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Rh-catalyzed intramolecular debenzylative cyclization of amines. Butyrolactams from benzylamines having a chloroacetylene moiety

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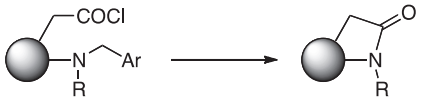
ABSTRACT

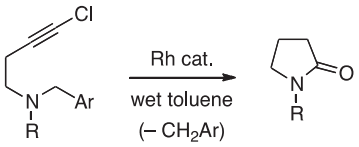
When benzylamines having a chloroacetylene moiety were heated in wet toluene with a catalytic amount of rhodium trifluoroacetate dimer, intramolecular debenzylative cyclization took place to give butyrolactams. This method is a new entry to selective debenzylation of amines.

Benzylamines are widely distributed in natural products[1] and are useful building blocks[2] as well as a versatile form of protected amines.[3] When one considers to use these benzylamines for further synthetic modification, one should require a debenzylation process to give back to the parent amines or, more preferably, directly to other requisite amino derivatives. Although there are many standard protocols for the removal of benzyl group(s) on amino group,[3,4] which include hydrogenation,[4a] dissolving-metal reduction,[4b] oxidation,[4c] or dealkylation via quaternarization,[4d] new methods are still called for, as these may contribute to the development of selective and mild transformations that are hitherto unexpected. While the former three methods afford the parent amines, the last one is characteristic of the formation of amides. If this amide formation can be carried out in an intramolecular manner, this will become a unique debenzylative cyclization, directly forming lactams as shown in Eq. 1.



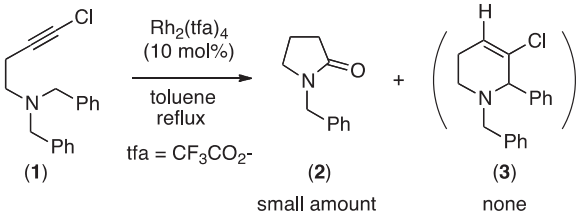
(1)

However, such applications have not been documented due perhaps to the incompatibility of labile acid chloride with other functional groups and/or their harsh reaction conditions. We report herein that a chloroacetylene moiety is a convenient surrogate of acid chloride in Eq. 1 so that an alternative debenzylative lactamization is viable under Rh catalysis as shown in Eq. 2.



(2)

During our study on a new Rh-catalyzed cyclization between sulfonylacetylene and benzyl ether,[5] we happened to examine the same reaction between haloacetylene[6] and benzylamine, that is, **1** as shown in Eq. 3. While this reaction did not afford a desired product **3**, a new product, butyrolactam **2**, was detected albeit in a low yield.



(3)

As this reaction provides a new debenzylative cyclization just as formulated in Eq. 2, we started optimization of its reaction conditions that are summarized in Table 1. The overall outcome of Eq. 3 suggested the necessity of water for this transformation, because the amide oxygen in **2**, in any event, must come from hydrolysis

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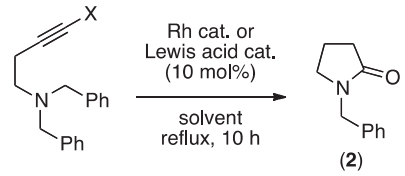
Table 1
Optimization of Rh-catalyzed intramolecular debenzylative cyclization

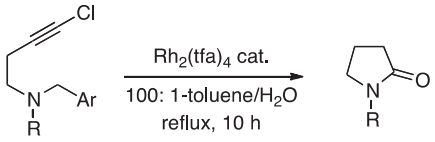


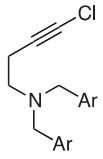
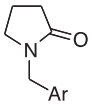
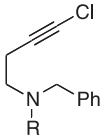
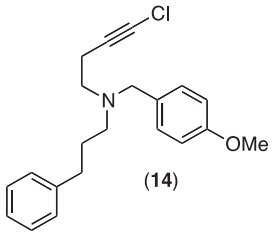
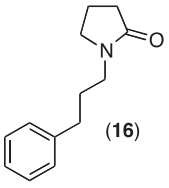
(**2**)

