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Wittig Reaction : A New Route to α-Methoxyketones. Application to the Synthesis of Simplified Analogs of Artemisinin.

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Abstract: C-4 substituted antimalarial Artemisinin analogs were synthesised *via* an unusual Wittig reaction between methoxymethyltriphenylphosphonium ylide and nitriles.

Artemisinin **1** extracted from *Artemisia annua. L.* is effective against chloroquine-resistant malaria[1]. The development of Artemisinin simplified analogs preserving the 1,2,4-trioxane has allowed to establish structure-activity relationships[1,2]. Avery *et al.*[3] reported the synthesis of 4-alkylartemisinins, 4-(alkylaryl) and 4-carboxyalkyl artemisinins by the reaction of hydrazone enolates and alkylating agents. SAR studies showed that the introduction of either a propyl group or a polar substituant (COOR) increased *in vitro* activity.

In a continuation of our study on the syntheses of 1,2,4-trioxanes[4,5], we were interested in preparing 4-alkoxymethyl Artemisinin analogs **2** to accumulate the positive aspects described by Avery[3].

In the present paper, we wish to report the methodology we used to synthesise ketones **5** in order to introduce a methoxymethyl group on the C-4 at the A/B ring junction.

α-Methoxymethylketones are known but usually obtained by the reaction of diazoketones with methanol and boron trifluoride etherate[6], oxidation of silyl enol ethers[7] or by multisteps syntheses, frequently in low yields. Our approach is based on the reaction between phosphorus ylides and nitriles. This reaction has been described firstly by Barnhardt and McEwen in 1967 with aromatic nitriles[8] but has not been developed furthermore. In a previous paper[5], we have demonstrated that this particular reaction could apply to an aliphatic nitrile and was compatible with an enol ether function.

Ketones **5** were prepared in good yields by the reaction of ketonitriles **3** and methoxymethyl ylides in a one step synthesis when PhLi was used to deprotonate methoxymethyltriphenylphosphonium chloride. Unlike, when a base with potassium as counter ion such as KHMDS was used to prepare methoxymethyl ylide, the nitrile group was not affected. The transformation of enol ethers **4** into ketones **5** was achieved by using methoxymethyl ylide generated by the use of PhLi .

It is noteworthy that the reaction was totally chemoselective owing to the choice of a judicious counter ion of the base : when PhLi was used to deprotonate the methoxymethyltriphenylphosphonium chloride, LiCl generated remained dissolved in THF and reacted as a Lewis acid to activate the nitrile function, when KHMDS was used, KCl precipitated in THF and the nitrile group was not enough reactive towards methoxymethyl ylides contrarily to the keto function. One can interestingly note that the hydrolysis of the mixture was carried out with water[9] in order to preserve an enol ether function. At least, the reaction of a large excess of ylide on compound **4** (R = CN) reacted only with the more accessible nitrile group.

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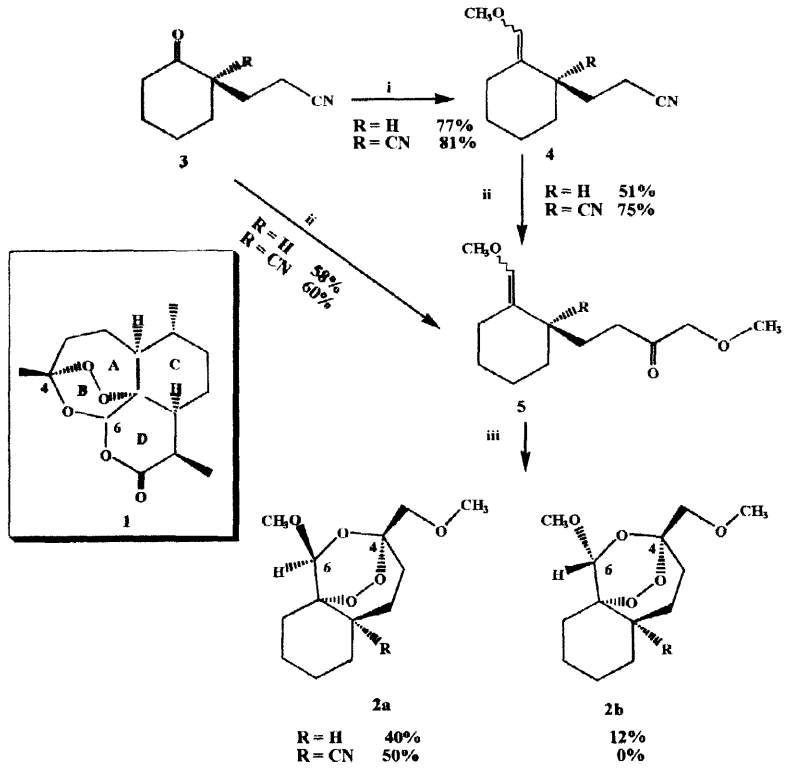

i) $P^+Ph_3CH_2OMe$, Cl^- (4eq), KHMDS (4eq) ii) $P^+Ph_3CH_2OMe$, Cl^- (4eq), PhLi (4eq) ; H_2O iii) $^1O_2$ -78°C ; TMSOTf

Finally, oxygenative cyclization was accomplished at -78°C in CH_2Cl_2 in 2 hours and the resulting solution was then treated with TMSOTf. When R = CN, the cyclization of *Z* and *E* enol ethers **5** leaded to the same 1,2,4-trioxane **2a** in a totally diastereoselective reaction. When R = H, two C-6 epimeric trioxanes were obtained in a ratio (**2** '*endo*' / **2** '*exo*' : 4 / 1).

In conclusion, the conversion of aliphatic nitriles into α-functionalized ketones has been accomplished with phosphorus ylides. This reaction is an excellent alternative method to the use of organometallic derivatives. Reactions using nitriles and ylides bearing other functional groups (SMe, CF_3...) are under study.

The analogs **2a-b** were tested *in vitro* against the 'H' strains of *P. falciparum*. When R = H, compounds **2** showed a significantly antimalarial activity. SAR will be published furthermore in a biological full paper.

References and Notes

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9. Typical General Procedure: To a 0°C cooled solution of 3.5 g (10 mmol) of methoxymethyltriphenylphosphonium chloride in dry THF (50 ml) were added dropwise 10 mmol of Phli. The red solution was stirred at 0°C for two hours and 2.5 mmol of nitrile in 10 ml of THF were added slowly. After the reaction was completed, as juged by TLC, the solution was pourred into water and extracted with ether.