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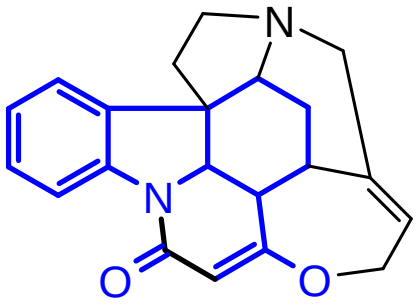
Syntheses and reactions of 5-alkyl- and 5-aryl-11b-methyl-1,2,3,11b-tetrahydro-pyrido[3,2,1-*jk*]carbazoles



Tetrahydropyrido[3,2,1-*jk*]carbazol-6-one (**blue** structure) is part of the heterocyclic skeleton of many natural products (e. g. **Strychnos alkaloids** such as strychninolones and derivatives, i.e. Brucine (dimethoxystrychnin) and Vomicin (12-hydroxy-N-methylpseudostrychnine). It possesses the biological interesting combination of the well-known **indole** structure and the **4-hydroxy-2-pyridone** structure.

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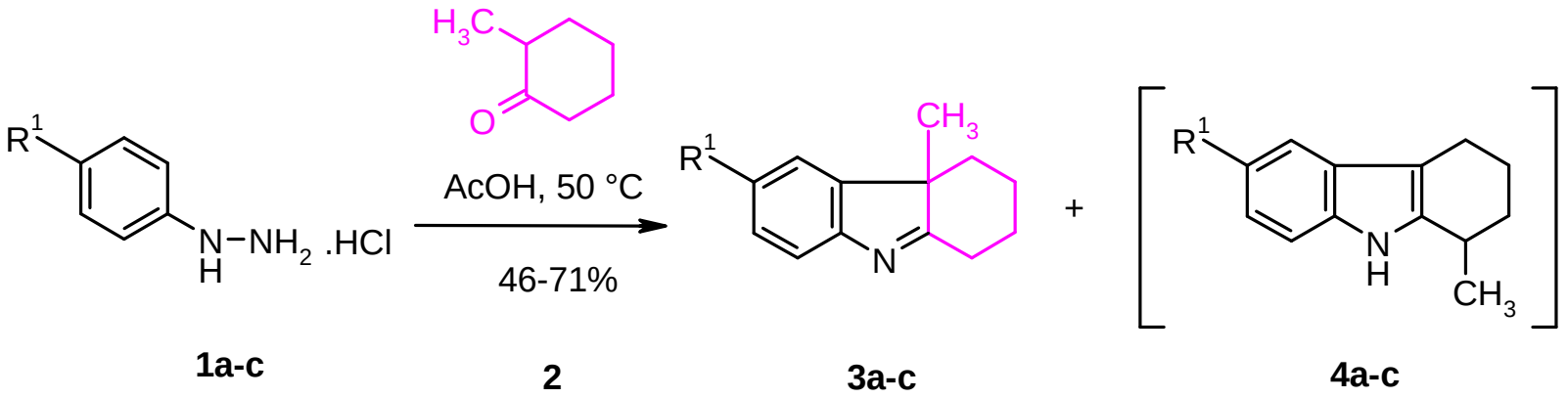
Synthesis of 4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazoles (3)



1a-c **2** **3a-c** **4a-c**

R^1 = H, OMe, Cl

Arylhydrazines **1** react with 2-methylcyclohexanone **2** via *Fischer indole synthesis* to 4a-methyl-2,3,3,4a-tetrahydro-1*H*-carbazoles **3**; the formation of the isomeric 1-methyl-2,3,4,9-tetrahydro-1H-carbazoles **4** could be excluded by suitable reaction conditions.

