Notes

Beckmann Rearrangement of 1-Indanone Oxime Using Aluminum Chloride

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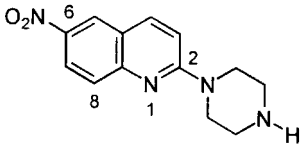
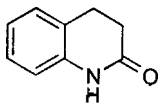
Beckmann rearrangements (BR)[1] of 1-indanone and α-tetralone oximes were reported by Lansbury and Mancuso.[2] While the BR yield of α-tetralone was higher than 65%, that of 1-indanone was only 20% at 110-120 °C for 10 min in the presence of polyphosphoric acid (PPA).[3]

Even though 6-nitroquipazine has been known as one of the most potent and selective antagonist of 5-hydroxyltryptamine (Serotonin or 5-HT) transporter, the studies of structure-activity relationship of its derivatives are not sufficient. Surprisingly, the regioselective synthesis of 6-nitroquipazine has not been reported. We have reported a new efficient synthesis of 6-nitroquipazine derivatives.[3]



6-Nitroquipazine



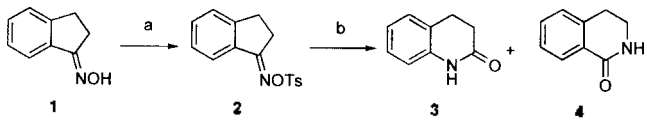
Hydrocarbostyril

6-Nitroquipazine was prepared by three steps from a commercially available starting material, hydrocarbostyril (**3**), in 82% yield. Using this method, one can make the derivatives of 6-nitroquipazine from the various derivatives of hydrocarbostyril.

In order to improve the low BR yield of 1-indanone oxime and to synthesize hydrocarbostyril (**3**) derivatives from other 1-indanone derivatives, we tried to modify the reaction conditions, reagents such as protic acid, thionyl chloride in dioxane, *p*-toluenesulfonyl chloride in pyridine, triethylamine in 80% ethanol. Most reactions under these reaction conditions were not proceeded at all, but only a few reactions gave lower yield than the previous method. While the BR in the presence of protic acid such as H_2SO_4, HCl, H_3PO_4, and PPA led undesired results, the BR reaction in the presence of a Lewis acid, aluminum chloride, provided hydrocarbostyril in 91% yield.[3] Moreover, this method is very efficient as well as mild because the reaction undergoes at room temperature and even lower temperatures like −40 °C.

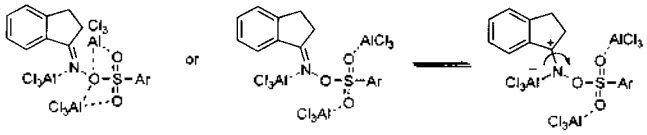
Although a few BRs using organoaluminum[4-6] and aluminum chloride[6] have been reported, there are no studies for 1-indanone and its derivatives up to now. As shown in Scheme 1, 1-indanone oxime tosylate (**2**) was prepared by reaction of *p*-toluenesulfonyl chloride and 1-indanone oxime, which is a commercially available compound, under basic condition in 95% yield.

At the first time, aluminum chloride was thought to act as a catalyst. But the best results were obtained when using of



Scheme 1. Reaction condition: a) TsCl, 4 N NaOH, acetone, −10 °C - rt. b) $AlCl_3$, CH_2Cl_2, −40 °C - rt.

three equivalents of aluminum chloride. It seems that three aluminum chlorides coordinate to tosylate as shown below; the aluminum chlorides, coordinated to nitrogen as well as oxygen of sulfonate, contribute to increase reactivity for migration of aryl or alkyl moiety. Once aluminum chloride coordinates to the nitrogen atom, free rotation through single bond of C-N is possible to reach pre-equilibrium.



