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A New Synthesis of 2,3-Di- or 2,3,3-Trisubstituted 2,3-Dihydro-4-pyridones by Reaction of 3-Ethoxycyclobutanones and *N*-*p*-Toluenesulfonyl Imines Using Titanium(IV) Chloride: Synthesis of (±)-Bremazocine

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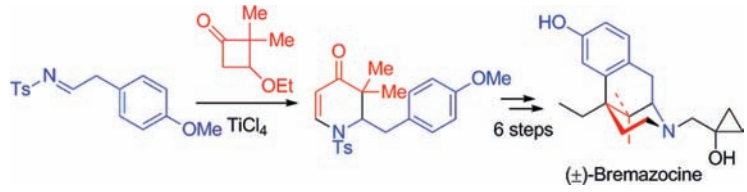
ABSTRACT



***N*-*p*-Toluenesulfonyl (Ts) aldimines reacted with 3-ethoxycyclobutanones by catalysis of titanium(IV) chloride to afford 2,3-di- or 2,3,3-trisubstituted *N*-Ts-2,3-dihydro-4-pyridones. Synthesis of (±)-bremazocine was efficiently accomplished by using this method.**

2,3-Dihydro-4-pyridones are versatile synthetic intermediates in organic synthesis.[1] 2-Monosubstituted dihydropyridones are usually prepared by *N*-acylation or *N*-alkylation of 4-methoxypyridine followed by addition of a Grignard reagent and subsequent hydrolysis.[1] Another alternative method to these systems, reported by Abramovitch,[2] involves the [4 + 2] cycloaddition between *N*-Ts-imine and Danishefsky's diene.[3] By these conventional methods, additional mono- or dialkylation is required for preparation of 2,3-di- or 2,3,3-trisubstituted dihydropyridones, which are often employed in the synthesis of biologically active compounds.[4] Therefore, a short synthesis of these multisubstituted dihydropyridones would be valuable for the rapid synthesis of various piperidine derivatives such as benzomorphans.[4]

We have recently reported that zwitterionic intermediate **2**, which is formed by Lewis acid-catalyzed ring cleavage of 3-alkoxycyclobutanones **1**, reacts with aldehydes or ketones to afford tri- or tetrasubstituted tetrahydropyrones or dihydropyrones.[5,6] It was thought that zwitterionic inter-

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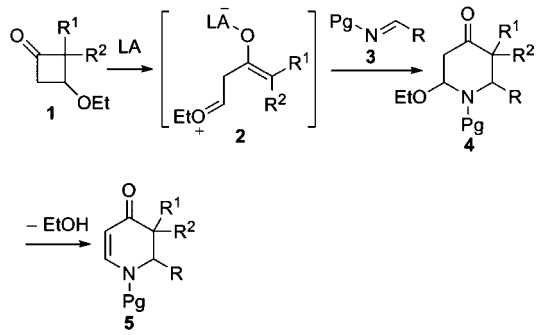
mediate **2** would also react with imines **3** to afford tetrahydropyridones **4** or dihydropyridones **5** (Scheme 1). In this

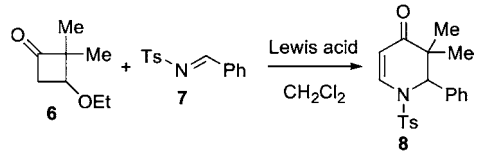
Scheme 1. Synthesis of Dihydropyridones **5** by Reaction of Cyclobutanone **1** with Imine **3**



regard, we now report here a direct method for the synthesis of multisubstituted dihydropyridones **5** by the reaction of 3-ethoxycyclobutanone **1** with *N*-Ts imines, and we also describe herein a synthesis of (±)-bremazocine, whose (−)-enantiomer is a benzomorphan-based *κ*-opioid agonist.[7] For the latter, this was achieved using a newly developed synthetic method for dihydropyridones.

First, we explored a suitable Lewis acid for the reaction of cyclobutanone **6** and *N*-Ts-benzylideneimine **7** (Table 1).

Table 1. Effects of Lewis Acids[a]



entry	Lewis acid	conditions	yield[b] (%)
1	$TiCl_4$	−45 °C, 1 h	80
2	$TiBr_4$	−45 °C, 1 h	56
3	$SnCl_4$	−45 °C to rt, 1 h	74
4	$SnBr_4$	−45 °C to rt, 3.5 h	41
5	BF_3−OEt_2	−45 °C to rt, 4 h	34
6	$EtAlCl_2$	−45 to 0 °C, 2 h	10
7	Me_3SiOTf	−45 °C, 1 h	41

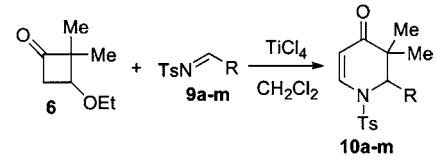
[a] Imine **7** (1 equiv), cyclobutanone **6** (1.6 equiv), and Lewis acid (1.3 equiv) were employed. [b] Isolated yield.

