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Synthesis of Cantharidinimide Derivatives via the Mitsunobu Reaction

Key Words

Cantharidin

Cantharidinimide

Mitsunobu reaction

ABSTRACT

Derivatives of cantharidinimide compounds **4a-c** were synthesized from reactant **2** and **3a-c** in dry tetrahydrofuran with triphenylphosphine and diisopropylazodicarboxylate, using a novel application of the Mitsunobu reaction.

INTRODUCTION

Cantharidin (**1**), a strong acantholytic, is isolated from the family Molodae.¹ It is reported to have extremely high potency² and shows toxic properties which make it an antineoplastic agent. Its potential bioactivity has stimulated research on cantharidinimides and related imides. Several modifications of cantharidinimide compound **2** have been made to reduce toxicity and promote bioactivity. N-methylcantharidinimide compounds have shown an inhibitory action on tumors in animals.³ These compounds were synthesized from cantharidin and amines in triethylamine by heating to 200 °C. Walker used the Mitsunobu reaction to successfully synthesize N-alkylmaleimides.⁴ This procedure also allows the direct formation of N-alkylcantharidinimide as shown in Scheme 1. It is a more general procedure since it can be carried out under anhydrous conditions and at room temperature or with reflux. A review of the literature revealed that these conditions have not been used before to synthesize N-arylcantharidinimide.

RESULTS AND DISCUSSION

As shown in Table 1, compound **2** is well suited as

a nucleophile in this reaction and was successfully condensed with p-chlorobenzyl alcohol **3b** in a variety of conditions, providing **4b** in a 18%-62% yield. The study was then extended to a series of alcohols, the results of which are summarized in Table 2. By using the same method at room temperature, we treated p-methylbenzyl alcohol **3a** and p-nitrobenzyl alcohol **3c** with **2** in THF and successfully obtained **4a** in a yield of 70% and **4c** at 48%, respectively. We assumed that the methyl and halogen groups might exhibit an activating effect on the benzene ring and the methyl, chloro, and nitro functional groups might exert an inductive effect with their acidity influencing the reaction. As shown in Table 2, **4a** has the highest yield, followed by **4b**, and then **4c**. Our results indicate that the electron-withdrawing capabilities at the meta and

Scheme 1

