

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

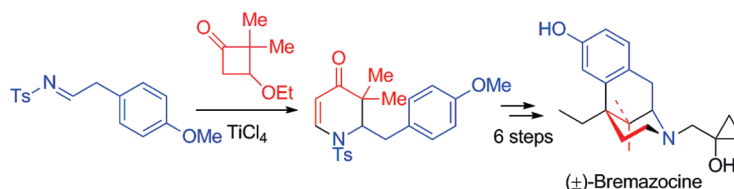
Jun-ichi Matsuo,* Ryohei Okado, and Hiroyuki Ishibashi

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

jimatsuo@p.kanazawa-u.ac.jp

Received May 28, 2010

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-

(1) (a) Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491–1500. (b) Joseph, S.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870–880. (c) Koulocheri, S. D.; Pitsinos, E. N.; Haroutounian, S. A. *Curr. Org. Chem.* **2008**, *12*, 1454–1467.

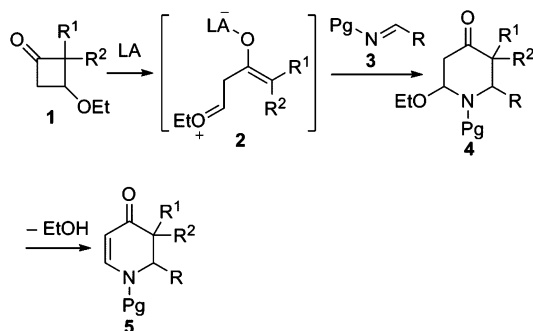
(2) (a) Abramovitch, R. A.; Stowers, L. R. *Heterocycles* **1984**, *22*, 671–673. (b) Pégot, B.; Vo-Thanh, G. *Synlett* **2005**, 1409–1412.

(3) Recently reported methods for synthesis of 2,3-dihydro-4-pyridones: (a) Donohoe, T. J.; Connolly, M. J.; Walton, L. *Org. Lett.* **2009**, *11*, 5562–5565. (b) Flick, A. C.; Padwa, A. *ARKIVOC* **2009**, 4–14. (c) Harmata, M.; Lee, D. R. *ARKIVOC* **2007**, 91–103. (d) Svetlik, J.; Kettmann, V.; Zaleska, B. *Tetrahedron Lett.* **2005**, *46*, 5511–5514. (e) Dong, D.; Bi, X.; Liu, Q.; Comg, F. *Chem. Commun.* **2005**, 3580–3582. (f) Kumar, A. S.; Haritha, B.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 4261–4263.

(4) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1–36.

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

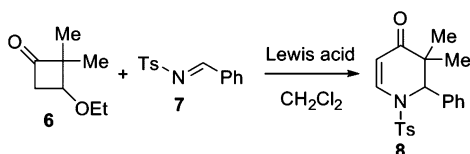
Scheme 1. Synthesis of Dihydropyridones **5** by Reaction of Cyclobutanone **1** with Imine **3**



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 ₃ SiOTf	–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.

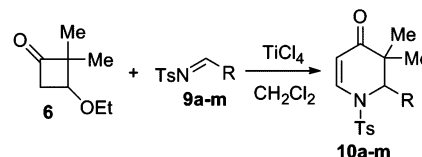
It was found that titanium(IV) chloride catalyzed the desired cyclization most efficiently, with dihydropyridone **8** being isolated in 80% yield (Table 1, entry 1). Tetrahydropyridone **4** was not obtained under these conditions probably due to the participation of nitrogen in the elimination of ethanol 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 performed, 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



