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A New Route to *N*-Substituted 11-Azaartemisinins

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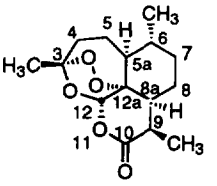
Abstract: A series of *N*-substituted 11-azaartemisinins were prepared in high yield by Michael additions to the amide nitrogen in **2a**. The presence of substituents on the unsaturated system of the Michael acceptor markedly decreased the yield of the reaction.

The discovery of a sesquiterpene lactone endoperoxide, **1**, artemisinin, by Chinese investigators and their demonstration that it was an effective antimalarial against drug-resistant strains of *Plasmodium falciparum* stimulated a host of studies to prepare more active drugs[1] and to determine their mechanism of action.[2] In our efforts to prepare new, more active artemisinin derivatives we synthesized[3] a series of *N*-substituted 11-azaartemisinins such as **2b** by employing a variety of amines. The most active derivative **2c** was obtained by reductive ozonolysis of the allyl group in **2b**, and it was 26 times more active *in vitro* and 4 times more active *in vivo* than artemisinin. In order to pursue this lead and also to shed light on the possible mode of action, we wanted to prepare *N*-substituted 11-azaartemisinins with free carboxylic groups that could be employed for making affinity chromatographic columns. Therefore, we required an efficient and direct route to analogs of **2c**. The most direct approach, alkylation of 11-azaartemisinin, **2a**, unfortunately yields an *O*-alkyl derivative **4** in low yield.[3]

A possible alternative route we envisaged to alkylation was the use of a Michael addition to **2a** to generate a series of analogs of **3**. Danishefsky et al.[4] were able to annulate a series of thiolactams with methyl methacrylate or diazomethylvinylketone in their syntheses of the ACE inhibitor, iso-A58365A. Later Hiemstra *et al.*[5] employed a Michael addition of acrylonitrile to a protected pyroglutamic acid to prepare analogues of 1,5-diazobicyclo[4.3.0]non-5-ene. Although both groups indicated the reaction proceeded in good yield, it was uncertain that this methodology could be employed with **2a** which contains a labile endoperoxide that is essential for antimalarial activity. In this Letter we report data on the scope and limitations of the Michael acceptor in annulations of **2a**.



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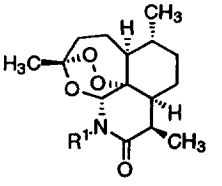

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a) $R^1 = H$
b) R^1 = allyl
c) $R^1 = CH_2CHO$

Reaction of **2a** with catalytic amounts of sodium hydroxide, and ethyl acrylate in THF at room temperature yielded the *N*-alkyl derivative **3a** in 86% yield.[6] Under the same mild reaction conditions acrylonitrile produced the adduct **3b** in 88% yield. Michael additions to **2a** thus offer a new and high yield route to materials which were accessible with difficulty by our earlier synthesis of *N*-substituted 11-azaartemisinins. In probing the scope and limitations of this approach we quickly encountered problems in isolating products from the reaction of cyclohex-2-enone with **2a**. Since Danishefsky et al. successfully employed a methylvinylketone derivative in their study we examined the reaction of methylvinylketone with **2a** and found the reaction proceeded to form the adduct, **3f**, in high yield. Reaction of **2a** with α- or β-substituted acrylic esters produced adducts in low to vanishing yield. Thus, it appears that the presence of substituents on the double bond retards or stops the addition of the amide moiety. In each of the two reported additions to amides, there were no substituents on the double bond of the acceptor.

In addition to examining the effect of substituents on the double on the addition, several vinylic compounds conjugated to a variety of electron withdrawing groups were also investigated. Adducts **3c**, **3d**, and **3e** were formed with phenyl vinylsulfonate, phenyl vinylsulfone, and the phenyl vinylsulfoxide.

The antimalarial activities of these adducts are currently being determined and the results of those studies will be described elsewhere.

Acknowledgments.

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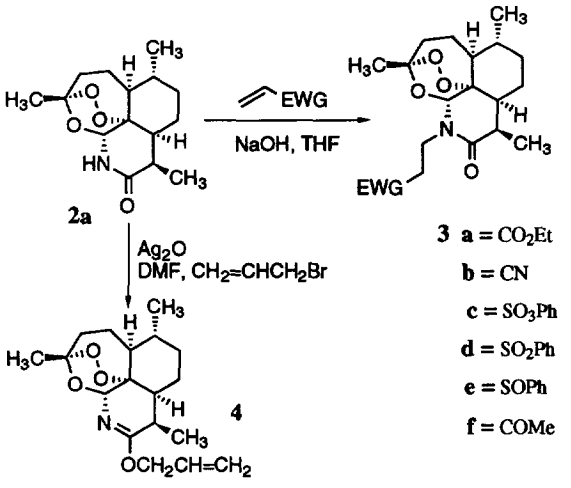

Table 1. Michael Reaction Products of 11-Azaartemisinins.

Product	Alkene	Reaction Time (h)	Yield (%)	CIMS ($M+NH_4^+$)
3a	CO_2Et	2	86	399
3b	CN	1.5	88	352
3c	SO_3Ph	3	80	483
3d	SO_2Ph	3	90	467
3e	SOPh	18	76	451
3f	COMe	10	73	369

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6. Typical Experimental: To a solution of **2a** (27 mg, 0.01 mmol) in anhydrous THF (2 ml) were added at room temperature a trace of powdered sodium hydroxide and freshly distilled ethyl acrylate (31 µl, 0.03 mmol). After stirring for one hour, another trace of sodium hydroxide was added and stirring continued for one additional hour. The reaction was then quenched by adding dilute aq. Na_2SO_3 solution (5 ml). The water layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were successively washed with a saturated aqueous $NaHCO_3$, brine, water, and dried over Na_2SO_4. Evaporation of the solvent gave a crude oily product which was purified by silica gel chromatography (ethyl acetate/hexane, 4:1). This gave **3a** as a clear oil (31.6 mg, 86 %): CIMS (NH_3) 399 ($M+NH_4^+$, 100), 382 (M+1, 90); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92-0.98 (2H, m), 0.99 (3H, d, J = 5.97 Hz), 1.13 (3H, d, J = 7.16 Hz), 1.25 (3H, t, J = 7.06 Hz), 1.37 (3H, s), 1.26-1.43 (3H, m), 1.63-1.78 (3H, m), 2.01 (2H, dm, J = 10.1 Hz), 2.41 (1H, m), 2.50-2.61 (1H, m), 2.75-2.85 (1H, m), 3.27 (1H, p, J = 6.95 Hz), 3.61-3.70 (1H, m), 3.79-3.88 (1H, m), 4.12 (2H, q, J = 7.13 Hz), 5.33 (1H, s); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.2, 14.5, 20.1, 23.0, 25.4, 25.8, 33.0, 33.5, 34.0, 37.0, 37.9, 38.8, 45.9, 51.8, 60.8, 79.2, 80.5, 105.2, 172.2, 172.9.

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