It was found that titanium(IV) chloride catalyzed the desired cyclization most efficiently, with dihydropyridone **8** being isolated in 80% yield (Table 1, entry 1). Tetrahydropyridone **4** was not obtained under these conditions probably due to the participation of nitrogen in the elimination of ethanol from **4** (see Scheme 1). Tin(IV) chloride also gave the desired cycloadduct **8** in a comparable yield (entry 3). With ethylaluminum dichloride, ethylation of imine **7** (33%) was also observed (entry 6).

Titanium(IV) chloride-mediated reactions of cyclobutanone **6** with *N*-Cbz-, *N*-Boc-, and *N*-Bn-benzylideneamines were perfomed, and the corresponding dihydropyridones were obtained in 28%, 41%, and 7% yields, respectively.

Next, the scope and limitations of the titanium(IV) chloride-catalyzed cyclization of cyclobutanone **6** were investigated using various *N*-Ts-imines **9** (Table 2). *N*-Ts-

Table 2. Synthesis of Dihydropyridones **10a**−**m** by the Reaction between Cyclobutanone **6** and Various *N*-Ts-imines **9a**−**m**[a]



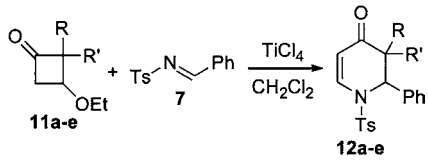
entry	R (imine **9**)	conditions	**10**	yield[b] (%)
1	4-$MeOC_6H_4$ (**9a**)	0 °C, 30 min	**10a**	40
2	4-MeC_6H_4 (**9b**)	0 °C, 30 min	**10b**	71
3	4-BrC_6H_4 (**9c**)	−45 °C, 1 h	**10c**	78
4	4-ClC_6H_4 (**9d**)	−45 °C, 1 h	**10d**	77
5	4-FC_6H_4 (**9e**)	−45 °C, 1 h	**10e**	76
6	4-$NO_2C_6H_4$ (**9f**)	0 °C, 30 min	**10f**	32
7	1-Naph (**9g**)	0 °C, 30 min	**10g**	31
8	2-Naph (**9h**)	−45 °C, 1 h	**10h**	62
9	PhCH=CH (**9i**)	−20 °C, 1 h	**10i**	84
10	PhC'C (**9j**)	−20 °C, 30 min	**10j**	64
11	*n*-Pr (**9k**)	−20 °C, 1 h	**10k**	62
12	*c*-Hex (**9l**)	−20 °C, 1 h	**10l**	67
13	*t*-Bu (**9m**)	−20 °C, 1 h	**10m**	trace

[a] For conditions, see Table 1. [b] Isolated yield.

imines **9a**−**h**, which were prepared from aromatic aldehydes, gave the corresponding dihydropyridones **10a**−**h** in good yields (62−78% yields) except **9a**, **9f**, and **9g** (entries 1−8). Reaction with conjugated *N*-Ts-imines such as alkenylimine **9i** and alkynylimine **9j** also proceeded smoothly to afford the corresponding cyclization adducts **10i** and **10j** in 84% and 64% yields, respectively (entries 9 and 10). Aliphatic aldimines such as **9k** and **9l** readily reacted with cyclobutanone **6** following activation with titanium(IV) chloride (entries 11 and 12). The fact that 1-naphthylimine **9g** and *tert*-butylimine **9m** gave the desired adducts **10g**,**m** in low yields suggests that the present reaction was strongly influenced by steric effects (entries 7 and 13). The reaction between **6** and *N*-Ts-ketimine derived from acetophenone gave the desired product only in a trace amount. Therefore, it was difficult to synthesize 2,2,3,3-tetrasubstituted 2,3-dihydro-4-pyridones by the present method.

Reactions between various 3-ethoxycyclobutanones **11a**−**e** and *N*-Ts-imine **7** were performed (Table 3). 2,2-Diethylcyclobutanone **11a** and spirocyclobutanone **11b** bearing a quaternary carbon center at their 2-position reacted smoothly at −20 °C to afford the corresponding adducts **12a** and **12b** in 74% and 75% yields, respectively (entries 1 and 2). 2-Monoalkyl-substituted cyclobutanones **11c**−**e** also reacted at −45 °C to afford the corresponding dihydropyridones **12c**−**e** in about 60% yield (entries 3−5).

Table 3. Reaction of Various 3-Ethoxycylobutanones **11a**−**e** with *N*-Ts-imine **7**[a]

