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RESEARCH ARTICLE

Investigation of the preparation of cycloalkanoindole derivative in ionic solvent

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Abstract

Optimization of the synthesis of carba analogs of physostigmine is described. Aza-Claisen-rearrangement, followed by aza-Alder-ene reaction of aniline derivatives gave the title product besides some byproduct. The effects of the amounts of catalyst, solvent, temperature and the method of heating were investigated.

Keywords

aza-Claisen rearrangement · aza-Alder-ene reaction · ionic solvent · optimization

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In recent years, we have published three papers on the convenient preparation of carba analogs of physostigmine [1]–[3]. Our method was based on the $BF_3 \cdot Et_2O$ catalyzed aza-Claisen rearrangement of (cycloalkylmethyl)benzenamine (Fig. 1, **1**), followed by aza-Alder-ene reaction. Besides the wanted product (**4**) more or less by-product (**3**) was also formed by the migration of the carbon-carbon double bond.

In a continuation of our investigation on the synthesis, we tried to improve the yield of the wanted product (**4**) and minimize the formation of the byproduct (**3**). For this optimization we chose the rearrangement reaction of the unsubstituted benzeneamine **1** ($X = H$, $n = 1$).

Since the replacement of an organic solvent with ionic liquid had been found useful in some areas, we tried to use ionic fluid, too [4]–[7]. Furthermore, the extremely low vapor pressure of the ionic solvents characterized them as green solvent, allowing a wider range of applications. The reactions were then performed in methylimidazolium tetrafluoroborate at different concentrations and temperatures, and with thermal or microwave-assisted heating. The main advantage of this modification was the easy preparation of the product, namely it could be isolated by a simple extraction of the reaction mixture with organic solvent, and then directly analyzed by GC.

In the experiments 0.5 g of benzeneamine (**1**, $X = H$, $n = 1$) was dissolved in 5 ml or 2 ml of methylimidazolium tetrafluoroborate and after adding the $BF_3 \cdot Et_2O$ catalyst (0.5 equiv.) portionwise, the mixture was heated to 175 °C for 150 min. Isolation of the product was carried out by extraction of the mixture with CH_2Cl_2. GC analysis of the extract showed that the concentrated solution gave preferential formation of the wanted product. In 5 ml of ionic solvent we got a ratio of compounds **4** and **3** ($X = H$, $n = 1$) 1:1 (18% and 17%, respectively). In 2 ml ionic solvent the result was the formation of 27% of wanted product and 14% of the by-product. (Besides these compounds, substantial amounts of unidentified tar were also formed).

We got better result when we added the catalyst ($BF_3 \cdot Et_2O$) in one portion. Fig.2 shows the time course of the reaction. Here, the rather fast consumption of the starting material could be seen and we achieved 50% yield of compound **4** ($X = H$, $n = 1$).

Fig. 1. Preparation of cycloalkano-indoles

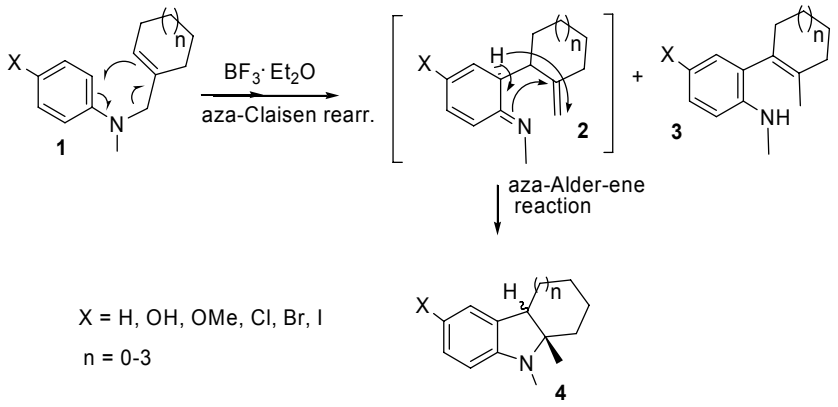
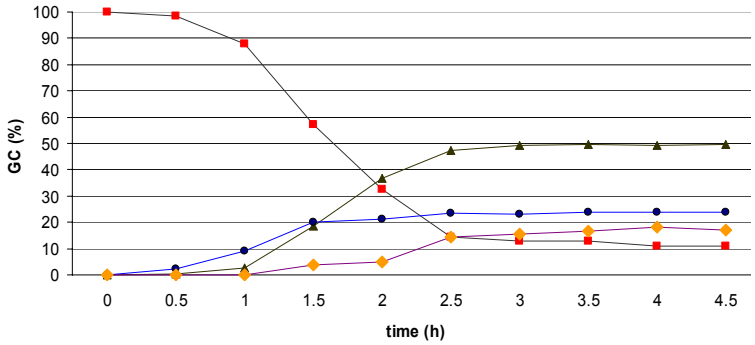


Fig. 2. Time course of preparation of compound **4** in methylimidazolium tetrafluoroborate



Compounds **1**, **4**, **3** and unidentified by-product are represented by squares (□), triangles (△), circles (○), and diamonds (◇).

We also examined the effect of the reaction time on the formation of the wanted product. Table 1 shows the results.

Tab. 1. Effect of the temperature on the reaction **1**→**4.**

Entry	Temperature (°C)	Time (min)	Starting compound (%)	Product (%)	Byproduct (**3**, %)
1	145	270	24	38	18
2	165	180	27	36	20
3	180	90	13	46	15
4	190	10	0	68	4

As can be seen, elevated temperature led to higher yield of the desired product (entries 1–3). We got the best yield of the product (68%, as a 2:1 mixture of *cis* and *trans* diastereomers) when we performed the reaction at 190 °C and added the catalyst in ionic solvent, and in one portion (entry 4). The ratio of diastereomers was determined by GC separation, followed by ^{1}H and ^{13}C NMR spectroscopy.

The reactions were also performed in microwave oven at elevated temperature (170 °C). The ring-closure reaction took place in both sulfolane and methylimidazolium tetrafluoroborate, and we isolated compound **4** ($X = H$, $n = 1$) in moderate yields (25% and 27%, respectively).

In conclusion, we have reported the optimization of the preparation of cycloalkanoindole derivative through thermal rearrangement of benzeneamine and got the title compound with moderate to good yields. Another advantage of this procedure was the use of a green solvent, methylimidazolium tetrafluoroborate, which among various reaction solvents (decalin, tetralin and sulfolane) examined, gave the best yield of the desired product. These optimized conditions were subsequently employed to prepare compounds **4**[1].

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[1]Generally we got 10% increase in yield. This will be the subject of a forthcoming publication.