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Zinc halide-promoted cyclization of propargyl amide enynes: novel six-membered ring formation

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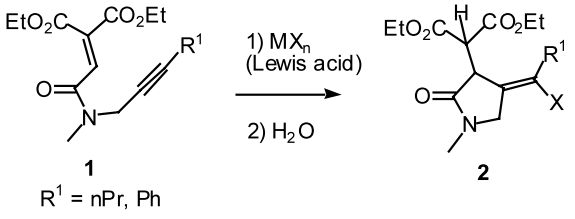
Abstract—Highly unusual zinc halide-promoted cyclization of propargyl amide enynes in the presence of an alcohol or a Brønsted acid afforded novel six-membered rings.

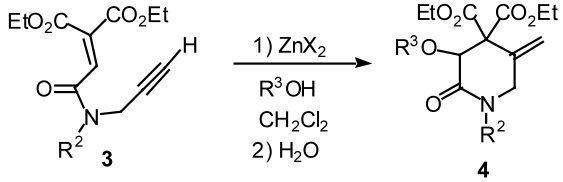
Transition metal catalyzed cyclization reactions of 1,6-enynes can lead to five-membered rings with the diene in various positions,[1a–e] to seven-membered rings,[1f] to five- or six-membered rings with incorporation of nucleophiles,[1g,h] and to complex polycyclic skeletons,[1i] in various reaction modes. Lewis acids are also important catalysts in modern organic reactions,[2] and Lewis acid-promoted reactions have been extensively utilized for various ring forming reactions.[3] However, very few examples of Lewis acid-promoted cyclizations of enynes have been reported so far.[4] Recently, we reported a novel Lewis acid-promoted intramolecular C–C bond forming reaction to give halogenated five-membered cyclic compounds as represented by the transformation shown in Eq. (1).[5]



1 R^1 = nPr, Ph **2** (1)

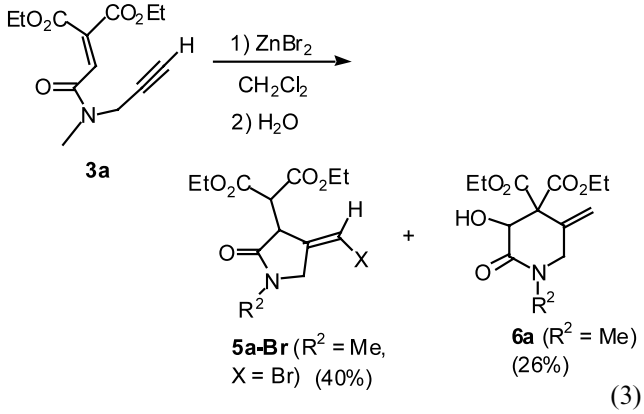
As part of our efforts to delineate the scope and limitations of this Lewis acid-promoted enyne cyclization, reactions of enynes with a terminal acetylenic moiety were examined since they are expected to have different reactivity to internal acetylenes. Whilst enynes (**3**) bearing a terminal alkyne were presumed to be less reactive in view of the previously proposed mechanism,[5] we were surprised that zinc halide-promoted cyclization of these propargyl amide enynes affords highly unusual alcohol incorporated six-membered rings in the presence of an alcohol as the main products (Eq. (2)). In this communication, we disclose the results of our preliminary investigations into this novel mode of ring closure.

We initially examined whether Lewis acid-promoted reaction of the terminal alkyne **3a** would afford five-membered products or not. Whilst amide–enyne **3a** reacted in the presence of $ZnBr_2$ in CH_2Cl_2 at room temperature to afford the expected bromine incorporated γ-lactam **5a**–**Br** in 40% yield, a major by-product was the unexpected δ-lactam **6a** in 26% yield (Eq. (3)). The stereochemistry of γ-lactams **5a** were determined by NOE experiments and the stereochemistry is the same as with alkyl and aryl-substituted substrates.[5]



3 **4** (2)

For R^2 and R^3, see Table 1



3a

5a-Br (R^2 = Me, X = Br) (40%) **6a** (R^2 = Me) (26%) (3)

Keywords: zinc halide; enyne; propargyl amide; six-membered ring formation.

