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Construction of functionalized/substituted bipyridines by means of Negishi cross-coupling reactions. Formal synthesis of (±)-cytisine

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Abstract—The use of Negishi cross-coupling reaction allows the construction of various substituted and functionalized bipyridines. The efficiency of the method permits to obtain in high yield a direct precursor of racemic cytisine. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, attention has been directed to the potential role of neuronal nicotinic acetylcholine receptors. They are involved in the various pharmacological effects of nicotine such as addiction, cognition enhancement, analgesia, neuroprotection and are altered in various pathologies such as Parkinson's disease and Alzheimer's disease. The use of nicotinic agonists have thus been envisaged for the prevention of neurodegeneration (Fig. 1).[1] With the aim of synthesizing new potential drugs and new ligands for the in vivo visualization of nicotinic receptors, we have previously synthesized new 2,2-disubstituted pyrrolidines[2] and derivatives of (–)-cytisine.[3]

(–)-Cytisine **1**, an alkaloid extracted from many *Leguminosae*, exhibits a high affinity (0.4–1 nmol) for nicotinic receptors of subtype $\alpha_4\beta_2$[4,5] and is commonly used as a reference in the study of new nAChRs. In order to compare the biological profile of the (+) and (–) enantiomers and to have a general access to substituted derivatives we focused part of our work on the enantioselective synthesis of cytisine.

The initially envisioned retrosynthesis is represented in Scheme 1. Total syntheses of racemic cytisine were reported 40 years ago[6–8] and new interest in this compound emerged recently with the publication of two new different approaches from the Pfizer group.[9]

One of these involved the pyridinium **6**, which led after reduction then cyclization to racemic cytisine in high yield. The key step in the preparation of compound **6** was either a Stille coupling (direct or in situ) or a Suzuki reaction.[9a,10] These papers prompt us to report

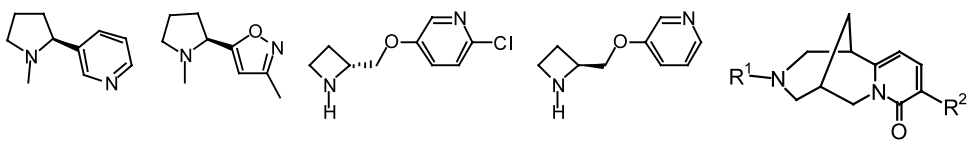

Figure 1. High affinity $\alpha_4\beta_2$ nAChRs ligands.

Keywords: alkaloid; bipyridine; cross-coupling reaction.

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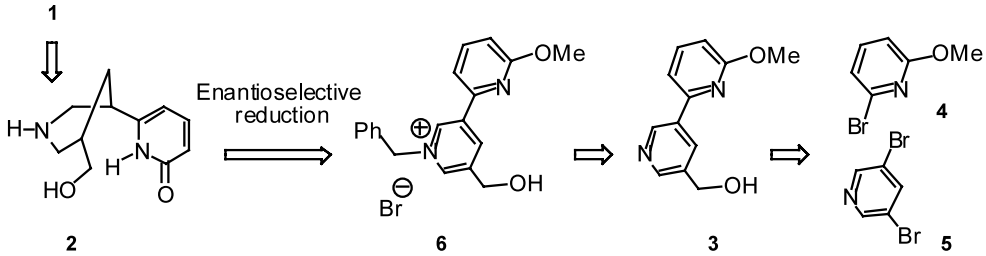


Scheme 1.

herein our own preliminary work on the synthesis of the cytisine skeleton. Our approach is based on the Negishi cross-coupling reaction[11] of pyridine **4** (Scheme 2).

The first step consisted of preparing the bipyridine **7** (Scheme 2).

As shown in Scheme 2 and Table 1 the Negishi cross-coupling yielded a mixture of the expected bipyridine **7** in an efficient manner (79%, corrected yield: 84%), along with a small amount of the terpyridine **8** (11%). The reaction mixture was easily separated by flash chromatography on silica gel. In order to minimize the amount of terpyridine, other reaction conditions were tested by varying experimental conditions (duration time, reactant ratio), but all of them gave a lower yield in the required bipyridine **7** (Table 1). Since both the yield and the purification procedure were satisfactory, we continued the synthetic sequence en route to cytisine.

The following step consisted in the formylation of the bipyridine unit, in order to obtain the precursor of the alcohol function. Several methods were tried, using different organolithium reagents and formylating agents (Table 2). The best result is reported in Scheme 3, and involved *n*-BuLi and DMF as reagents. Worthy of note is that the use of diethylether as a solvent for the halogen–metal exchange reaction gave a higher yield than THF (80% versus 20–30%), as sometimes observed in this series.[12]

Table 2. Synthesis of aldehyde **9**

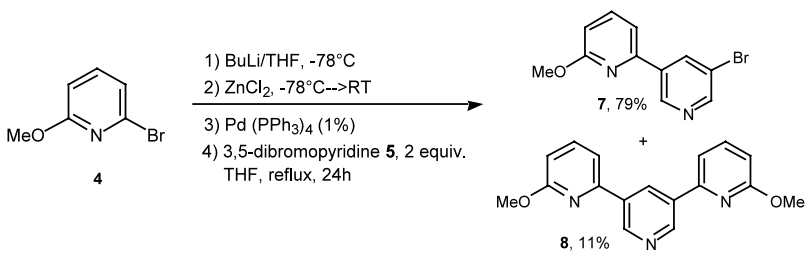
Entry	RLi	Solvent	Electrophile	Yield **9** (%)
1[a]	*n*-BuLi	THF	DMF	31
2[b]	*n*-BuLi	THF	*N*-Formylpiperidine[d]	28
3[b]	*t*-Buli	THF	*N*-Formylpiperidine[d]	23
4[b]	PhLi	THF	*N*-Formylpiperidine[d]	24
5[c]	*t*-BuLi	Ether	DMF/THF	48
6[c]	*n*-BuLi	Ether	DMF/$POCl_3$/THF	25
7[c]	*n*-BuLi	Ether	DMF/THF	80
8[c]	*n*-BuLi	Ether	HCOOEt/THF	74

[a] The electrophilic reagent was added at −78°C, then the reaction mixture was allowed to warm up to rt. After cooling again to −78°C, the reaction was quenched by a mixture THF/concentrated HCl (10/1), then by water. After neutralization with solid potassium carbonate, the reaction mixture was worked up as usual.