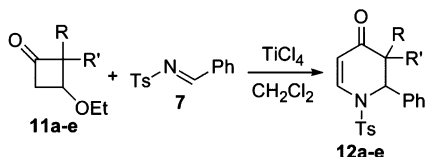
entry	R (imine 9)	conditions	10	yield ^b (%)
1	4-MeOC ₆ H ₄ (9a)	0 °C, 30 min	10a	40
2	4-MeC ₆ H ₄ (9b)	0 °C, 30 min	10b	71
3	4-BrC ₆ H ₄ (9c)	–45 °C, 1 h	10c	78
4	4-ClC ₆ H ₄ (9d)	–45 °C, 1 h	10d	77
5	4-FC ₆ H ₄ (9e)	–45 °C, 1 h	10e	76
6	4-NO ₂ C ₆ H ₄ (9f)	0 °C, 30 min	10f	32
7	1-Naph (9g)	0 °C, 30 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	<i>n</i> -Pr (9k)	–20 °C, 1 h	10k	62
12	<i>c</i> -Hex (9l)	–20 °C, 1 h	10l	67
13	<i>t</i> -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-Ethoxycyclobutanones **11a–e** with *N*-Ts-imine **7**^a

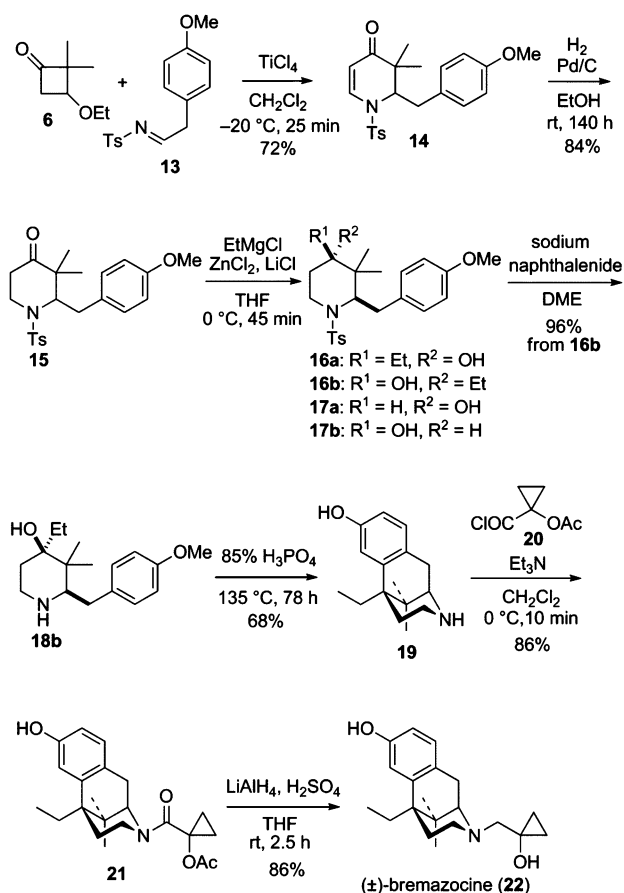


entry	cyclobutanone (11) R, R'	conditions	12	yield (%) ^b
1	Et, Et (11a)	–20 °C, 1 h	12a	74
2	–(CH ₂) ₅ – (11b)	–20 °C, 1 h	12b	75
3	Me, H (11c) (26:74) ^c	–45 °C, 1 h	12c	61 (59:41) ^c
4	Et, H (11d) (30:70) ^c	–45 °C, 1 h	12d	57 (63:37) ^c
5	<i>i</i> -Pr, H (11e) (40:60) ^c	–45 °C, 1 h	12e	60 (60:40) ^c

^a For reaction conditions, see Table 1. ^b Isolated yield. ^c Cis/trans ratio. The stereochemistry was determined by ¹H 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% yield⁹ 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, ZnCl₂, 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 cyclization¹² 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.

Acknowledgment. This work was supported by SUNBOR grant and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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

(5) Matsuo, J.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600–11601.

(6) Other reactions: (a) Matsuo, J. I.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822–3825. (b) Matsuo, J.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 5831–5833. (c) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Chem. Commun.* **2010**, *46*, 934–936.

(7) Roemer, D.; Buescher, H.; Hill, R. C.; Maurer, R.; Petcher, T. J.; Welle, H. B. A.; Bakel, H. C. K.; Akkerman, A. M. *Life Sci.* **1980**, *27*, 971–978.

(8) (a) Greiner, E.; Folk, J. E.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem.* **2004**, *12*, 233–238. (b) Thomas, J. B.; Brieady, L. E.; Boldt, K. G.; Perretta, C.; Carroll, F. I. *Synthesis* **2007**, 1481–1484.

(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.