2): 3289, 2982, 1654, 1527, 1352, 845 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{12}N_2O_3Na^+$: 255.0740; found: 255.0738. **27**: oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.0 Hz, 2 H), 8.18 (d, *J* = 8.0 Hz, 2 H), 4.80 (d, *J* = 3.0 Hz, 1 H), 4.33 (d, *J* = 3.0 Hz, 1 H), 1.48 (s, 6 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 167.2, 158.2, 149.6, 132.6, 129.1, 123.6, 83.5, 69.6, 29.5. IR (CH_2Cl_2): 3427, 3105, 2982, 1646, 1597, 1519, 1307, 1066 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{12}N_2O_3Na^+$: 255.0740; found: 255.0739.