To check whether product ratio depends on the *trans* and *cis* ratio of tosylates or not, each isomer of tosylate was isolated by flash column chromatography. Pure *trans* and *cis* isomers of oxime became mixture of isomers during tosylation. Two dimensional TLC (coated by silica gel) of both pure *trans* and *cis* oximes showed isomerization each other. The fact is one of strong evidence of isomerization even in mild acidic condition such on silica gel. As the *trans* and *cis* tosylates have a similar R_f value and *cis* isomer is a minor product, we could not get a pure *cis* isomer. But a pure trans isomer was obtained by recrystalization. Table 1 shows the results of the BR of 1-indanone oxime tosylate with different trans and cis ratio and at two different temperature; −40 °C and room

Table 1. The Beckmann Rearrangement of 1-Indanone Oxime Tosylates.

Compound	Tosylate ratio		Reaction temp.(°C)	Total yield(%)	Product ratio	
	trans	*cis*			**3**	**4**
2	97	3	−40 °C - rt	99	92	8
			−40 °C	95	86	14
			rt	98	75	25
	100	0	−40 °C - rt	98	76	24
	21	79[a]	−40 °C - rt	98	13	87

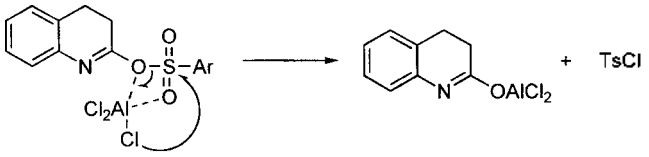
[a] As *cis* tosylate are formed in a small ratio and has very similar R_f with *trans* isomer, this was the best ratio we got.

temperature.

The *trans* and *cis* ratio of tosylates was calculated on the basis of NMR integration, and the ratio of hydrocarbostyril (**3**) to 3,4-dihydro-1(2*H*)-quinolinone (**4**) was obtained by practical isolation. The two final products synthesized from 1-indanone derivatives well characterized by clear assignment through NMR spectra. While protons of 3,4-dihydro-2(1*H*)-quinolinone derivatives **3** emerge in up-field, those of 3,4-dihydro-1(2*H*)-quinolinones **4** show at relatively down-field. Especially, two protons at C3 of 3,4,-dihydro-1(2*H*)-quinolinones couple with the NH proton of the amide group as well as the two protons at C4 to show at 3.55 ppm as triple of doublet (J=6.7, 3.0 Hz).

Based on the mechanism of BR and experimental results, *trans* tosylate gives hydrocarbostyril and *cis* gives 3,4-dihydro-1(2*H*)-quinolinone. To check whether product ratio depends on the *trans* and *cis* ratio of tosylates or not, each isomer would be isolated by flash column chromatography. The amount of 3,4-dihydro-1(2*H*)-quinolinone was slightly increased more than the amount of *cis* tosylate. It indicates that free rotation though C-N single bond is not easy due to high energy barrier required for isomerization. In order to check how the ratio of the product will be affected by changing temperature, the BR of tosylate was carried out at two different temperatures; −40 °C and room temperature. 3, 4-Dihydro-1(2*H*)-quinolinone (**4**) was formed more at room temperature than at −40 °C. But reaction temperature was considered as less important factor in product ratio. This result shows that this isomerization of aluminum chloride-coordinated species may have significant energy barrier.

After reaction was completed, *p*-toluenesulfonyl chloride (55%) was recoverd by flash chromatography. Based on this observations, it is thought that following mechanism is included in the reaction.



In conclusion, a Lewis acid, aluminum chloride improved the yield of Beckmann rearrangement of 1-indanone oxime providing hydrocarbostyril as a major product in 91% yield via tosylate at from −40 °C to room temeperature. Aluminum chloride is cheap, stable and easy to handle compared with organoaluminum reagents in the laboratory. This method will be useful for the synthesis of other hydrocarbostyril derivatives from corresponding 1-indanone derivatives.

Experimental

Materials and Methods. Column chromatography was done by flash chromatography with silica gel (EM Science, 230-400 mesh ASTM). Solvents and reagents were purchased from the following commercial sources: Aldrich, Kanto, Acros. Analytical thin layer chromatography (TLC) was performed with Merck silica gel F-254 glass-backed plates. Visualization was achieved by phosphomolybdic acid (PMA), $KMnO_4$, or anisaldehyde spray reagents, iodine, or UV illumination. ^1H and ^{13}C NMR spectra were obtained on Varian Gemini-2000 spectrometers and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained on HP590 GC/MS 5972 MSD spectrometer.