Entry	Rh cat. or Lewis acid cat.	X		Solvent	Isolated yield[a] (%)
1	$Rh_2(tfa)_4$	Cl	**(1)**	100:1-toluene/H_2O	95
2	$Rh_2(tfa)_4$	Cl	**(1)**	100:10-toluene/H_2O	58
3	$Rh_2(OAc)_4$	Cl	**(1)**	100:10-toluene/H_2O	37
4	$Rh_2(tfa)_4$	Br	—	100:1-toluene/H_2O	(13)
5	$Rh_2(tfa)_4$	I	—	100:1-toluene/H_2O	(28)
6	$BF_3{\cdot}OEt_2$	Cl	**(1)**	Toluene	(0)
7	$BF_3{\cdot}OEt_2$	Cl	**(1)**	100:1-toluene/H_2O	(0)

[a] Yields determined by ^1H NMR are in parentheses.

Table 2
Debenzylative cyclization of benzylamines



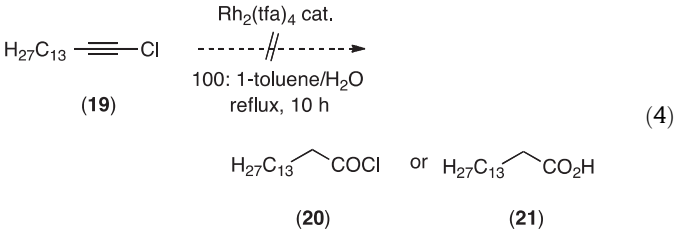
Entry	Substrate		$Rh_2(tfa)_4$ (mol %)	Product	Isolated yield (%)
					
1	Ar = Ph	**(1)**	10	**(2)**	95
2	*p*-MeC_6H_4–	**(4)**	20	**(7)**	81
3	*p*-ClC_6H_4–	**(5)**	20	**(8)**	82
4	*p*-$MeOC_6H_4$–	**(6)**	10	**(9)**	57[a]
					
5	R = $CH_3(CH_2)_8$–	**(10)**	10	**(15)**	59
6	$Ph(CH_2)_3$–	**(11)**	15	**(16)**	65
7	$BnO(CH_2)_6$–	**(12)**	20	**(17)**	58
8	C_6H_{11}–	**(13)**	20	**(18)**	68
9	 (**14**)		10	 (**16**)	56

[a] As a by-product, *N*,2-bis[(4-methoxyphenyl)methyl]butyrolactam was obtained in 9% yield.

of a certain intermediate with water. This expectation was soon found true, as the product yield increased to 95% when the reaction was performed in the presence of a small amount of water (entry 1). Increase in the amount of water (entry 2) or the use of rhodium acetate ($Rh_2(OAc)_4$) instead of $Rh_2(tfa)_4$ (entry 3) decreased the yield of **2**. Variation of the halogen on haloacetylenes was also examined (entries 1, 4, and 5). Of the three halides examined, chloro-derivative **1** afforded the best result. Probably, the other haloacetylenes are rather fragile under these reaction conditions. It should be also noted that the use of a Lewis acid, such as $BF_3{\cdot}OEt_2$, did not promote the cyclization at all (entries 6 and 7), showing the indispensable role of the Rh salt.