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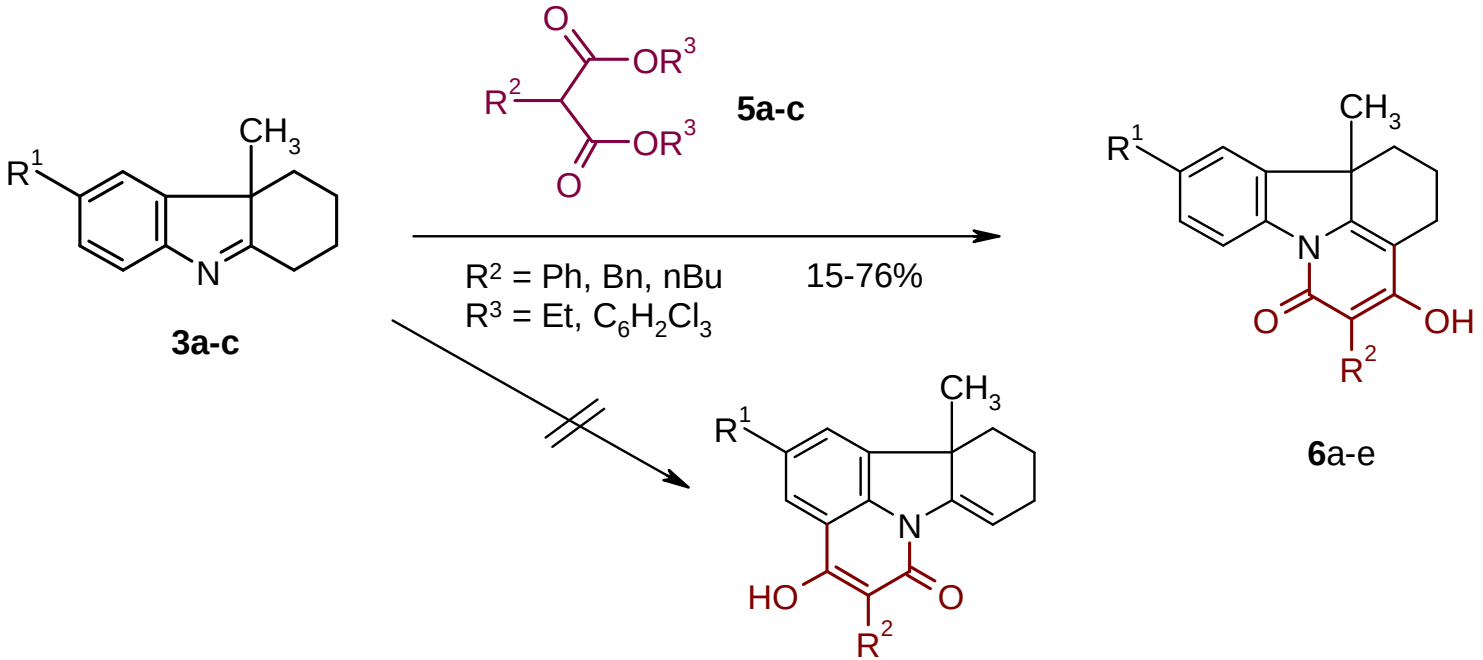
Cyclization of tetrahydrocarbazoles (3) to 4-hydroxy- 1,2,3,11b-tetrahydro-pyrido[3,2,1-*jk*]carbazol-6-ones (6)



4a-Methyl-2,3,3,4a-tetrahydro-1*H*-carbazoles **3** cyclize thermally with 2-substituted malonates **5** to give 5-aryl- and 5-alkylsubstituted 4-hydroxy-11b-methyl-1,2,3,11b-tetrahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-ones **6**. Isomers **7** were not formed.