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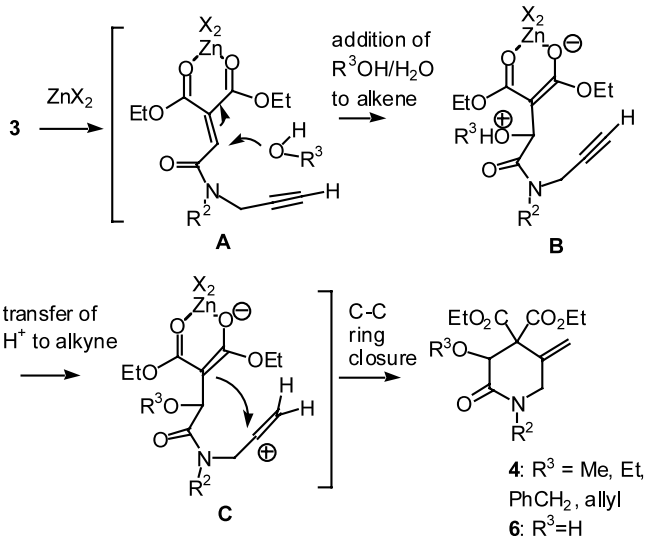
Table 1. Enyne cyclization with alcohol (in Eq. (2))[a]

Entry	Enyne	R^2	R^3	Lewis acid	**4**–R^3 (yield %)	**5**[b] (yield %)	**6**[b] (yield %)
1	**3a**	Me	Me	ZnI_2	**4a–Me** (75)	**5a–I** (9.8)	**6a** (1.6)
2	**3a**	Me	Me	$ZnBr_2$	**4a–Me** (65)	**5a–Br** (18)	[c]
3	**3a**	Me	Me	$ZnCl_2$	**4a–Me** (53)	[c]	**6a** (17)
4	**3a**	Me	Et	ZnI_2	**4a–Et** (49)	**5a–I** (29)	[c]
5	**3a**	Me	$PhCH_2$	ZnI_2	**4a–CH_2Ph** (53)	**5a–I** (18)	**6a** (6)
6	**3a**	Me	CH_2=CH–CH_2	ZnI_2	**4a–Allyl** (41)	**5a–I** (24)	[c]
7	**3b**	Propyl	Me	$ZnCl_2$	**4b–Me** (69)	[c]	(0)
8	**3c**	$PhCH_2$	Me	$ZnCl_2$	**4c–Me** (66)	(0)	(0)

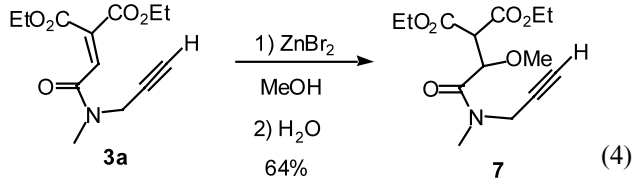
[a] Reactions were carried out using 0.3–0.5 mmol of **3a–c**, 1.2 equiv. of ZnX_2 and 1.0 equiv. of R^3OH at 0.5 M for **3a–c** in CH_2Cl_2 for 18 h at rt.
[b] For the structures of the minor products **5** and **6**, see Eq. (3).
[c] Small amounts of the product could not be purified.

This unusual formation of δ-lactam **6a** was hypothesized to arise from participation of water in situ, hence the reaction of enyne **3a** with zinc bromide in the presence of 1 equiv. of water was examined next. The yields of γ-lactam **5a** and δ-lactams **6a** changed to 39 and 31%, suggesting that our hypothesis was correct, however, exclusive formation of δ-lactam **6a** was not achieved. We therefore decided to examine reaction of **3** with zinc halides in the presence of 1 equiv. of an alcohol in the expectation of an increase in formation of δ-lactam due to greater nucleophilicity and solubility of the organic solvent relative to water. In line with our prediction, the reaction of **3a** with zinc halides in CH_2Cl_2 at room temperature in the presence of 1 equiv. of methanol afforded methoxy-substituted δ-lactams **4a–Me** as the major products in 53–75% yield together with trace amounts of γ-lactams **5a** and hydroxy-substituted δ-lactam **6a** (Eq. (2), Table 1, entries 1–3, for the structures of the minor products **5a** and **6a**, see Eq. (3)).[6] These results indicate clearly that we can change the course of the reaction simply by inclusion of an additive.



Scheme 1. Reaction pathways for formation of the six-membered rings **4** and **6**.

