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Ring Enlargement Reaction of 3-Hydroxy-3-propargylisoindolin-1-ones : A New Synthetic Method for the 2-Benzazepine-1,5-diones

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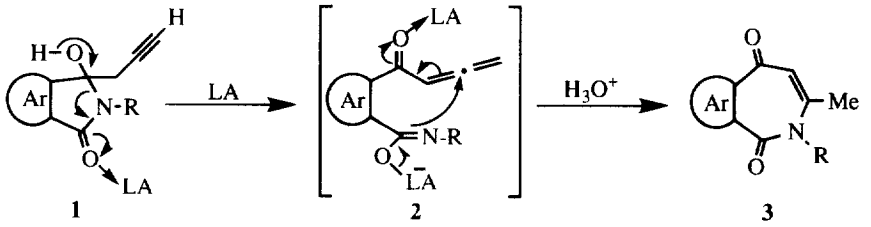
Abstract *:* Several 2-benzazepine-1,5-diones were efficiently obtained by treatment of the corresponding *N*-alkyl-3-hydroxy-3-propargylisoindolin-1-ones with some tentative Lewis acids *via* intramolecular endo-mode cyclization in the allenyl ketone intermediates generated *in situ*.

Recently, considerable interest has been focused on the development of new construction methods[1] for the benzazepine skeletons which are common structural moieties of pharmacologically active alkaloids.[1d,g] We have recently disclosed various carbocyclic endo-mode cyclization reactions by utilizing the intramolecular Michael type addition of the aromatic ring to the conjugated allenyl ketone moiety in the presence of some Lewis acids.[2] On the basis of our earlier studies,[2] we designed an expeditious synthetic method for the 3,4-olefinic 2-benzazepine-1,5-diones by utilizing the Lewis acid-promoted ring enlargement[3] of hydroxy propargyl γ-lactams **1** toward 7-membered lactams **3** *via* intramolecular endo-mode ring closure in the allenyl ketones **2** generated *in situ* as shown in Scheme 1. Thus, treatment of commercially available phthalimide **4a** and the Gabriel reaction[4]

