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A new method for the synthesis of *N*-substituted pyrroles

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Abstract

An unexpected reaction of 10-bromomethyl-12-oxocalanolide A (**2**) with primary amine was demonstrated and studied. Consequentially, a new method for the preparation of *N*-substituted pyrroles starting from γ-halo-α,β-unsaturated ketone was presented.

Keywords: 12-Oxo-calanolide A; Primary amine; *N*-Substituted pyrroles; Synthesis

(+)-Calanolide A (**1**), first acquired from *Calophyllum lanigerum* trees in Malaysia, has been reported as a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1]. In view of its unique anti-HIV-1 properties [2–4], we embarked on the synthesis and modification of (+)-calanolide A in order to obtain analogues with better potency against HIV-1 [5–7]. From a chemical library synthesized in our laboratory, a novel compound **2** termed as 10-bromomethyl-12-oxo-calanolide A was hence identified with EC_{50} value of 2.85 nmol/L [8a]. Its key structure feature comprised the bromomethyl group at C-10 position and the ketone form of C-12 position (Fig. 1).

The exciting result prompted us to further modify 12-oxo-calanolde A in purpose of ascertaining the pharmacophore of this compound type as potent anti-HIV-1 drug candidate [8b]. It should be addressed that the documented modifications in literature at C-10 position of the skeleton of (+)-calanolide A were usually fulfilled through decorating some lipophilic groups such as propyl or phenyl groups [8,9]. In order to increase the hydrophilic property of this compound type, the neucleophilic substitution reaction of the bromomethyl group of compound **2** had been utilized for preparing analogues of 12-oxocalanolide A with amino groups at C-10 position [8b]. In this contribution, we demonstrate and study an unexpected reaction of compound **2** with the primary amine, and hence present a new method to prepare *N*-substituted pyrroles.

As showed in Scheme 1, when compound **2** was reacted with the secondary amines, such as pyrrolidine or piperidine, in THF at reflux temperature, the classical nucleophilic substitution products **3** were obtained in which hydrophilic groups were introduced at the C-10 position of 12-oxocalanolide A [8b].

Interestingly, when compound **2** was treated with the primary amines under the same conditions, the dominant product **4** (M-18) was readily obtained in 50–60% yields as Scheme 2. Its molecular weight is 18 less than that of the

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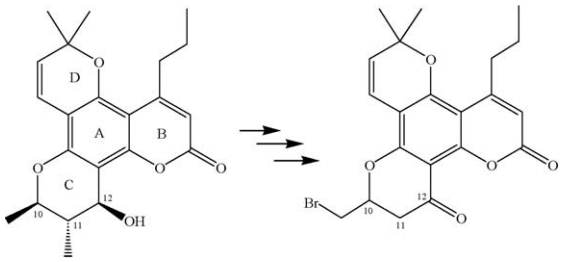
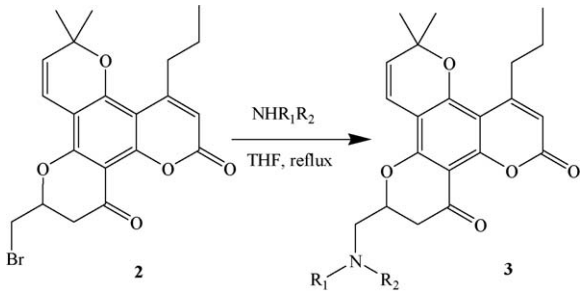
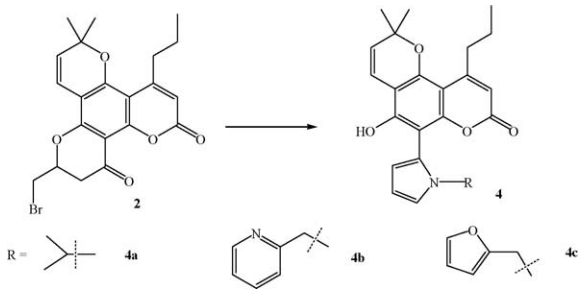


Fig. 1. The natural and modified calanolide A with anti-HIV-1 activity.



Scheme 1. Reaction of compound **2** with the secondary amines.



Scheme 2. Reaction of compound **2** with the primary amines (condition: NH_2R, THF, reflux).

normal nucleophilic substitution product. The ^{1}H NMR spectrum of product **4** showed that the original ring-C of the four-ring skeleton was opened and a new unsaturated aromatic ring containing a nitrogen atom was formed. Additional ^{13}C NMR, DEPT, HMQC and HMBC spectra indicated the existence of a pyrrole ring in the structure.

The hypothesized mechanism is illustrated in Scheme 3. Under the base conditions, ring-C opened to produce the γ-bromo-α,β-unsaturated ketone form which can react with the primary amines in a process of nucleophilic substitution. Subsequently, the intramolecular nucleophilic addition of the resulted second amine species to the carbonyl group at position C-12 afforded a five-member nitrogen cycle. Finally, the special product **4** containing a pyrrole ring was obtained after the removal of the hydroxyl group and the simultaneous rearrangement of the double bond under the base condition.

Based on our knowledge, pyrroles are important substructures of pharmaceutically compounds and also of numerous natural products [10]. The synthesis of pyrroles containing various substituents is a subject of continued research. Many methods for the synthesis of diversely substituted pyrroles have been developed [11,12]. From the above results, we deduced that *N*-substituted pyrroles could be prepared starting from γ-helo-α,β-unsaturated ketone species. Therefore, to verify this speculation, the reaction of compound **5** with primary amine was subsequently run in THF at reflux temperature and it successfully underwent to afford the pyrrole-containing product **6** in a yield of 86% (Scheme 4).