[b] The electrophilic reagent was added at −78°C, then the reaction mixture was allowed to stand for 2 h at −40°C. After cooling again to −78°C, the reaction was quenched by a mixture THF/water (1/1), then worked up as usual.

[c] The electrophilic reagent was added at −78°C, then the reaction mixture was allowed to stand for 2 h at this temperature. The reaction was then slowly warmed up to rt, in about 16 h. After cooling again to −78°C, the reaction mixture was poured into a sodium hydrogenocarbonate solution (5%).

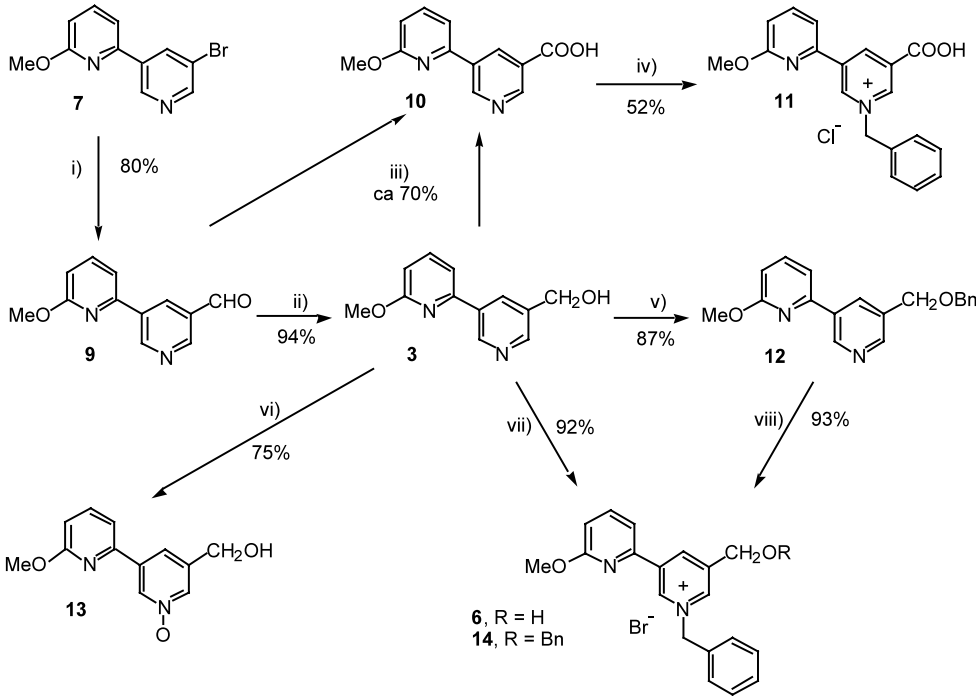
[d] See Ref. 15.



Scheme 2.

Table 1. Negishi cross-coupling conditions

Entry	Time (h)	**5** (equiv.)	Conversion (%)	Yield **7** (%)	Yield **8** (%)
1	24	1	75	51	Undetermined
2	48	1	79	55	19
3	24	1.5	88	70	12
4	24	2	93	79	11



Scheme 3. *Reagents and conditions*: *n*-BuLi, Et_2O, −78°C, 1 h, then DMF (5 equiv.), THF, −78°C to rt; (ii) $NaBH_4$, EtOH, rt; (iii) Jones oxidation; (iv) BnCl, DMF, 100°C; (v) NaH, DMF, BnBr, rt; (vi) MCPBA, $CHCl_3$, rt; (vii) BnBr (3 equiv.), MeOH; (viii) BnBr, MeOH, reflux.

Reduction of the carbonyl moiety by means of sodium borohydride yielded the alcohol **3** in almost quantitative yield. In some experiments, a small amount of the corresponding amine–borane was detected in addition to the reduced compound; a simple reaction of the amine–borane derivative with a water/THF solution of potassium carbonate transformed quantitatively the complex into the wanted carbinolbipyridine compound **3**. Finally, benzylation with an excess of benzyl bromide led to the bipyridinium salt **6** with a 92% yield. Benzylation was completely regioselective, in the sense that only the nitrogen in the 3′-pyridyl unit was alkylated. Such behavior has previously been described by us,[13] and others,[14] and is generally assumed to be due to the more crowded position of the nitrogen atom of the 2-pyridyl unit. A series of derivatives was obtained by means of standard procedures (Scheme 3): each of these compounds could be an interesting starting material for the construction of cytisine analogs and will be used in our further studies regarding the possibility of enantioselective reduction possibly giving access to chiral precursors of cytisine.

In conclusion, the present work describes the use of Negishi cross-coupling reaction for the construction of various substituted and functionalized bipyridines. The high efficiency of this method permits to elaborate a strategy for obtaining in rather high yield the compound **6**, which has been described as a direct precursor of racemic cytisine (overall yield: 55%, lit. overall yield: 35–44%,[9a] both syntheses starting from 2-bromo-6-methoxy-pyridine). In addition, we obtained with very simple methods a set of derivatives in the bipyridine and bipyridinium series, which will be used in further studies.

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