1-Indanone oxime (1). Hydroxylamine hydrochloride (0.68 g, 9.84 mmol) in 2 mL of water was added to a solution of 1-indanone (1.00 g, 7.57 mmol) in 20 mL of methanol. To the stirred mixture was added 4N NaOH (3.78 mL, 15.13 mmol) at −10 °C dropwise. After 5 min, the cooling bath was removed. The reaction was maintained for 1h at rt, and then quenched by adding 50 mL of water. The resulting mixture was extracted with ethylacetate (20 mL × 4). The combined extracts were dried over sodium sulfate, and evaporated under reduced pressure. The 1.05 g (94%) of 1-indanone oxime was obtained by flash chromatography (20% EtOAc/Hx) as a white crystal.

***trans*-*O*-(*p*-Toluenesulfonyl)indan-1-one oxime (*trans*-2).** To a stirred solution of 1-indanone oxime (0.90 g, 6.12 mmol) and *p*-toluenesulfonyl chloride (1.28 g, 6.73 mmol) in 30 mL of acetone was added 4N NaOH at −10 °C dropwise. After 5 min, the cooling bath was removed. The reaction was continued for 1h at rt, and then quenched by being poured into 200 mL of ice-crashed water. The resulting mixture was extracted with ethylacetate (20 mL × 4). The combined extracts were dried over sodium sulfate, and evaporated under reduced pressure. The 1.76 g (96%) of 1-indanone oxime was obtained by flash chromatography (20% EtOAc/Hx) as white crystal: IR (KBr) 3440, 3070, 2930, 1600, 1450, 1380 cm $^{-1}$; ^1H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.03 (br s, 4H), 7.46-7.22 (m, 5H), 7.68 (d, J =7.6 Hz, 1H), 7.94 (d, J=8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 26.0, 26.7, 121.3, 124.1, 125.6, 127.3, 127.9, 130.8, 131.5, 131.9, 143.3, 148.4, 169.7; MS (EI) m/z (relative intensity) 301 (M^+, 2), 260 (6), 209 (11), 155 (22), 139 (28), 130 (100), 116 (45), 106 (44), 91 (43), 77 (33).

3,4-Dihydro-2(1*H*)-quinolinone (3) and 3,4-dihydro-1(2*H*)-quinolinone (4). Aluminum chloride (0.66 g, 4.98 mmol) was added to a solution of *O*-(*p*-toluenesulfonyl)indan-1-one oxime (0.50 g, 1.66 mmol) in 15 mL of CH_2Cl_2 at −40 °C portionwise. After 10 min, The cooling bath was removed. The mixture was stirred for additional 1h at rt, and then quenched by adding 50 mL of water carefully. The mixture was extracted from aqueous phase with CH_2Cl_2 (20 mL × 4). The extract was dried over sodium sulfate, and evaporated under reduced pressure. The 222 mg (91%) of 3,4-dihydro-2(1*H*)-quinolinone (**3**) and 20 mg (8%) of 3,4-dihydro-1(2*H*)-quinolinone (**4**) was obtained by flash chromatography (40% EtOAc/Hx) as white crystal. The 174 mg (55%) of *p*-toluensulfonyl chloride was also recovered. **3**: commercially available; IR (KBr) 3470, 3140, 2985, 1685, 1590, 1440, 1340, 1280 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.64 (t, J=7.5 Hz, 2H), 2.96 (t, J=7.5 Hz, 2H), 6.89 (d, J=7.8 Hz, 1H), 6.99 (t, J=7.2 Hz, 1H), 7.14 (d, J=7.6 Hz, 1H), 7.16 (t, J=7.8 Hz, 1H), 9.78 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.6, 29.0, 114.1, 121.4, 121.9, 125.9, 126.2, 135.8, 171.1; MS (EI) m/z (relative intensity) 147 (M^+, 87), 128 (8), 118 (100), 104 (20), 91 (22), 77 (12). Anal. Calcd for C_9H_9NO: C, 73.44; H, 6.16; N, 9.52. Found: C, 73.84; H, 6.44; N, 9.50. **4**: IR (KBr) 3450, 3085, 2965, 1670, 1600, 1485 cm − 1; ^1H NMR (200 MHz, $CDCl_3$) δ 2.96 (t, J=6.7 Hz, 2H), 3.55 (td, J=6.7, 3.0 Hz, 2H), 7.19 (d,

