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Mechanically activated ring-opening reactions of *N*-acyl-1,2,3,4-tetrahydroisoquinolines derived from the synthesis of praziquantel intermediate

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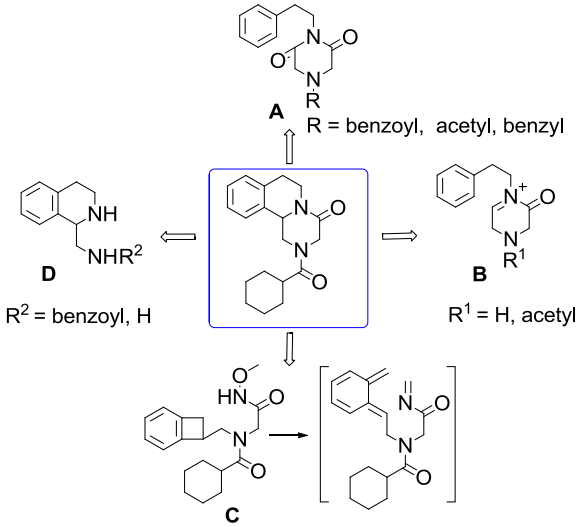
ABSTRACT

An unexpected DDQ-promoted ring-opening reaction of *N*-chloroacetyl-tetrahydroisoquinoline under ball milling conditions was revealed during the synthesis of Praziquantel. A variety of *N*-acyl-tetrahydroisoquinolines were then tested to further investigate the reaction, and plausible reaction mechanism was proposed. Ball milling was demonstrated to be an efficient tool to promote this oxidative ring-opening reaction to give products in satisfactory yields with good selectivity in short reaction times.

1. Introduction

Praziquantel (PZQ) is an anthelmintic developed by Bayer and Merck in 1970s, which effectively against flatworms and has been widely used in treatment of hydatid disease, cysticercosis, and toxocariasis. Hitherto, there have been considerable efforts at analog synthesis given PZQ's status as the preferred drug for the treatment of the more than 200 million patients currently infected with bilharziosis.[1,2] Although there have been a couple of synthetic routes to prepare PZQ via different intermediates (Scheme 1),[3] most of them are marred by one or another drawback such as multiple steps, harsh conditions, use of carcinogenic solvent, environmentally harmful reagents and toxic substrates. Therefore, it is still highly desirable to develop a simpler and more efficient synthetic protocol for the preparation of PZQ and analog under environmentally benign conditions.

Cross-dehydrogenative-coupling (CDC) reaction has been widely researched during the past decade, which shows as a mild method for the direct coupling of appropriate C–H bonds.[4] Our group had reported a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-promoted solvent-free CDC reaction under ball-milling conditions.[5] During the study of a novel synthesis of PZQ, we planned to extend this solvent-free coupling method to the synthesis of 1-aminomethyl tetrahydroquinoline, a key-intermediate of praziquantel, by reduction and deprotection of the CDC product. Unexpectedly, the reaction was also found to afford oxidative



Scheme 1. Preparation of PZQ via different intermediates.

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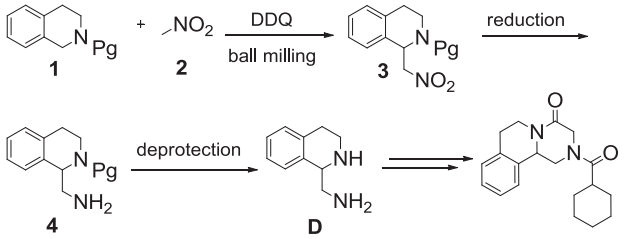
ring-opening products and acylated DDQ derivatives using different acyl protecting groups on tetrahydroisoquinoline.

Oxidative ring-opening reaction is one of the most important processes in organic transformations. The oxidative ring opening of heterocycles,[6] metal-containing heterocycles[7] and carbocycles[8] are well documented, these valuable ring-opened synthetic intermediates can be further manipulated to afford ring-contraction or ring-expansion products.[9] In addition, a great number of works have applied oxidative ring opening reaction to the synthesis and modification of bioactive natural products, such as Lavandulol,[10] (+)-Lycoricidine,[11] Taxane derivatives[12] and Paclitaxel analogs.[13] However, most of the oxidative ring-opening reactions are conducted in hazardous organic solvents, together with metal oxidants or other explosive oxidants. In this paper, we describe an efficient synthetic strategy of PZQ and the derivative solvent-free oxidative ring-opening reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinolines under ball milling conditions.