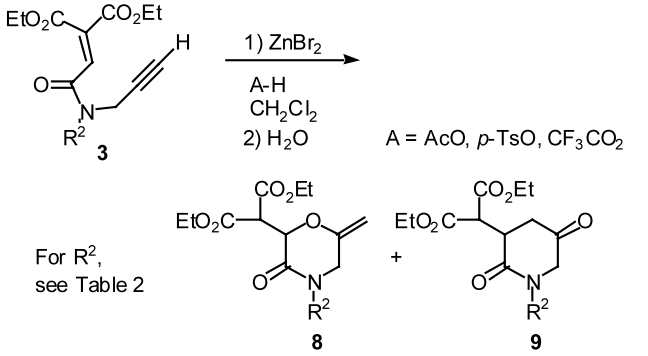
Besides methanol, ethanol, benzyl alcohol, and allyl alcohol also worked well as nucleophiles. The corresponding alkoxy group-incorporated δ-lactam derivatives were formed as the major products (entries 4–6). The reaction of propyl and benzyl propargyl amides with methanol in the presence of $ZnCl_2$ also gave δ-lactams **4b** and **4c** as major products (entries 7 and 8). The reaction of **3a** in the presence of $ZnBr_2$ in methanol as a solvent gave noncyclized methanol adduct **7** in 64% yield (Eq. (4)).[7]



(4)

The probable mechanism for formation of these novel six-membered rings **4** and **5** is shown in Scheme 1. For five-membered ring formation, the alkyne moiety works as a nucleophile.[5] On the other hand, in Scheme 1 alkyne is protonated and functions as an electrophile.

To further explore possible incorporation of additives, the reaction of **3** in the presence of acetic acid, trifluoroacetic acid and *p*-toluenesulfonic acid was examined next. The reaction of **3** in the presence of 1 equiv. of these Brønsted acids with $ZnBr_2$ in CH_2Cl_2 afforded the novel six-membered heterocycles **8** and **9** in various ratios (Eq. (5), Table 2, entries 1–3).[8]



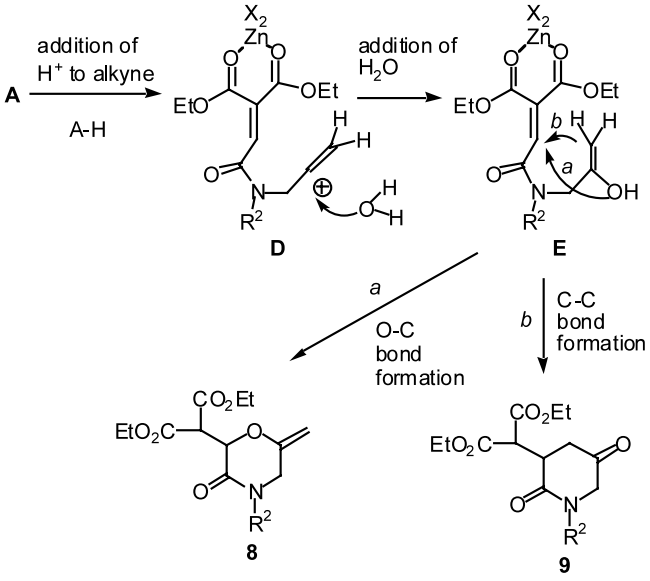
(5)

Table 2. Enyne cyclization in the presence of Brønsted acid (in Eq. (5))[a]

Entry	Enyne	R^2	A–H	**8** (yield %)	**9** (yield %)
1	**3a**	Me	AcOH	**8a** (42)	**9a** (20)
2	**3a**	Me	CF_3CO_2H	**8a** (49)	**9a** (40)
3	**3a**	Me	*p*-TsOH	**8a** (19)	**9a** (78)
4	**3a**	Me	3.6N HCl/AcOEt	**8a** (24)	**9a** (57)
5	**3b**	Propyl	*p*-TsOH	**8b** (61)	[b]

[a] Reactions were carried out using 0.3–0.5 mmol of **3a**–**b**, 1.2 equiv. of $ZnBr_2$ and 1.0 equiv. of Brønsted acid (A–H) at 0.4 M for **3a**–**b** in CH_2Cl_2 for 17–18 h at rt.

[b] Small amounts of the product could not be purified.



Scheme 2. Reaction pathways for formation of the six-membered rings **8** and **9**.