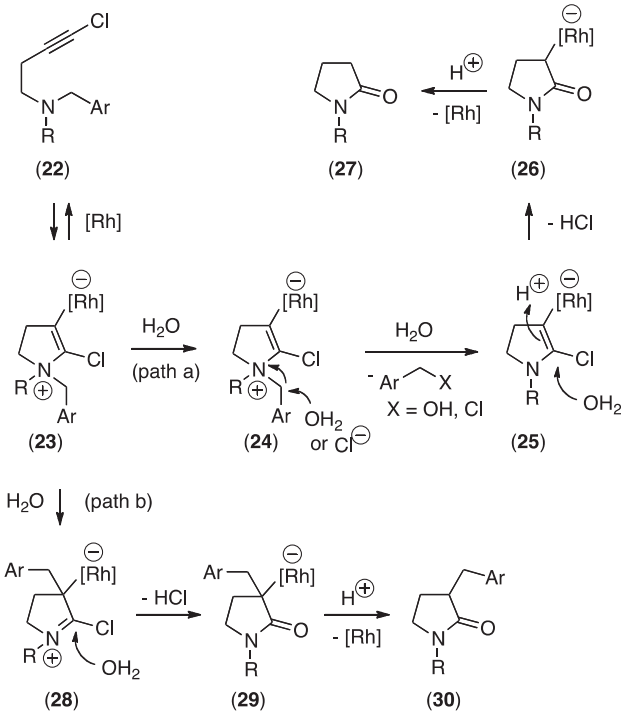
Other products prepared from various dibenzylamines or benzylamines are summarized in Table 2.[7] Dibenzylamines **1**, **4**, and **5** having an electron-rich or -deficient aromatic ring gave the desired products in almost similar yields (entries 1–3). However, in the case of bis[(4-methoxyphenyl)methyl]amine **6** (entry 4), the product yield decreased owing in part to the formation of a by-product, *N*,2-bis[(4-methoxyphenyl)methyl]butyrolactam, which will be discussed later. In all cases of dibenzylamines, only one benzyl group was cleanly dealkylated to give desired butyrolactams. This is in stark contrast to other debenzylation methods, where exhaustive debenzylation often occurs. Mono-benzyl derivatives **10**–**14** (entries 5–9) also underwent debenzylative cyclization to give alkyl-substituted butyrolactams **15**–**18** in good yields. A benzyloxy group in the side chain of **12** survived the reaction conditions to give desired compound **17** retaining this group (entry 7), which is again an advantageous feature of this method over other debenzylation methods. Even sterically hindered benzylamine **13** having a cyclohexyl group smoothly reacted to afford *N*-cyclohexylbutyrolactam (**18**) (entry 8). When mono[(*p*-methoxyphenyl)methyl]amine **14** was submitted to this cyclization, the benzyl-migrated product such as that in entry 4 was not detected (entry 9).

At first glance, this reaction appears to involve hydrolysis of the chloroacetylene moiety under Rh catalysis to give acid chloride, which then effected the debenzylative cyclization as mentioned in Eq. 1. However, the treatment of **19** with the Rh catalyst under the same reaction conditions as shown in Table 2 yielded neither the corresponding acid chloride **20** nor carboxylic acid **21** in a detectable amount (Eq. 4). Thus, this experiment negotiates the above possibility that the chloroacetylene works solely as a precursor of acid chloride.



(4)

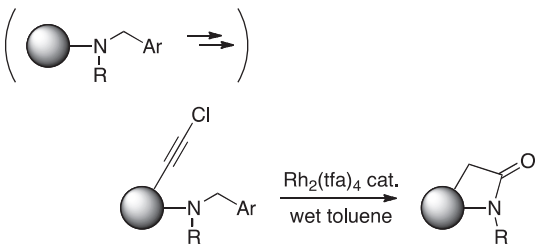
An alternative and more likely mechanism of this reaction is proposed in Scheme 1. The Rh catalyst first activates the acetylenic bond of **22** like a Lewis acid to promote quaternarization of the amino group (to **23**).[8] The resulting benzylammonium salt **23** is attacked by water or chloride anion (via **24**), which cleaves the benzyl-nitrogen bond (path a) to give transient **25**.[9] This scission of the carbon–nitrogen bond appears important to bring the first equilibrium to an irreversible process. Subsequent hydrolysis of α-chloroenamine **25** and the carbon–Rh bond in **26** affords the observed butyrolactam **27**.[10] This mechanism is consistent with the formation of the by-product, *N*,2-bis[(4-methoxyphenyl)-methyl]butyrolactam, in entry 4 of Table 2, because the side path



Scheme 1. Proposed mechanism.

b from the common intermediate **23**, involving 1,3-benzyl migration (→**28**) and the hydrolysis as above via **29**, afforded the by-product **30**. While this type of 1,3-benzyl migration has been documented in the relevant transition metal-catalyzed isomerization of acetylenic ethers and sulfides,[8a–d] it is retarded in the present reaction, as evidenced by the fact that product **30** was not usually isolated (except for entry 4 of Table 2) even in dry toluene (Eq. 3). Thus, the chloroacetylene serves for controlling the reaction to proceed exclusively along the path a.

