

An Efficient Approach To Novel Tetrahydropyridoazepines. Expansion Of Azepines' Drug-like Chemical Space

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Introduction and Aim

The quest for lead-oriented synthesis proposed by medicinal chemistry in early 2010s have prompted the design and study of low-molecular-weight, hydrophilic, conformationally restricted and sp³-enriched molecular scaffolds. Fused azepanes are promising chemotypes which comply with these criteria and in most cases possess sufficient novelty; moreover, the azepane motif is in the top 100 most frequently used ring systems for small molecule drugs. 6,7,8,9-Tetrahydro-5*H*-pyrido[3,2-*c*]azepines (1), which contain fused azepane and pyridine rings, were evaluated as cannabinoid (CB2) receptor modulators (2), H1-antihistamines (3), or serotonin $(5HT_{2c})$ receptor agonists (4).¹



Herein, we report an alternative approach to 5-substituted

6,7,8,9-tetrahydro-5H-pyrido[3,2-c]azepines, which also relies on the formation of imines as the key step.





Synthesis



(i) LDA (1.2 eq), THF, –78 °C, 90 min; (*ii*) (1.13 eq), THF, –78 °C, 80 min; (*iii*) CrO₃·2py (3 eq), CH₂Cl₂, rt, 24 h or CrO₃ (3 eq), acetone, rt, 18 h; (*iv*) 2-prop-2-ynyloxytetrahydropyran (1.5 eq), Pd(OAC)₂ (1% mol), PPh₃ (2% mol), Cul (0.19% mol), Et₃N, 80 °C, 16 h; (v) H₂ (1 atm), 10% Pd-C (4% mol), MeOH, rt, monitored by TLC; (v) TsOH·H₂O (1.05 eq), MeOH, rt, 12 h.

Literature synthesis of 5H-pyrido[3,2-c]azepines³



(*i*) MsCl (1.05 eq), Et₃N (1.5 eq), CH₂Cl₂, 0 °C to rt, 24 h; (*ii*) phthalimide (1.5 eq), DIAD (1.5 eq), PPh₃ (1.5 eq), THF, -30 °C to rt, 24 h; (*iii*) DIAD (1.5 eq), PPh₃ (1.5 eq), NaHCO₃ (3% mol), THF, (PhO)₂P(O)N₃ (1.5 eq), -30 to 20 °C, 3 h; (*iv*) PMe₃ (1.4 eq), THF, rt, 6 h; (*v*) NaBH₄ (3 eq), MeOH, 0 °C to rt, 8 h; (*vi*) sat. HCl in Et₂O, rt

Results



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