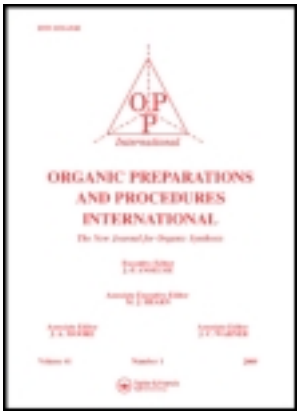

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An Efficient Synthesis of Zolpidem

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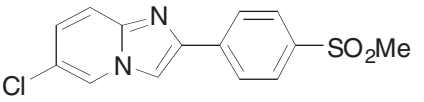
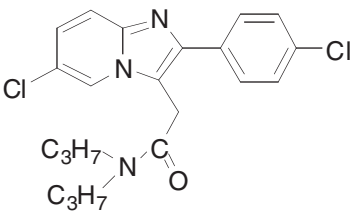
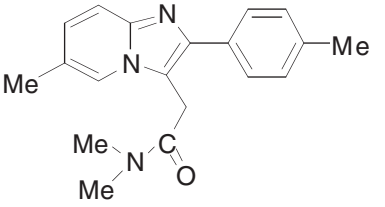
Imidazo[1,2-a]pyridines (IPs) have received considerable attention because of their interesting therapeutic properties,[1] including antibacterial,[2] antifungal,[3,4] antiviral,[5,6] antiulcer,[7] and anti-inflammatory behavior.[8] They have also been identified as selective cyclin-dependent kinase inhibitors,[9] calcium channel blockers,[10] β-amyloidal formation inhibitors,[11] and benzodiazepine receptor agonists,[12] and constitute a novel class of orally active non-peptidic bradykinin B_2 receptor antagonists.[13] Drug formulations containing imidazo[1,2-a]pyridines such as *alpidem* (anxolytic), *zolpidem* (hypnotic), and *zolimidine* (antiulcer) are currently marketed.



Zolmidine



Alpidem



Zolpidem

Zolpidem (**7**) is a prescription medication used for the short-term treatment of insomnia, as well as some brain disorders. It is a short-acting non-benzodiazepine hypnotic that potentiates γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to $GABA_A$ receptors at the same location as benzodiazepines.[14] Although its hypnotic effects are similar to those drugs of the benzodiazepine class, it is molecularly distinct from benzodiazepines and is classified as an imidazopyridine.

One reported synthesis[15,16] of zolpidem proceeds in overall 19% yield from 2-bromo-4′-methylacetophenone (1) as depicted in *Scheme 1*.

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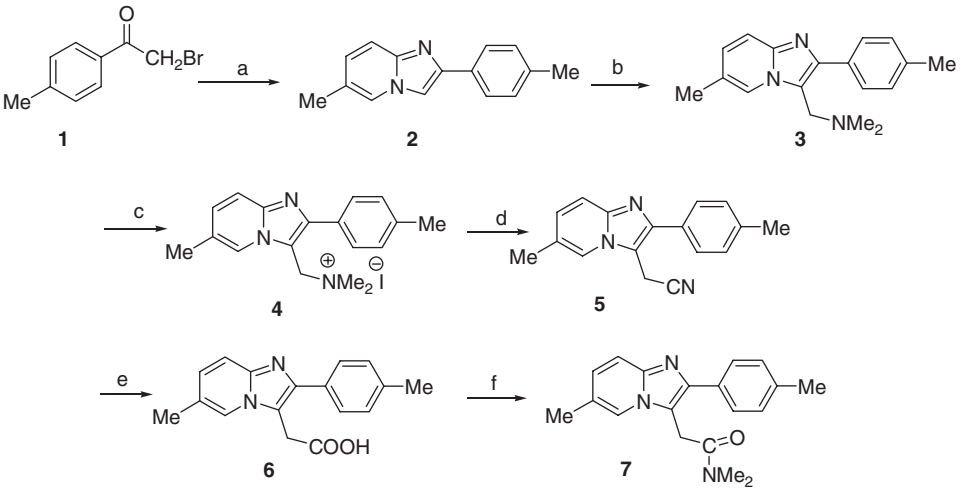