The reaction of **3a** in the absence of ZnX_2 and presence of 1 equiv. of *p*-TsOH in CH_2Cl_2 did not proceed, therefore cyclization reaction requires both zinc halide and Brønsted acid. The conceivable mechanism for the formation of **8** and **9** involves addition of H^+ to the terminal alkyne carbon leading to intermediate **D**. The subsequent addition of water gives **E**. The intermediate **E** undergoes ring closure by *a* (O–C bond formation) and *b* (C–C bond formation) paths to lead to **8** and **9** as shown in Scheme 2.

In summary, zinc halide promoted reactions of enynes (**3a**–**c**) give novel six-membered heterocycles (**4**, **8**, and **9**) in the presence of an additive such as an alcohol and a Brønsted acid. Further studies to identify the required conditions to cause the novel six-membered formation are under investigation. Because the obtained piperidine skeleton[9] is biologically of interest, further transformation of the products to useful compounds is also under investigation.

Acknowledgements

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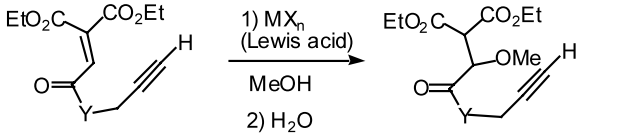
6. **Typical experimental procedure**: To a solution of **3a** (91.5 mg, 0.34 mmol) in dichloromethane (0.6 mL) was added methanol (11 mg, 14 μL, 0.34 mmol) and ZnI_2 (126 mg,

0.39 mmol) at 0°C. The mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched by water (1 mL) and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane–ether as eluent to give **4a**–**Me** (77 mg, 75%), **5a**–**I** (13.2 mg, 9.8%) and **6a** (1.6 mg, 1.6%). **4a**–**Me**: $R_f = 0.2$ (ether); colorless crystals; mp 51°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (t, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 2.99 (s, 3H), 3.49 (s, 3H), 3.74 (d, $J = 14.6$ Hz, 1H), 4.15–4.34 (m, 4H), 4.29 (s, 1H), 4.30 (d, $J = 14.6$ Hz, 1H), 5.45 (s, 1H), 5.60 (d, $J = 0.9$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 13.81 (q), 14.04 (q), 33.91 (q), 53.34 (t), 59.12 (q), 61.94 (t), 62.31 (t), 63.22 (s), 80.13 (d), 118.37 (t), 133.82 (s), 166.55 (s), 166.82 (s), 167.40 (s). Selected HMBC correlations are between δ 3.74 (H6), 4.30 ($H_{6'}$), 5.45 (=CH*H*), 5.60 (=C*H*H) and 63.22 (C_4); IR (neat): 2986, 2942, 1760, 1735, 1675, 1450, 1402, 1250, 1200, 1093, 1062, 1017 cm^{-1}; MS (EI): *m*/*z* 299 (17), 226 (8.7), 196 (15), 154 (13), 28 (46), 18 (100); exact mass M^+ 299.1378 (calcd for $C_{14}H_{21}NO_6$ 299.1369). Anal. calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.02; H, 7.02; N, 4.71%.

7. In the $ZnBr_2$-promoted reaction of the amine–enyne substrates with an internal acetylenic moiety (propyl and phenyl acetylenes) **1** (in Eq. (1)) in the presence of methanol, the corresponding six-membered ring compounds could not be obtained: the main products were bromine-incorporated five-membered products **2** (in Eq. (1)), which form in the conditions without methanol.[5] Probably, transfer of H^+ to the alkyne step is slow due to steric reasons. The Lewis acid-promoted reactions of other terminal alkynes with tethers such as **10a**–**b** in the presence of methanol were also examined. However, the reactions gave the noncyclized methanol adducts **11a**–**b** as the only identified products (Eq. (6)). The alcohol-incorporated six-membered ring formation seems to specific tethers, Lewis acids, and additives.



10a: Y = CH_2
10b: Y = O

$ZnBr_2$, **11a**: Y = CH_2 (69%)
$ZnBr_2$, **11b**: Y = O (87%)
$FeCl_3$, **11b**: Y = O (92%)

(6)

8. Compound **8a** was converted partially to **9a** under the same reaction conditions ($ZnBr_2$, *p*-TsOH in CH_2Cl_2) along with decomposition.
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