Highly Efficient Synthesis of CF_3-Containing 7-Aminoquinolines From Cyclocondensation Reaction of Trifluoroacetyl Enamine Precursors

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INTRODUCTION

The quinoline ring system occurs in numerous natural products, especially in alkaloids, and presents a wide spectrum of physiological activities.[1] Much attention is still being given to the synthesis of quinoline derivatives because of their industrial applications and pharmacological properties.[2] Trifluoromethyl substituted quinolines are the subject of growing interest because of their medicinal importance, particularly as antimalarial agents (e.g., mefloquine and halofantrine).[3] Since the classical antimalarial molecules are encountering increased drug resistance, considerable efforts have been directed toward the synthesis of new fluorinated quinolines that can provide improved anti-parasitic activity.[4] The purpose of this work is to report the results of a chemical behavior study of the reactions of ketones **1** with 2,6-diaminotoluene (2,6-DAT).

RESULTS AND DISCUSSION

Trifluoromethylated ketones **1a-f** when added to 2,6-DAT at a molar ration of 1:1, in pure methanol as solvent at 0 ℃ for 2 h, furnished a new series of six enaminone intermediates **2a-f** in 46–70% yields. In addition, we found that enones **1g-i** under the same or optimized reaction conditions described above allowed us to directly obtain 7-aminoquinolines **3g-i** (21-36%) instead of the corresponding enaminones **2g-i**. In a second reaction step, the acyclic enaminones **2a-f** were subjected to reactions carried out in the presence of a strongly acidic medium (polyphosphoric acid, PPA). The cyclization of **2a-f** showed that the best results were at 90 ℃ for 6 h, affording the corresponding new series of 7-aminoquinolines **3b-f** in 86–93% yields (Scheme 1). It is not surprising that only traces of compound **3a** were obtained since enaminone derivatives of enone **1a** present a different chemical behavior from other enones.[5]

CONCLUSION

We described a simple, highly efficient and inexpensive route to prepare trifluoromethyl substituted aminoquinolines through cyclization of a variety of enaminones. Our strategy was effective, rapid and allowed adequate diversity of substituents in the construction of the quinoline ring system.

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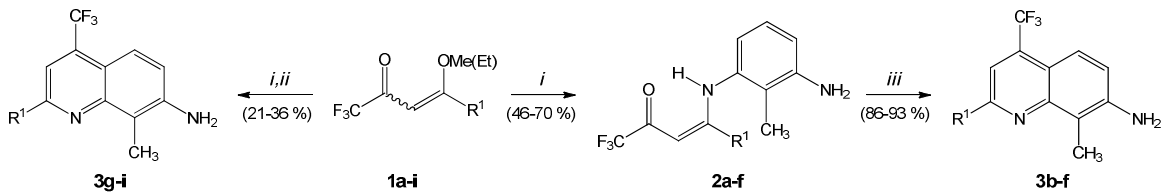

3g-i **1a-i** **2a-f** **3b-f**

1-3	a	b	c	d	e	f	g	h	i
R^1	H	Me	Ph	4-FPh	4-BrPh	4-MePh	4-OMePh	2-Thienyl	2-Furyl

(*i*) = 2,6-Diaminotoluene (1.0 equiv.), MeOH, 0 °C, 2 h; (*ii*) = MeOH, reflux, 24 h; (*iii*) = PPA, 90 ºC, 6 h.

Scheme 1. Synthesis of trifluoromethyl substituted 7-aminoquinolines.