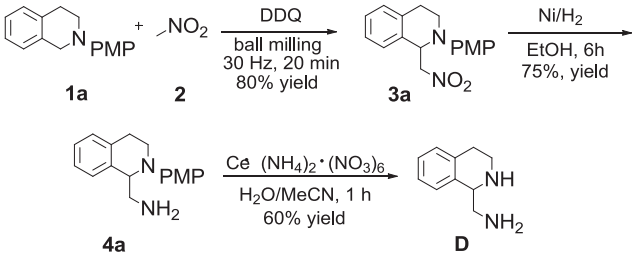
2. Results and discussion

Our synthetic strategy of PZQ by using 1-aminomethyl tetrahydroisoquinoline as key intermediate was shown in Scheme 2. CDC reaction was used to introduce the nitromethyl group to the *N*-protected 1,2,3,4-tetrahydroisoquinoline. Then the target product 1-aminomethyl tetrahydroisoquinoline could be obtained after a two-step sequence of reduction and deprotection. After the sequential formation of piperazinone and acylation, Praziquantel could be finally obtained.



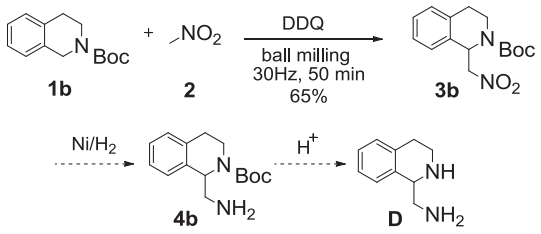
Scheme 2. Synthesis of PZQ with 1-aminomethyl tetrahydroisoquinoline as key intermediate.

We initiated our synthesis from *N*-PMP tetrahydroisoquinoline, which was subjected to a solvent-free CDC reaction under ball-milling conditions (Scheme 3). The expected 1-nitromethyl tetrahydroisoquinoline **3a** was obtained in 20 min with 80% yield, which was followed by nitro reduction with Raney-Ni/H_2 under atmospheric pressure. After purification, PMP was removed by ammonium ceric nitrate (CAN)[14] to afford the target compound in 60% yield. Recently, Todd et al. reported their research on the synthesis of PZQ using **D** as key intermediate.[15] According to their work, the amino group of **4a** should be pre-protected before the removal of PMP, otherwise the deprotection yield would be very low. In our synthetic route, moderate deprotection yield was obtained but the



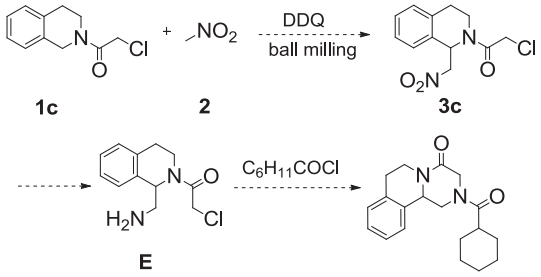
Scheme 3. Synthesis of 1-aminomethyl tetrahydro-isoquinoline from *N*-PMP tetrahydroisoquinoline **1a**.

procedure was found to be relatively difficult. To ease the deprotection, PMP was replaced by Boc group, which afforded **3b** as the CDC product (Scheme 4). However, it could hardly undergo nitro reduction and affording a hardly separable mixture.



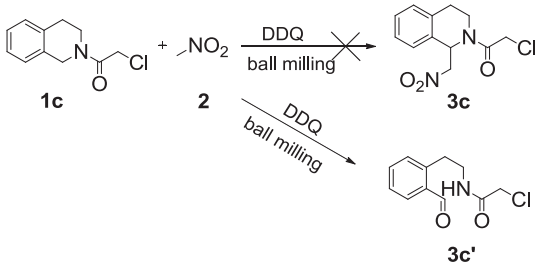
Scheme 4. Synthesis of 1-aminomethyl tetrahydro-isoquinoline from *N*-Boc tetrahydroisoquinoline **1b**.

Although the designed route in Scheme 3 gave the ideal products, the protection and deprotection of tetrahydroisoquinoline resulted in relatively low atom economy, which was not in accord with green chemistry. Therefore, we turned to use chloroacetyl as the protecting group, by which piperazinone might form directly after nitro reduction to eliminate the deprotection procedure (Scheme 5).



Scheme 5. Designed synthetic route of PZQ with 1-aminomethyl-2-chloroacetyl-tetrahydroisoquinoline **1c** as intermediate.

The *N*-chloroacetyl-tetrahydroisoquinoline **1c** was examined as substrate to perform the same CDC reaction under ball milling conditions. To our disappointment, though most of the substrate had reacted within 50 min of ball milling, no desired product could be isolated. After identification, we surprisingly found that oxidative ring-opening product benzaldehyde derivative **3c′** was obtained in 67% yield (Scheme 6). However, no matter changing the reactant ratio or the amount of DDQ, the reaction gave only the benzylaldehydes **3c′**. The best results were obtained when 1.1 equiv of DDQ was used, an excess of oxidant was detrimental to the yield of the product, whereas less than 1 equiv of DDQ would result in incomplete conversion of the starting materials. An examination of the effect of ball milling vibration frequency on the reaction was undertaken subsequently (Table 1). The yield declined with decreased frequencies, and almost no reaction occurred when the frequency was reduced to 15 Hz even with prolonged reaction times. Besides, without nitromethane, the reaction still proceeded



Scheme 6. Oxidative ring-opening reaction of *N*-chloroacetyl-tetrahydroquinoline **1c**.