

A New Modification of the Pomeranz-Fritsch Reaction

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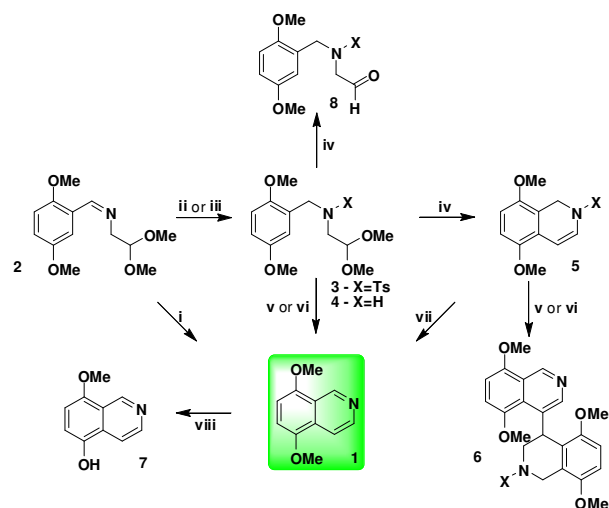
INTRODUCTION

Pomeranz-Fritsch reaction is a well known strategy to generate isoquinoline nucleus, despite its drawbacks. It is a substrate dependent reaction and alkoxyated substrates may react in particular ways producing undesired products. Depending on alkoxy group position cyclization rate is reduced and intermolecular reactions, solvolysis or ether deprotection begin to occur.

Some modifications of the original procedure were introduced in the past by Bobbit¹ and Jackson² but, although they improved the yield for most of substrates, these variants still show dependence on pattern substitution.

RESULTS AND DISCUSSION

In this work we prepared 5,8-dimethoxyisoquinoline (**1**) using Pomeranz-Fritsch based reactions. The starting material (**2**) has two methoxy groups in critical positions, both depleting the course of cyclization step. Methoxy group at position 2 has electronic influence and methoxy group at position 5 has steric influence.



i) concd H_2SO_4 ; ii) a) $NaBH_4$, MeOH; b) $TsCl$, Na_2CO_3 , DCM to 3; iii) $NaBH_4$, MeOH to 4; iv) HCl 6M/dioxane; v) H_2SO_4 /dioxane/EtOH; vi) CF_3COOH , O_2 ; vii) $t-BuOH/t-BuOK$; viii) concd HCl , EtOH 95%.

Figure 1. Pomeranz-Fritsch reaction (i) and Jackson (ii) and Bobbit variations (iii).

Used conditions are shown in figure 1 and table 1. Jackson variation (ii) as well as Bobbit variation (iii) showed low yields when applied to substrate **2**. We

observed formation of concurrent products as aldehyde³ **8** and dimer⁴ **6**, as well as incomplete transformation product³ (**5**) instead of the desired one (**1**), which generated the isoquinoline only after treatment with $t-BuOK/t-BuOH$ (vii).³ Nevertheless the use of more drastic reaction conditions leads to ether deprotection products such as **7**.⁵ In order to circumvent all these drawbacks we investigate the use of a less nucleophilic counterion to reduce the ether deprotection (viii), and higher dilution to avoid dimerization (v or vi). The addition of alcohols as cosolvents to minimize acetal deprotection was also investigated and we find that ethylene glycol and H_2SO_4 (entry 7 at Table 1) was the most effective condition.

Table 1. Selected conditions used in Pomeranz-Fritsch based reactions of compound **2**.

Entry	Starting Material ^a	System	Acid equivalent ^b	Total volume (mL)	Temperature (°C)	Time (min)	Yield (%)
1	2	H_2SO_4 /dioxane	187	5	105	5	—
2	3a	H_2SO_4 /dioxane	11	6.5	105	150	30
3	3a	H_2SO_4 /dioxane	20	10	105	30	38
4	3a	H_2SO_4 /dioxane/EtOH	40	20	105	150	46
5	3a	H_2SO_4 /dioxane/EtOH	40	20	105	90	38
6	3a	H_2SO_4 /dioxane/EtOH	40	20	105	30	39
7	3a	H_2SO_4 /CH ₂ OH	40	20	105	150	57
8	3b	CF_3COOH	269	10	60	120	20
9	3b	CF_3COOH	364	13.5	60	120	60
10	3b	CF_3COOH	404	15	60	120	60

^a 0.05 mmol of starting material

^b Equivalents in relation to starting material

CONCLUSION

We have studied Pomeranz-Fritsch based reactions of a well known low reactive substrate (**2**). Careful tuning of concentrations and conditions allowed yield improvement from less than 15% to up to 60%. We confirmed the previous statements: dilution, counterion nucleophilicity and ketal deprotection have crucial importance on reaction course of less reactive substrates.

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