Scheme 1

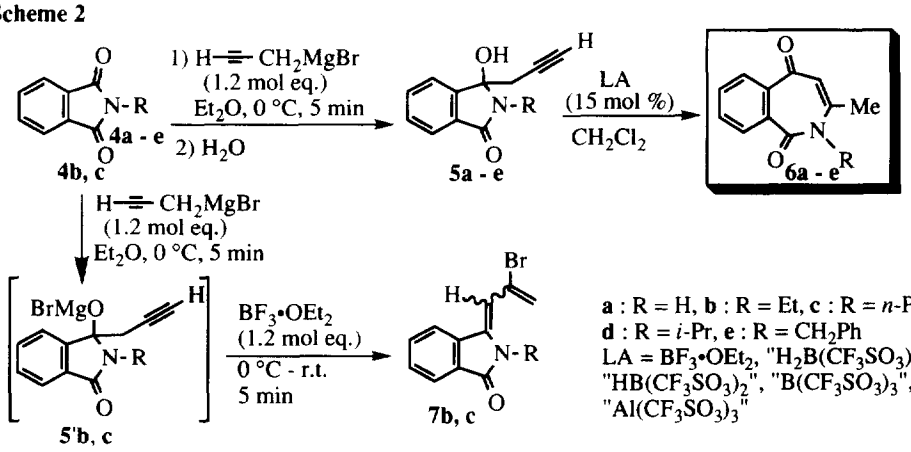


1 **2** **3**

R = H, alkyl ; LA = Lewis acid

products **4b** - **e** with 1.2 mol eq. of propargylmagnesium bromide[2a] in Et_2O at 0 °C for 5 min readily afforded the corresponding *N*-alkyl-3-hydroxy-3-propargylisoindolin-1-ones **5a** - **e** as a colorless powder or needles in 69 - 85% yields (Scheme 2 and Table 1). The structures of **5a** - **e** were confirmed by their characteristic spectroscopic data [IR ($CHCl_3$) ν 3295–3272 (-C≡CH), 3138–2922 (–OH), and 1713–1669 (lactam carbonyl) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) **5a** : δ 2.00 (t, 1H, *J* = 2.68 Hz, -CH_2-C≡C-H), δ 2.94 (d, 1H, *J* = 2.68 Hz, -CH_2-C≡C-H), and δ 2.96 (d, 1H, *J* = 2.68 Hz, -CH_2-C≡C-H) ppm **5b** - **5e** : δ 1.81-1.83 (ABX, 1H, $J_{AX, BX}$ = 1.47-2.69 Hz, -CH_2-C≡C-H), 2.67-2.92 (ABX, 1H, J_{AB} = 16.84-16.85, J_{AX} = 1.47-2.69 Hz, -CH_2-C≡C-H), and 2.93-3.08 (ABX, 1H, J_{AB} = 16.84-16.85, J_{BX} = 1.47-2.69 Hz, -CH_2-C≡C-H) ppm ; MS (M^+ ion)].

Scheme 2



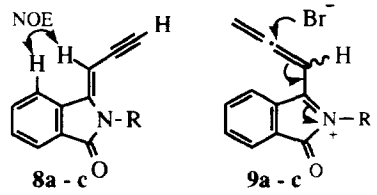


Table 1. Preparation of *N*-Alkyl-3-hydroxy-3-propargylisoindolin-1-ones **5a - e**

Product **5**	Yield (%)[a)]	mp (°C)
5a	69	158-159
5b	83	111-112
5c	70	132
5d	83	160-161
5e	85	156

a) All yields are those of the isolated compounds.

First, we tentatively carried out the ring enlargement reaction without isolation of **5b, c**. Namely, after reaction of **4b, c** with 1.2 mol eq. of propargylmagnesium bromide in Et_2O at 0°C for 5 min, 1.2 mol eq. of BF_3•OEt_2 was immediately added at 0 °C and then the mixture was stirred at room temperature for 5 min. However, we could not obtain the desired 2-benzazepine-1,5-diones **6b, c** at all. Instead, unexpected bromo dienes **7b, c** were obtained in 65% and 79% yields each as sole products. The stereochemistry (*E* or *Z*) of **7b, c** could not be determined by the ^1H NMR NOE experiment because of difficulty in assignment of the three olefinic proton signals. These compounds **7b, c** might be furnished by bromination onto plausible allenyl acyliminium species **9b, c** generated *in situ* from the corresponding ene-ynes **8b, c**, which were formed by BF_3-promoted elimination of BrMgOH from the propargylmagnesium bromide adducts **5'b, c**, respectively. The detailed mechanistic study is now in progress.

Subsequently, the reaction conditions to obtain a satisfactory amount of 2-benzazepine-1,5-dione **6c** were examined by employing 3-hydroxy-3-propargylisoindolin-1-one **5c** and a range of 2.4 - 0.05 mol eq. of BF_3•OEt_2. Consequently, **6c** was best obtained in 56% yield in the presence of 0.15 mol eq. (15 mol %) of BF_3•OEt_2 in CH_2Cl_2 at -78 °C over room temperature. Treatment of some other compounds **5a, b, d, e** with 15 mol% of BF_3•OEt_2 also resulted in 27 - 56% yields of 7-membered lactams **6a, b, d, e**, as shown in Table 2. Then, similar reactions of **5** toward **6** were examined in detail by exploiting slightly soft Lewis acids (15 mol%) such as "$H_2B(CF_3SO_3)$", "$HB(CF_3SO_3)_2$", "$B(CF_3SO_3)_3$", and "$Al(CF_3SO_3)_3$".[5] Table 2 summarizes the experimental results.[6]

Table 2. Ring Enlargement Reaction of 3-Hydroxy-3-propargylisoindolin-1-ones **5** to 3,4-Olefinic 2-Benzazepine-1,5-diones **6**

