CONCISE AND VERSATILE SYNTHESES OF *N*-ARYLALKYLPIPERIDINES AS POTENTIAL INTERMEDIATES FOR 4-ANILIDOPIPERIDINE ANALGESICS

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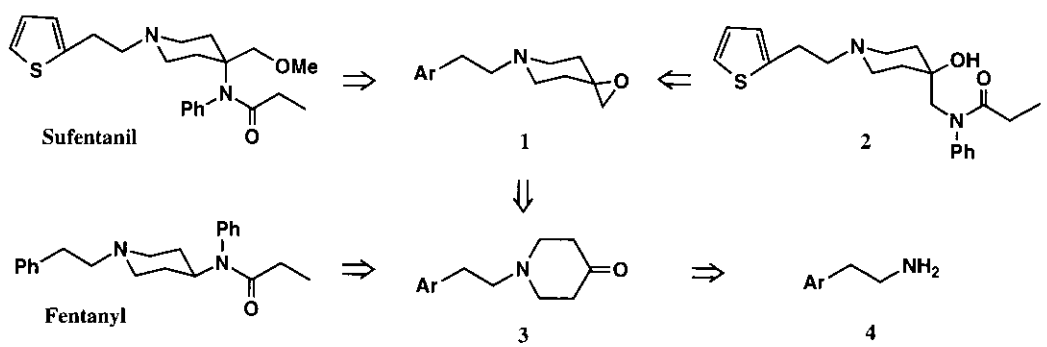
Abstract - *N*-Arylalkylpiperidones and *N*-arylalkylspiroepoxypiperidine as potential intermediates for 4-anilidopiperidine analgesics and their structural analogues have been efficiently synthesized from the simple arylalkylamines by two and three step sequences respectively.

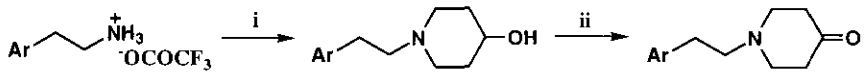
4-Anilidopiperidine represents a class of potent analgesics.[1] Particularly fentanyl[2] and sufentanil[3] which are typical structures of this series, have been the recent subjects due to their potent analgesic properties. Consequently, some extensive synthetic studies focused on fentanyl, sufentanil and their analogues have been carried out although few synthetic studies on sufentanyl have been reported.[4-6] We have recently been searching for a synthetic method for easy access to the potential intermediates of widespread utility in syntheses of diverse anilidopiperidine analgesics. Herein we report our recent studies on concise and efficient synthetic method for potential *N*-arylalkylpiperidine intermediates.

Scheme 1



Our synthetic approach shown in Scheme 1 involves a facile construction of the initial *N*-arylalkylpiperidone intermediate (**3**) by the expedient two step sequence of aminomethano desilylation-cyclization[7] followed by oxidation. The *N*-arylalkylpiperidone (**3**) has been also directly converted to the spiroepoxypiperidine (**1**) as a second potential intermediate which reacted with aniline to afford 4-anilinopiperidine or 4-anilinomethylpiperidine as its regioisomer. The arylalkylpiperidones (**3a**)[4] and (**3b**) were efficiently prepared by subjection of phenylethylamine (**4a**) or thiophenylethylamine(**4b**)[8] to Grieco's conditions[7] followed by Swern oxidation[9] of the resulting hydroxypiperidine (**5**) as shown in Scheme 2. It is noteworthy that only Swern oxidation was effective for oxidation of hydroxypiperidine (**5**). The known intermediate (**3a**) was straightforwardly transformed into fentanyl in 58% overall yield by analogy of the reported procedure.[6]

Scheme 2



4 a : Phenyl
b : Thiophenyl

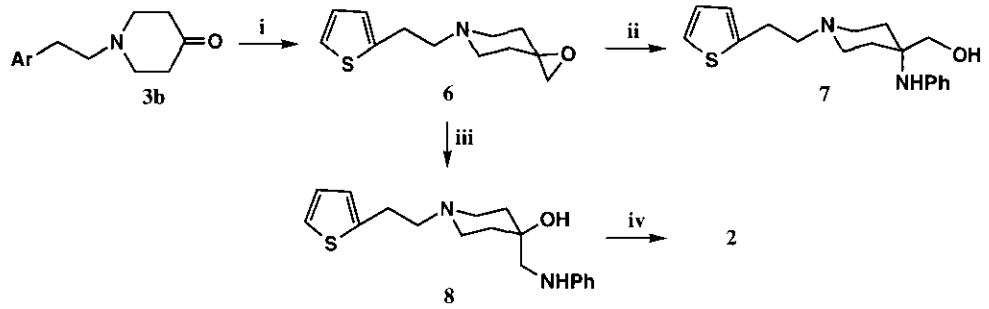
5

3

i) allylsilane, 37% HCHO (2.5 eq), H_2O, 58 °C, 63% for 5a, 45% for 5b ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 84% for 3a, 83% for 3b