As both introduction of an alkynyl group to amines and chlorination of terminal acetylenes can be carried out by various standard methods, the above reaction provides a useful tool for the debenzylative cyclization, directly giving butyrolactams as formulated in Eq. 5. Further application of this method to more complex substrates or naturally occurring products is in progress in our laboratory.



(5)

Acknowledgment

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7. *Typical procedure for chlorination of terminal acetylene.* Bis[(4-chlorophenyl)methyl](4-chloro-3-butynyl)amine (**5**): To a solution of bis[(4-chlorophenyl)methyl](3-butynyl)amine (115 mg, 0.362 mmol) in THF (4 mL) was added BuLi (1.57 M in hexane, 0.370 mL, 0.580 mmol) at −78 °C under argon. After stirring at −78 °C for 1 h, *N*-chlorosuccinimide (87.1 mg, 0.652 mmol) in THF (6 mL) was introduced to the mixture at −78 °C and the solution was stirred at room temperature for 7 h. The reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic products were extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane) to afford the title compound (110 mg, 86%) as an oil. The yield has not been optimized. ^{1}H NMR δ 2.31 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 7.1 Hz, 2H), 3.55 (s, 4H), 7.23–7.35 (m, 8H). ^{13}C NMR δ 17.59, 51.82, 57.50 (2 carbons), 58.21, 68.01, 128.48 (4 carbons), 129.26 (4 carbons), 132.83 (2 carbons), 137.72 (2 carbons). IR (neat) 3060, 3030, 2243, 1489, 1090, 1014, 838, 808 cm^{-1}. Anal. Calcd for $C_{18}H_{16}Cl_3N$: C, 61.30; H, 4.57. Found: C, 61.54; H, 4.84.
Typical procedure for debenzylative cyclization. N-[(4-Chlorophenyl)methyl]-butyrolactam (**8**): A mixture of bis[(4-chlorophenyl)methyl](4-chloro-3-butynyl)amine (**5**) (31.8 mg, 0.090 mmol) and rhodium trifluoroacetate dimer ($Rh_2(tfa)_4$, 11.8 mg, 0.018 mmol) in toluene (1.0 mL) and water (0.01 mL) was heated at reflux for 10 h under argon. After being cooled to room temperature, the mixture was filtered through a short pad of Celite with the aid of ethyl acetate. The combined filtrates were concentrated to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (15.5 mg, 82%) as an oil. ^{1}H NMR δ 2.01 (quintet, J = 7.7 Hz, 2H), 2.45 (t, J = 7.7 Hz, 2H), 3.26 (t, J = 7.7 Hz, 2H), 4.42 (s, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H). ^{13}C NMR δ 17.78, 30.81, 46.02, 46.60, 128.87 (2 carbons), 129.51 (2 carbons), 133.51, 135.22, 174.97. IR (neat) 3060, 3049, 2926, 1682 (C=O), 1493, 1093, 1016, 802 cm^{-1}.
An authentic sample of this compound was prepared by the alkylation of butyrolactam with [(4-chlorophenyl)methyl] bromide and NaH in DMF. The two samples prepared by the rhodium-catalyzed reaction and the alkylation were identical in all respects.
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9. In a typical case, the formation of benzyl alcohol and the corresponding chloride (ca. 1:1 ratio, from **24**) was detected in a comparable yield to that of **27**.
10. An alternative mechanism, consisting of demetallation of the rhodium moiety followed by the hydrolysis of the resultant chloroenamine as shown below, is also likely, but we could not isolate the intermediate chloroenamine **31** or **32** for now.