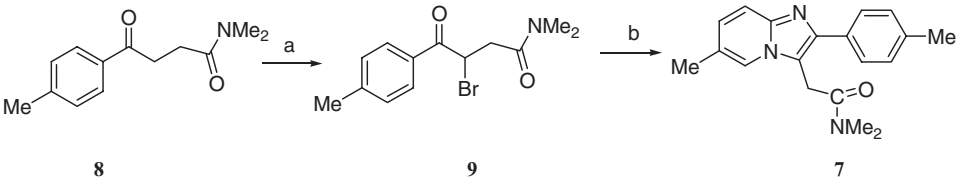
1 2 3 4 5 6 7

(a) 2-Amino-5-methylpyridine, EtOH, $NaHCO_3$, Δ. (b) Acetic acid, aq. Dimethylamine, formalin, RT (c) Acetone, CH_3I, Δ (d) NaCN, EtOH, Δ (e) KOH, EtOH /Δ (f) Carbonyldiimidazole, THF, dimethylamine / RT

Scheme 1

In a related procedure,[17] an alternative preparation of **5** involves a Vilsmeier-Haack formylation of **2** followed by sodium borohydride reduction of the aldehyde to the alcohol. Tosylation of the alcohol and subsequent treatment with cyanide ion gave **5** 30% yield from **2**.

Another literature method[18,19] involved bromination of *N,N*-dimethyl-4-oxo-4-tolylbutanamide (**8**) to 3-bromo-*N,N*-dimethyl-4-oxo-4-tolylbutanamide (**9**) followed by condensation of resultant bromo derivative **9** with 2-amino-5-methylpyridine to give zolpidem (**7**) in 17% yield (*Scheme 2*).



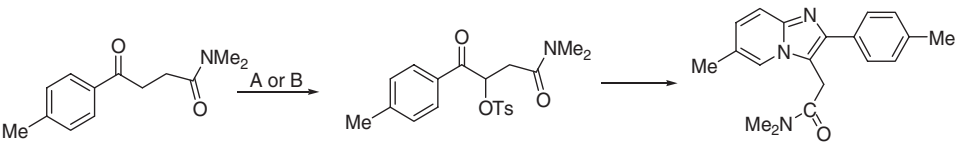
8 9 7

(a) Bromine, acetic acid (b) 2-Amino-5-methylpyridine

Scheme 2

However, these procedures suffer from several disadvantages from a commercial production standpoint such as (*a*) difficulty in handling the lachrymatory bromo compounds **1** and **9** on a large scale which requires precaution to avoid exposure, (*b*) multistep synthesis for compound **6** as illustrated in *Scheme 1* (3 steps from compound **3**), (*c*) isolation (drying operations) of intermediates such as compounds **1**, **4** and **5** and the work-up procedures

which lead to increased cycle time and hence increase in the manufacturing cost, (*d*) the work-up procedure of the cyanation step is hazardous and requires safety measures as it may contain residual cyanide (*e*) in the hydrolysis step (**5** to **6**), compound **2** is formed as by-product (*f*) the use of carbonyldiimidazole (CDI) is expensive and is a highly moisture sensitive reagent and the reaction does not proceed to completion (*g*) the low overall yields in these procedures make them less viable for commercial production.



