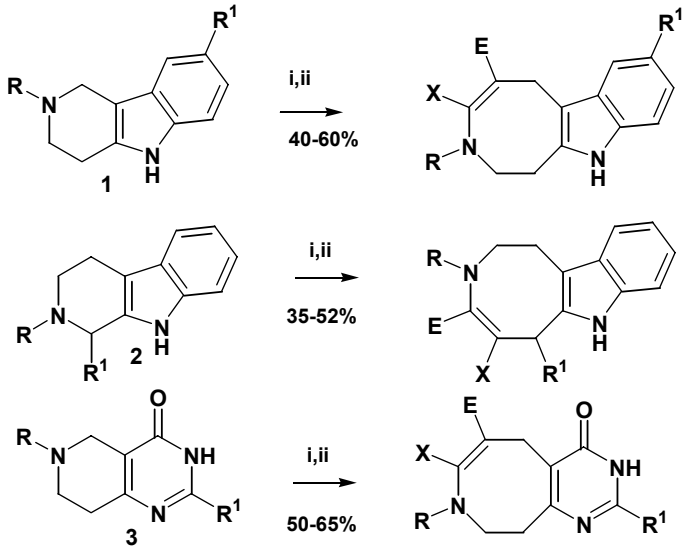
3rd EuroAsian Heterocyclic Meeting "Heterocycles in Organic and Combinatorial Chemistry" (EAHM-2004)
September 12-17, 2004, Novosibirsk, Russia
Poster Presentation

New Practical Approach to the Synthesis of Annulated Azocine Derivatives – Potential AChE Inhibitors

Voskressensky L.G., Borisova T.N., Kostenev I.S., Kulikova L.N., Varlamov A.V.

Organic Chemistry Department of the Russian peoples friendship university,
6, Miklukho-Maklayia St., Moscow, Russia, 117198 Fax 7 095 9550779
e-mail: lvoskressensky@sci.pfu.edu.ru

Eight-membered (azocine) and larger *N*-containing fused ring systems are not sufficiently studied, although many of them have shown substantial bioactivity; azocine fragment was found in many indole alkaloids. One barrier to the exploration of these compounds has been a general lack of satisfactory preparative methods. We here wish to report on new synthetic route to annulated azocine derivatives starting from ready-available annulated tetrahydropyridines. We have previously demonstrated that tetrahydropyrrolo[3,2-c]pyridines as well as tetrahydro-γ-carbolines (**1**) undergo tandem cleavage process under the action of activated alkynes in protic solvents, yielding (alk)oxymethyl pyrroles or indoles in high yields. The latter compounds were easily converted to target azocine derivatives under the action of a suitable Lewis acid. This methodology has been further successfully applied to tetrahydro-β-carbolines (**2**) and tetrahydropyridopyrimidines (**3**). The resulting azocine derivatives were subjected to a preliminary evaluation of the in-vitro inhibitory activity of acetylcholinesterase (AChE). Most of them were found to inhibit AChE with IC_{50} values in the micromolar range.



i: DMAD (EP), ROH, r.t ii: Lewis acid, CH_3CN
E=COOMe(Et), X=H, COOMe

DMAD - dimethyl acetylene dicarboxylate
EP - ethyl propyolate

The reaction scope and limitations as well as experimental procedure and possible mechanism will be discussed.

This work was supported by the Russian foundation for basic research (grant # 02-03-32941)