J=7.2 Hz, 1H), 7.46-7.28 (m, 3H), 8.04 (dd, J=7.6, 1.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.5, 38.4, 125.4, 125.6, 126.2, 127.4, 130.5, 137.3, 165.2; MS (EI) m/z (relative intensity) 147 (M^+, 61), 128 (10), 118 (100), 90 (56), 77 (4).

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Unexpected Carbon-Nitrogen Bond Hydrolysis of Terminal Amides Catalyzed by Porcine Liver Esterase

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Enzymatic resolution of ester derivatives with esterase are the most commonly used approaches for the synthesis of optically active acids or esters. The esterases are very popular in the biotransformations.[1] Most of the esterases catalyze the hydrolysis or the formation of ester bond. In some cases, the carboxyl groups have been protected as amides which are very stable in the mild alkaline hydrolysis. The general deprotecting reagents of amide are butyl nitrite,[2] nitrosyl chloride,[3] and nitrosonium tetrafluoroborate.[4] The hydrolysis of amide into carboxylic acid usually requires severe condition, for example, heating in the presence of a strongly basic or acidic catalyst. However, the advantages of enzymatic hydrolysis require a neutral pH, room temperature, very few side product and atmospheric pressure. Esterases are generally unable to cleave amide bonds because of the greater stability of an amide bond as compared to that of an ester. The report of the hydrolysis of a highly strained β-lactam derivative by pig liver esterase is an exception.[5] Enzymatic resolution of amino acid amides by amino acid amidases (aminopeptidases) are generally used to obtain the L-amino acid[6] and (S)-naproxen.[7] We screened the enzymes for the hydrolysis of terminal amide. Accidently, the porcine liver esterase showed the activity of hydrolysis of the amide bond of lipoamide. Here we wish to report the deamination of the carboxy amide group by the porcine liver esterase.

A typical hydrolysis procedure was carried out under the following condition; lipoamide (50 mg, 0.24 mmol), porcine liver esterase (750 unit) suspended in 3.2 M $(NH_4)_2SO_4$ solution (pH=8) from sigma, 0.1 N potassium phosphate buffer (pH=7, 25 mL). The reaction was carried out at 36 °C and 250 rpm. After 2 days of reaction period, the mixture was filtered and washed with 10 mL of methanol. The combined solution was evaporated under reduced pressure to obtain lipoic acid. For the isolation with silicagel column chromatography, the crude lipoic acid in MeOH (4 mL) was treated with diazomethane[8] to give methyl lipoate in 71% yield. The yield of enzymatic reaction was based on the isolated methyl lipoate.

Comparative hydrolysis of lipoamide in mixture of phosphate buffer and various organic solvents were carried out with porcine liver esterase. The conversion yield of lipoamide into lipoic acid decreased from nonpolar solvent to polar solvent. Because of the good solubility of substrate, it was expected that the reaction would proceed very fast in polar solvents, but no product was obtained in these solvents. One of the possible speculations is that the enzyme is deactivated in polar solvents.[9] When isooctane was used as a cosolvent, the best conversion yield was obtained as shown in Table 1.

The pH-dependence of the hydrolysis reaction was studied over a pH range of 5-9. The best conversion yield was obtained at pH=7 as shown in Table 2. At pH 8 and 9, the reaction progressed faster than that of pH 5 and 6. At the higher pH, the reaction rate and yield of the product are

Table 1. Hydrolysis of lipoamide in various phosphate buffer-organic solvents with porcine liver esterase at 36 °C

solvent[a]	reaction time (hr)	yield[b] (%)
isooctane	70	71
n-hexane	87	54
toluene	90	33
methanol	115	8
acetone	120	none
acetonitrile	129	none

[a] The ratio of buffer: organic solvent was 80:20. [b] The yield was based on methyl lipoate.