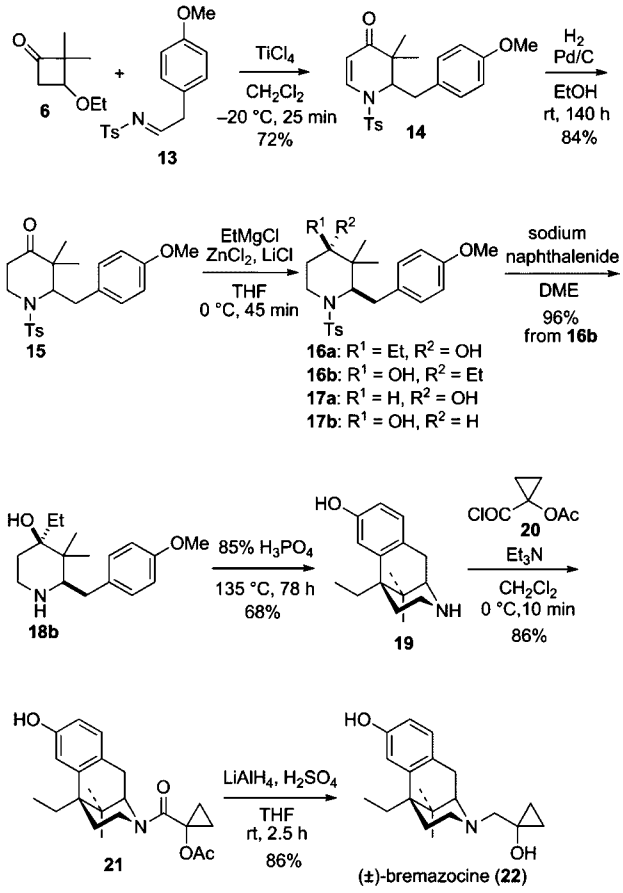


entry	cyclobutanone (**11**) R, R′	conditions	**12**	yield (%)[b]
1	Et, Et (**11a**)	−20 °C, 1 h	**12a**	74
2	−$(CH_2)_5$− (**11b**)	−20 °C, 1 h	**12b**	75
3	Me, H (**11c**) (26:74)[c]	−45 °C, 1 h	**12c**	61 (59:41)[c]
4	Et, H (**11d**) (30:70)[c]	−45 °C, 1 h	**12d**	57 (63:37)[c]
5	*i*-Pr, H (**11e**) (40:60)[c]	−45 °C, 1 h	**12e**	60 (60:40)[c]

[a] For reaction conditions, see Table 1. [b] Isolated yield. [c] Cis/trans ratio. The stereochemistry was determined by ^{1}H NMR spectra (see the Supporting Information).

The present new method for preparation of dihydropyridones was applied to a synthesis of (±)-bremazocine (**22**)

Scheme 2. Synthesis of (±)-Bremazocine (**22**)



(Scheme 2).[8] The titanium(IV) chloride-promoted reaction between cyclobutanone **6** and *N*-Ts-imine **13** proceeded effectively to afford dihydropyridone **14** in 72% yield. Catalytic hydrogenation of **14** with palladium on carbon gave ketone **15** in 84% yield. Addition of ethylmagnesium chloride to ketone **15** gave the desired ethylated product **16b** in 23% yield[9] along with reduction products (**17a** (25%) and **17b** (19%)) and recovered ketone **15** (9%). Ishihara's method of using the zinc(II) ate complex (EtMgCl, $ZnCl_2$, and LiCl)[10] greatly improved the yield of **16** to 89% (**16a** (1%) and **16b** (88%)). These products were formed alongside a small amount of reduction products (**17a** (3%) and **17b** (2%)).[11] Deprotection of the *N*-Ts group of **16b** with sodium naphthalenide afforded **18b** in 96% yield. Intramolecular Grewe-type carbocation cyclization[12] of **18b** and deprotection of the methyl ether moiety took place under carefully optimized reaction conditions using 85% phosphoric acid at 135 °C for 78 h to give benzomorphan **19** in 68% isolated yield.[13] Selective acylation of the secondary amino group in **19** with carboxylic acid chloride **20** gave the corresponding amide **21** in 86% yield, and reduction of **21** with aluminum hydride, which was prepared from lithium aluminum hydride and sulfuric acid, gave (±)-bremazocine (**22**) in 86% yield.

In summary, we have developed a new method for the synthesis of dihydropyridones that involves a reaction between 3-ethoxycyclobutanones and *N*-Ts-imines under catalysis by titanium(IV) chloride. This method provides rapid access to 2,3-di- or 2,3,3-trisubstituted dihydropyridones and is useful for the synthesis of benzomorphans.

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Supporting Information Available: Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1012313

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(9) Compound **16a** was not obtained. For details, see the Supporting Information.

(10) (a) Hatano, M.; Suzuki, S.; Ishihara, K. *Synlett* **2010**, 321–324. (b) Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun.* **2010**, *46*, 2674–2676.

(11) 1,2-Addition of lithium trimethylsilylacetylide to ketone **15** gave a 1,2-adduct in 84% yield. Deprotection of trimethylsilyl group with potassium carbonate in methanol followed by hydrogenation of the terminal alkynyl group with palladium on carbon gave **16** in 84% yield for two steps. For details, see the Supporting Information.

(12) (a) Grewe, R.; Mondon, A. *Chem. Ber.* **1948**, *81*, 279–286. (b) Takeda, M.; Jacobson, A. E.; Kanematsu, K.; May, E. L. *J. Org. Chem.* **1969**, *34*, 4154–4157. (c) Comins, D. L.; Zhang, Y.-m.; Joseph, S. P. *Org. Lett.* **1999**, *1*, 657–659.

(13) The use of hydrobromic acid instead of phosphoric acid gave **18** in lower yields.