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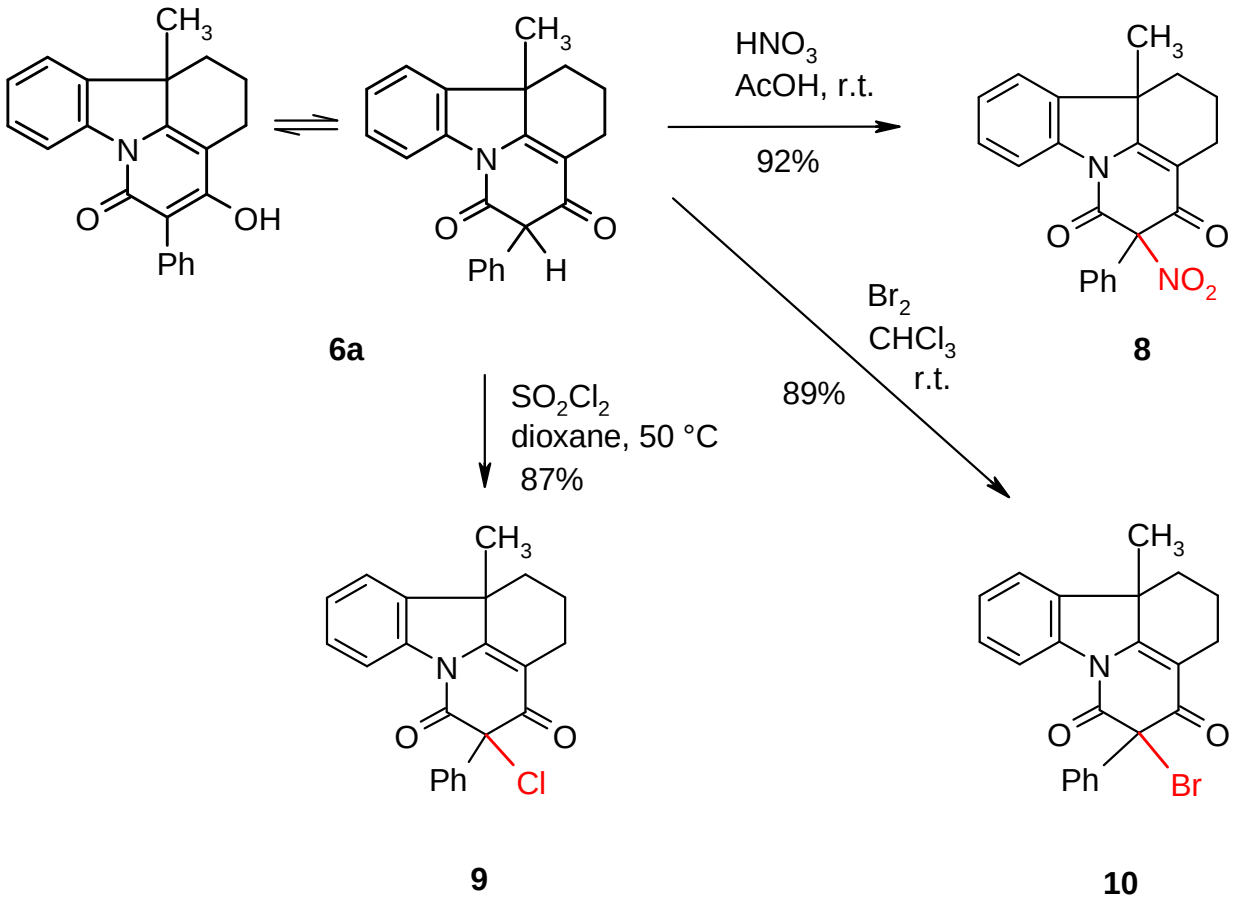
Electrophilic attack at 4-hydroxy-11b-methyl-5-phenyl-1,2,3,11b-tetrahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (6a)



Electrophilic attack directed to tetrahydro-pyrido[3,2,1-*jk*]carbazolone **6a** takes place at position 5 in the heterocyclic ring. Nitration with conc. nitric acid leads to 5-nitro-5-phenyl derivatives **8**, chlorination with sulfuryl chloride forms 5-chloro-5-phenylpyridocarbazoledion es **9** and bromination gives 5-bromo-5-phenyl derivatives **10.**

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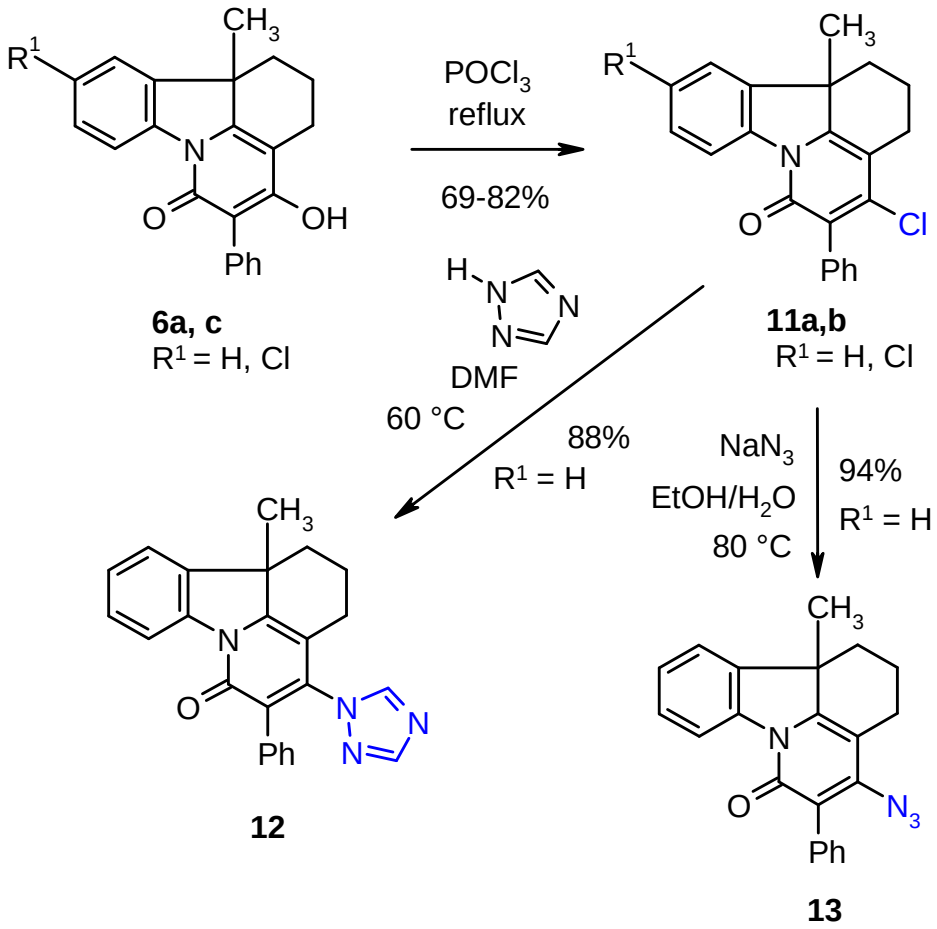
Nucleophilic attack at 4-hydroxy-11b-methyl-5-phenyl-1,2,3,11b-tetrahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (6a)



