A Convenient Way to Synthesis of Analgesic Tramadol (Tramal)

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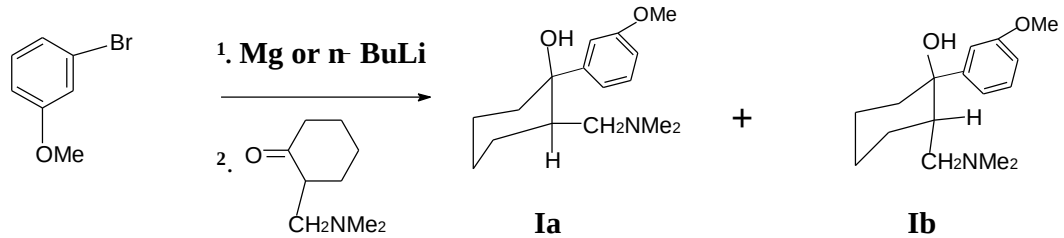
The analgesic Tramadol [1-(*e*)-methoxyphenyl-2-(*e*)-dimethylaminomethylcyclohexan-1(*a*)-ol hydrochloride, **trans-form]** is used for the therapy of strong physical pain and has become a valuable tool in opiod research [1]. The synthetic route to Tramadol consist in interaction of 2-dimethylaminomethyl-cyclohexanone with organomagnesium or organolithium compounds of 3-bromoanisole in tetrahydrofurane (THF) or in THF/ether solutions [1,2]. We are investigated the possibility for use of another solvents in this reactions as well as a more convenient manner of separation of resulting products.

We have observed that the ratio of isomers (**Ia**) and (I**b**) is depended on the reaction conditions. Use a mixture 2-methyl-2-methoxypropane/THF (5:1) as solvent in Grignard reaction yield the ratio of (I**a)** and (**Ib)** equal 72 to 28 (the ratio was detected directly from the crude reaction mixture by analytical HPLC). The better results are received in 1,4-dioxane/THF (5:1) solution, the contents of isomer (I**a**) rise to 85%. The employment of 4,4-dimethyl-1,3-dioxane produced similar results. In addition, it was found that the reaction of organolithium compound of 3-bromoanisole with aminomethylcyclohexanol derivative in petrol ether leads to (**Ia**) and (**Ib**) in a ratio of 78:22. The reaction proceeds more selectively in petrol ether/THF media (ratio 86:14).

The isolation of the title compound was performed by the follow. By treatment of the crude reaction mixture with 15% solution hydrogen chloride in 1,4-dioxane, hydrochlorides of (**Ia**) and (**Ib**) (95% of the title compound) are obtained in a overall yield of 55%. The following recrystallization from 1,4-dioxane leads to pure Tramadol.



Ia **Ib**

References:

1. K.Flick, E.Frankus,E.Friderichs, Arzneim.-Forsch./Drug Res., 1978, 28, 107-113.

2. Pat. Brit. 997399, 1965; Pat. USA 3652589, 1972.