Compd 5	Reaction Conditions			Product 6	Yield (%) [b]	mp (°C)
	LA [a]	Temp (°C)	Time (h)			
5a[c]	B	-78 - r.t.	6.5	**6a**	27[d]	120 - 122
"	AT	-78 - 0	2.5	"	40[e]	"
"	BT	-78 - 10	2.6	"	81[f]	"
"	HBT	"	1.8	"	30[g]	"
5b	B	-78 - r.t.	6.5	**6b**	56	92 - 94
"	AT	-78 - 0	3	"	68	"
"	BT	-78 - 10	2.5	"	79	"
"	HBT	"	3	"	80	"
5c	B	-78 - r.t.	6.5	**6c**	56	73 - 74
"	AT	-78 - 0	6.5	"	51	"
"	BT	-78 - 10	3	"	78	"
"	HBT	"	3	"	98	"
"	H_2BT	"	1.5	"	93	"
5d	B	-78 - r.t.	6.5	**6d**	50	83 - 84
"	AT	-78 - 0	6.2	"	80	"
"	BT	-78 - 10	2.8	"	93	"
"	HBT	"	2.8	"	94	"
5e	B	-78 - r.t.	6.5	**6e**	54	125 - 126
"	AT	-78 - 0	3.2	"	71	"
"	BT	-78 - 10	4	"	79	"
"	HBT	"	3.5	"	85	"

a) LA : Lewis acid (15 mol%), B = BF_3•OEt_2, AT = "$Al(CF_3SO_3)_3$", BT = "$B(CF_3SO_3)_3$", HBT = "$HB(CF_3SO_3)_2$", H_2BT = "$H_2B(CF_3SO_3)$". b) All yields are those of isolated compounds. c) A solution (CH_2Cl_2 : THF = 2 : 1) was employed. d-g) Ene-yne compound **8a** was also obtained in various yields [d) 25%, e) 9%, f) trace, and g) 42%].

The desired ring enlargement reactions (**5** → **6**) with these slightly soft Lewis acids [approximate softness order[7]: "$H_2B(CF_3SO_3)$" > "$HB(CF_3SO_3)_2$" > "$B(CF_3SO_3)_3$" ≥ "$Al(CF_3SO_3)_3$" > BF_3] proved to be excellent in the yields of the 3,4-olefinic 2-benzazepine-1,5-diones **6b - e** except for compound **5a** with easy imine formation. These slightly soft Lewis acids may coordinate better with a soft Lewis base, "carbonyl oxygen atom" than with a hard base, "hydroxyl oxygen atom".[7] Thus, these tentative Lewis acids were efficient for essential ring-opening of the γ-lactam moiety of **5** followed by intramolecular endo-mode cyclization between the resulting imidate moiety and the conjugated allenyl ketone moiety generated *in situ* as shown in Scheme 1. Treatment of **5c** with a hard acid reagent system, a mixture of BF_3•OEt_2 with CF_3SO_3H[8] resulted in 57% yield of **6c**. Interestingly, with compound **5a**, ene-yne compound **8a** [mp 138-140 °C dec. (CH_2Cl_2-Et_2O)] was always produced as a by-product of **6a**. The structures of the synthesized 3,4-olefinic 2-benzazepine-1,5-diones **6a-e** were deduced from their characteristic spectroscopic data [IR (KBr) ν 1724-1713

(PhCOCH=CR_2) and 1686-1575 (PhCONR_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.43-2.26 (s, 3H, =CR-CH_3) and 6.22-6.01 (s, 1H, -COCH=CR_2) ppm ; MS (M^+ ion)].

In summary, we have established a new expeditious synthetic method for the 3,4-olefinic 2-benzazepine-1,5-diones based on the ring enlargement reaction of *N*-alkyl-3-hydroxy-3-propargylisoindolin-1-ones in the presence of a catalytic amount of the Lewis acid prepared from BH_3•THF (or Me_3Al) and CF_3SO_3H.

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6. A typical experimental procedure for the preparation of **6** : To a solution of BH_3•THF (1M solution in THF) (32.7 μl, 0.03 mmol) in anhydrous CH_2Cl_2 (2 ml) was added CF_3SO_3H (6.3 μl, 0.07 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C for 10 min and then compound **5c** (50 mg, 0.2 mmol) was added at -78 °C. After being stirred at -78 over 10 °C for 3 h, the reaction mixture was submitted to the usual work-up and chromatographic purification (silica gel, ether : hexane = 1 : 2) to give compound **6c** (49 mg, 98% yield) as colorless needles from CH_2Cl_2 - ether.
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