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LETTERS

An Improvement to the Vaultier Tandem Sequence : A Practical Highly Stereoselective Three-Component Reaction

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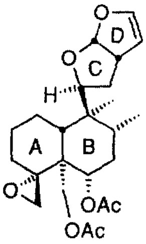
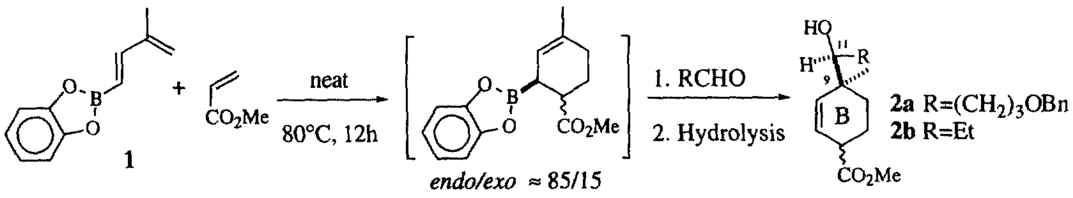
Abstract: We describe an improvement to the Vaultier tandem reaction involving the simple heating of a mixture of bora-1,3-diene, dienophile and aldehyde, which gives direct access to substituted compounds that could not be prepared using the previously existing methodology. © 1999 Elsevier Science Ltd. All rights reserved.

We have recently published[1] a new route towards the synthesis of Clerodin[2], a potent insect antifeedant (**Scheme 1**). In this approach, the preparation of Cycle B is based on a tandem reaction developed by Vaultier et al[3], which enabled us to prepare the highly functionalised alcohol **2a** in two steps in 63% yield from the bora-1,3-diene **1** with complete control of the relative configuration of centres 9 and 11 (**Scheme 2**)[1]. The cycloaddition was shown to be further activated by the use of a Lewis acid[4]



Clerodin

Scheme 1



Scheme 2

We next investigated the reactivity of the more substituted dienes **3a-d** (**Scheme 3**)[5]. Our first attempts to react these dienes with methyl acrylate under thermal conditions led to extensive degradation after one night at 80°C. However, NMR monitoring studies revealed that the expected adducts **4a-c** were initially formed. We thus tried running the cycloaddition in the presence of an aldehyde in order to trap the apparently unstable intermediates and obtain directly the corresponding alcohols after hydrolysis. Our results are summarised in **Table 1.**

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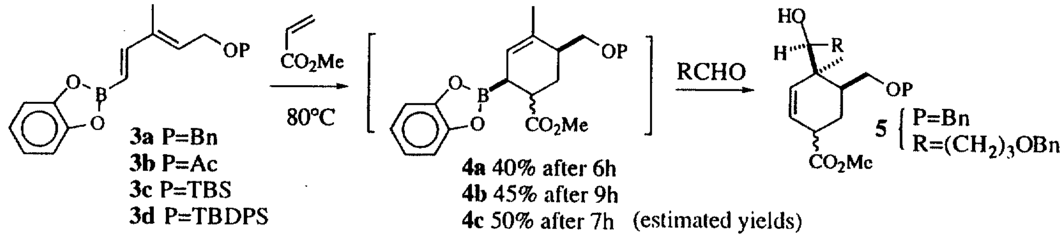

Scheme 3

Diene	Methyl acrylate	Aldehyde	Reaction conditions	Product ; Isolated yield
1 (1 eq.)	7.7 eq.	EtCHO (7.7 eq.)	60°C (temp. of oil bath), 12h	**2b** ; 22%
1 (1 eq.)	5 eq.	$BnO(CH_2)_3CHO$ (1.5 eq.)	80°C, 15h	**2a** ; 29%
1 (1 eq.)	5 eq.	$BnO(CH_2)_3CHO$ (1.5 eq.)	10 kbar, room temp., 24h	**2a** ; 22%
1 (1 eq.)	5 eq.	$BnO(CH_2)_3CHO$ (2 eq.)	80°C, 16h	**2a** ; 38%
1 (1 eq.)	8 eq.	$BnO(CH_2)_3CHO$ (3 eq.)	80°C, 16h	**2a** ; 50%
3a (1 eq.)	8 eq.	$BnO(CH_2)_3CHO$ (3 eq.)	80°C, 15h30	**5** ; 33%

Table 1

The lower yield obtained with EtCHO (bp=46-50°C) may be a result of the lower temperature involved. Optimisation showed that the reaction was limited by partial degradation of the aldehyde when less than three equivalents of this reagent were used.The reaction was also tested under high pressure at room temperature. The product **2a** could then be accessed with a good diastereoselectivity (> 90/10 as estimated by NMR), whereas the thermal reactions gave a similar diastereoselectivity to that obtained using the previous two-steps methodology (85/15).

In summary, we have shown that the transformation **1** -> **2** or **3** -> **5** can be regarded as a three-component reaction. This constitutes an important improvement over former procedures as they did not allow the preparation of the highly substituted alcohol **5** ; in addition, the reaction is practical, easy to perform[6] and can be run at room temperature under pressure using standard apparatus. One might also conceive its application in new intramolecular reactions[7]. The synthesis of an advanced intermediate towards Clerodin from the new compound **5** is due to be reported shortly[8].

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References and notes

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6. A typical experimental procedure is as follows. Freshly distilled methyl acrylate (46.4 mmol, 4.2 ml) and 4-benzyloxybutanal (17.4 mmol, 3.10 g) were added at 0°C to diene **1** (5.8 mmol, 1.08 g) in a flask fitted with a condenser. The mixture was heated at 80°C for 16h, then diluted with petroleum ether 40/60 (50 ml) and stirred at room temperature for 30 minutes with a saturated solution of sodium hydrogen carbonate (50 ml). The organic layer was separated and the aquous layer extracted several times with petroleum ether 40/60 (50 ml portions). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford 2.05 g of crude product. Purification by flash column chromatography (10% ethyl acetate/petroleum ether 40/60) led to the isolation of the alcohol **2** (0.96 g, 50%) as a colourless oil.
7. For instance, using a dienophile bearing an aldehyde functionality could be an interesting possibility.
8. Six, Y. and Lallemand, J-Y. *to be published.*