The one step conversion of thiophenylethylpiperidone (**3b**) to the spiroepoxide (**6**) as a second potential intermediate was achieved by dimethylsulfonium ylide[10] treatment as shown in Scheme 3. The synthetic utility of spiroepoxide (**6**) was demonstrated by transformation to anilinopiperidines (**7**) and anilinomethylpiperidine (**8**). The variety of reaction conditions for regioselective ring opening of the epoxide (**6**) at more substituted carbon by aniline[11] were examined and triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$) as Lewis acid in methylene chloride below -78 °C turned out to be the best choice for the highest regioselection (1.8 : 1) in favor of (**7**). Use of other Lewis acids afforded the regioisomer (**8**) as a predominant product or only byproducts by retro-Mannich type reaction. Although the regioselectivity and yields are not satisfactory yet, the direct introduction of aniline nucleophile to spiroepoxide at more substituted carbon enables two step conversion of the arylalkylpiperidone (**3b**) to the highly advanced sufentanyl intermediate (**8**) which has been prepared from *N*-benzylpiperidone by seven steps.[4] The complete regioselection in epoxide ring opening at less substituted carbon could be also achieved by reaction of epoxide (**6**) with aniline in the absence of Lewis acid. The anilinomethylpiperidine (**8**) was further transformed into the sufentanil analogue (**2**)[13] which is presently under biological evaluation.

Scheme 3



i) $Me_3S^+I^-$, $NaCH_2SOMe$, THF, 78% ii) $Et_3O^+BF_4^-$, $PhNH_2$, -78 °C, CH_2Cl_2, 23% based on 60% conversion iii) $PhNH_2$, 35 °C, 82% after recycle iv) $(EtCO)_2O$, 110°C then NaOMe, MeOH, 60%

In conclusion, arylalkylpiperidone (**3**) and spiroepoxypiperidine (**1**) have been prepared from arylalkylamine by two and three steps respectively. One step conversion of piperidone (**3b**) to the potential spiroepoxypiperidine intermediate (**6**) followed by direct regioselective epoxide opening with aniline envisions easy access to sufentanyl as well as variety of its structural analogues.

ACKNOWLEDGEMENT

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8. Thiophenylethylamine was conveniently prepared from the commercially available thiophene-acetonitrile by LAH reduction.

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11. Regioselective ring opening of unsymmetrical spiroepoxide by aniline has not been reported yet. For the related references, see; M. Onaka, K. Sugita, and Y. Izumi, *Chem. Lett.*, 1986, 1327; H. B. Mereyala and B. Frei, *Helv. Chim. Acta*, 1986, **69**, 415.

12. The low yields for (**7**) is mainly attributed to decomposition of the substrate as the reaction proceeds. Currently, intensive studies for yield optimization are in progress.

13. Spectral data for the sufentanyl analogue (**2**): IR 3368, 1637 cm^{-1}; ^{1}H-NMR (400 MHz) 7.35 (dd, J=7.3, 7.3 Hz, 2H), 7.26 (dd, J=7.3, 7.3 Hz, 1H), 7.13 (d, J=7.3 Hz, 2H), 7.03 (dd, J=4.9, 1.0 Hz, 1H), 6.83 (dd, J=4.9, 3.7 Hz, 1H), 6.73 (d, J= 3.7 Hz, 1H), 4.89 (br s, 1H), 3.72 (s, 2H), 2.93 (t, J=7.8 Hz, 2H), 2.59 (br t, J=7.8 Hz, 4H), 2.42 (t, J=10.7 Hz, 2H), 2.05 (q, J=7.3 Hz, 2H), 1.63 (d, J=10.7 Hz, 2H), 1.46 (t, J=10.7 Hz, 2H), 0.98 (t, J=7.3 Hz, 3H); MS (*m/z*) 373 (M^++H), 355, 275; HRMS Found, 373.5415 Calcd for $C_{21}H_{29}N_2O_2S$(MH), 373.5321.

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