Nucleophilic attack directed to tetrahydro-pyrido[3,2,1-*jk*]carbazolone **6a** takes place at position 4 in the heterocyclic ring. The reaction of **6a** with boiling phosphoryl chloride gave 4-chloro-tetrahydropyridocarbazolones **11a,b**, which can be used as reactive intermediates. 1,2,4-Triazole sodium reacted with 4-chloro derivative **11a** in excellent yields to 4-triazolyl-tetrahydro-pyridocarbazolone **12**, a structure related to antifungal agents. **11a** and sodium azide gave the thermally labile 4-azidotetrahydropyrido-carbazolone **13**.

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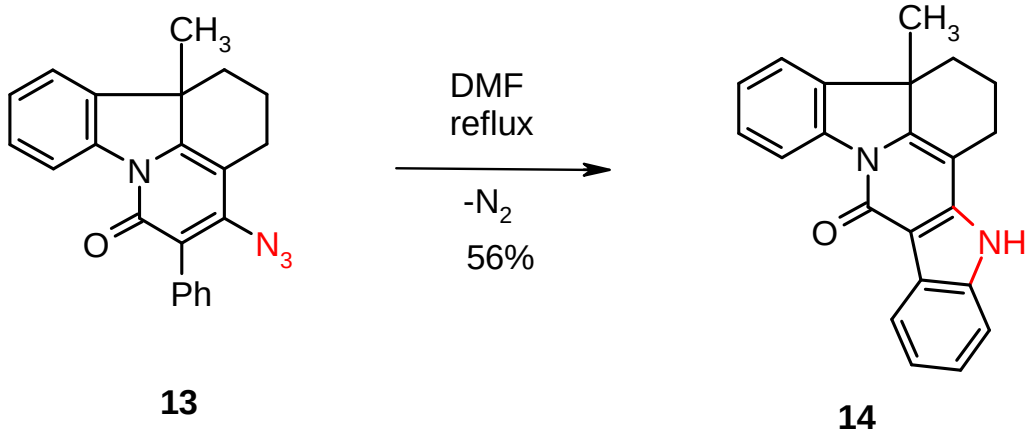
Thermal cyclization of 4-azido-5-phenyl-tetrahydropyridocarbazolone (13)



13 **14**

The thermal properties of 4-azido-5-phenyl-tetrahydropyridocarbazolone **13** were investigated by differential scanning calorimetry (DSC**).** The thermolytic ring closure reaction in boiling dimethylformamide leads to 3a-methyl-2,3,3a,14-tetrahydroindolo[2',3':4,5] pyrido[3,2,1-*jk*]carbazol-9(1*H*)-one (**14**)

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Conclusion

It could be shown, that 4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazoles **3** are obtained without isomeric by-products **4** in yields of 50-70%.

Cyclocondensation of tetrahydrocarbazoles **3** with substituted malonates results in the formation of 4-hydroxy-11b-methyl-1,2,3,11b-tetrahydro-6*H*-pyrido[3,2,1-*jk*]carbazol-6-ones **6** without formation of the isomeric pyridocarbazoles **7**.

Both electrophilic as well as nucleophilic attacks at pyridocarbazoles **6** gave regioselective substitutions in the heterocyclic pyridone ring either in position 5 or position 4, respectively.

Thermal cyclization of 4-azido-5-phenyl-tetrahydropyridocarbazolone **13** was investigated by differential scanning calorimetry (DSC) and produced indolo-pyridocarbazole **14** under suitable thermal conditions obtained from DSC data.