8 **10** **7**

Method A: (i) HTIB, CH_3CN, reflux 2 h; (ii) 2-Amino-5-methylpyridine, reflux

Method B: (i) (PhIO) + p-TsOH/CH_3CN, reflux 2 h; (ii) 2-Amino-5-methypyridine, reflux

Scheme 3

We herein report a novel synthesis of zolpidem (**7**) by condensation of α-tosyloxyketone **10**,[20] prepared *in situ* by reaction of *N,N*-dimethyl-4-oxo-4-tolylbutanamide **8** and [hydroxy(tosyloxy)iodo]benzene (HTIB), with 2-amino-5-methylpyridine to give zolpidem (*Method A*). [Hydroxy(tosyloxy)iodo]benzene (HTIB), known as Koser's reagent has been gaining increasing popularity as versatile reagent for the preparation of α-tosyloxy ketones from enolizable ketones.[21–23] We also established that it is possible to use a combination of iodosobenzene and *p*-toluenesulfonic acid [(PhIO)n + p-TsOH] in place of HTIB. This combination reagent generates HTIB *in situ*, which then reacts with ketone **8** to give the intermediary α-tosyloxyketone **10** (*Method B*) which further reacted *in situ* with 2-amino-5-methylpyridine to give zolpidem; however, the overall yield in this method was less than that of *Method A*.

In conclusion this investigation describes a simple and efficient one-pot procedure for the synthesis of zolpidem under mild conditions.

Experimental Section

Melting points are uncorrected and were determined on a Buchi Melting Point apparatus. ^{1}H NMR spectra were obtained in $CDCl_3$ using TMS as internal standard on Brucker spectrometer at 300MHz. Mass spectra were recorded on Shimadzu LCMS-QP8000, LC-MS and AB-4000 Q-trap LC-MS/MS. The elemental analysis was performed on Perkin-Elmer model 2400 CHNS/O analyzer. The reaction was monitored by TLC on silica gel plates.

Procedure for the Synthesis of Zolpidem

Method A

A solution of *N,N*-dimethyl-4-oxo-4-tolylbutanamide (**8**, 2.19 g, 1.0 mmol)[24] and hydroxy(tosyloxy)iodo]benzene (HTIB) (3.98 g, 1.0 mmol) in acetonitrile (25 mL) was refluxed for 2 hrs. After the completion of reaction, as monitored on TLC (EtOAc:hexane, 80:20), 2-amino-5-methylpyridine (1.1 g, 1.0 mmol) was added to the reaction mixture which was further refluxed for 2h. After completion of reaction as indicated by TLC, (solvent system $CHCl_3$:methanol 9:1) acetonitrile was distilled off. The residue was dissolved in dichloromethane (25 mL) and washed with a 5% aqueous sodium carbonate (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and the solid residue was crystallized from toluene, dried at 50°C under vacuum, to yield zolpidem as a yellow solid (1.84 g, 60%) mp.192–194°C, *lit.*[15] mp. 194–195°C.

Method B

A solution of iodosobenzene (2.20 g, 10 mmol), *p*-toluenesulfonic acid (1.72 g, 10 mmol) in acetonitrile (20 mL) was stirred at room temperature for 5 min and N,N-diethyl-4-oxo-4-tolylbutanamide (2.19 g, 1.0 mmol) was added and the mixture was refluxed for 2h. To this solution, 2-amino-5-methylpyridine (1.1g, 1.0 mmol) was added and the resulting mixture was further refluxed for 2 hrs. The product was isolated (1.44 g, 47%) as described in the procedure given in *Method A*.

^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H, $ArCH_3$), 2.34 (s, 3H, $ArCH_3$), 2.85 (s, 3H, NCH_3), 2.94 (s, 3H, NCH_3), 4.16 (s, 2H, $COCH_2$), 7.05 (d, 2H, ArH), 7.43–7.66 (m, 4H, ArH), 8.11 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 17.92, 20.79, 29.31, 35.34, 37.03, 113.79, 115.37, 121.82, 130.26, 137.27, 142.11, 142.81, 167.63. MS: M^+ 308, 235, 219, 92

Anal. Calcd. For $C_{19}H_{21}N_3O$: C, 74.25; H, 6.88; N, 13.67; Found: C, 74.10; H, 6.74; N, 13.79.

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