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Preparation of 10-Trifluoromethyl Artemether and Artesunate. Influence of Hexafluoropropan-2-ol on Substitution Reaction

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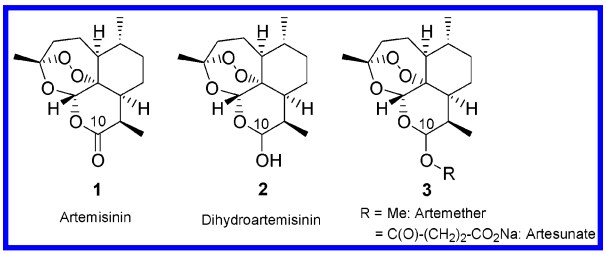
Received August 11, 2003

To prepare 10-trifluoromethyl analogues of important antimalarials such as artemether and artesunate, the substitution reaction of the 10-trifluoromethyl hemiketal **6** and bromide **4** derived from artemisinin was investigated. While **6** appeared to be unreactive under various conditions, bromide **4** could easily undergo substitution with methanol under electrophilic assistance or noncatalyzed conditions. Optimization of the reaction revealed the role of CH_2Cl_2 as solvent to avoid the competitive elimination process and the crucial influence of hexafluoro-2-propanol (HFIP) in increasing the rate and the stereoselectivity of the substitution reaction (de >98%). The efficiency of this reaction was exemplified with various alcohols and carboxylates (yield up to 89%).

Introduction

Artemisinin **1** is a natural efficient antimalarial drug for the treatment of multidrug-resistant forms of *Plasmodium falciparum*.[1] However, pharmacological problems associated with artemisinin **1**, especially a short plasma half-life, with, as consequence, a limited biodisponibility, prompted scientists to search for more metabolically stable derivatives. In this context, we investigated the chemistry of 10-trifluoromethyl artemisinin derivatives.[2] In this paper, we report our studies aimed at preparing trifluoromethyl analogues of ethers and esters **3** of dihydroartemisinin **2** (DHA), which were expected to be more stable toward metabolism process. Our strategy is based on substitution reaction at the CF_3-substituted C-10 carbon of bromide **4**.



Results and Discussion

In a first approach, an obvious route to 10-CF_3 ketals **5** was to start from hemiketal **6**, easily prepared from artemisinin and trifluoromethyltrimethysilane ($TMSCF_3$),[2] and was the direct etherification or acylation of the hydroxyl moiety. However, all our attempts failed, probably because of the very weak nucleophilicity of the corresponding alkoxide, due to the trifluoromethyl group. An alternative route could be a substitution reaction of the hydroxyl of **6** (or the corresponding mesylate) as already described for trifluoromethyl furanose derivatives.[3] However, it is well-known that substitution of trifluoromethyl alcohols is difficult by either S_N1 or S_N2 process.[4] The electron-withdrawing character of the CF_3 group strengthens the C−O bond. Furthermore, combination of steric and electronic repulsion of the incoming nucleophile by fluorine atoms decreases the reaction rate of S_N2 process and most examples of S_N2 reaction concern primary and secondary trifluoromethyl alcohol derivatives.[5] In addition, the high electron-withdrawing effect of the CF_3 group destabilizes the intermediary carbocation thus disfavoring an S_N1 process. Such S_N1 substitution is highly favored when an adjacent stabilizing substituent counteracts the attractive effect of the CF_3 group. This is the case for trifluoromethyl alcohols substituted in α or β with aryl groups, heteroatoms or metals with vacant d orbitals.[6]

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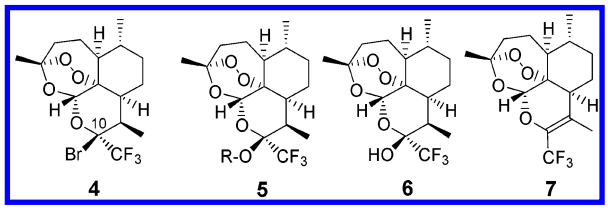
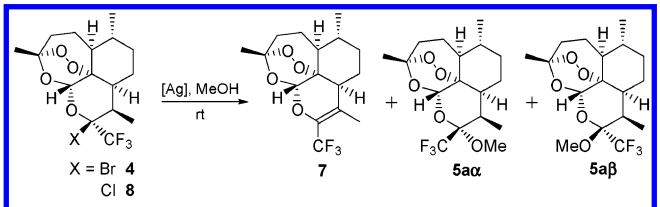
10.1021/jo035174o CCC: $25.00
Published on Web 11/19/2003



As for acylation, the mesylate of **6** could not be obtained, and the hemiketal **6** was then directly submitted to S_N1-type conditions. However, when placed with $BF_3{\cdot}Et_2O$ in the presence of MeOH, hemiketal **6** remained unchanged. Substitution of **6** with benzoic acid under the Mitsunobu S_N2 conditions also failed.

However, hemiketal **6** was found to be reactive in bromination reaction. Reaction of **6** with thionyl bromide provided the trifluoromethylated bromide **4** in very high yield.[7] The reaction proceeded with retention of configuration at C-10 (SNi reaction) as usually observed with $SOCl_2$ and $SOBr_2$. Bromine atom being more labile than a hydroxyl group, substitution reactions were then investigated from **4**.

SCHEME 1. Substitution of Bromide 4 and Chloride 8 with MeOH[a]



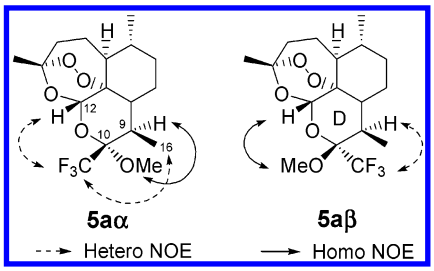
Entry	X	[Ag]	Time	7	5aα	5aβ
1	Br	AgOTf	1 h	29%	28%	43%
2	Cl	AgOTf	1 day[a]	32%	23%	45%

[a] 12% of starting material was recovered.

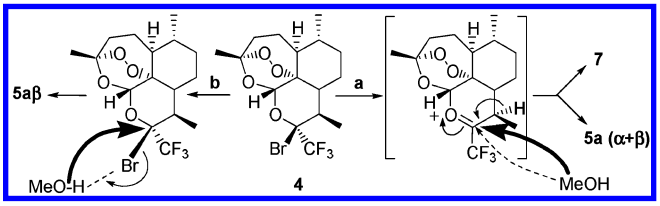
Bromide **4** was first placed under silver salt assisted solvolysis conditions, since silver salts are well-known to favor S_N1 substitution reactions or push−pull processes. When bromide **4** was placed in methanol, in the presence of 1 equiv of silver salt, **5a** was obtained as a mixture of 2 diastereoisomers and was accompanied by the pseudo glycal **7** (Scheme 1). With AgOTf (entry 1), bromide **4** provided after 1 h a 71:29 ratio of **5a** and **7**, and **5a** was obtained as a 39:61 mixture of **5a**α (in which OMe is α) and **5a**β. When bromide **4** was replaced with its chloride analogue **8** (prepared from **4** with $SOCl_2$),[7] the reaction rate strongly decreased, and chemoselectivity was not improved (entry 2). Similar results were obtained with other silver salts.

Configurations at C-10 were assigned with NOESY experiments, performed on the mixture of both diastereoisomers resulting from the reaction with AgOTf. The homo-NOE indicated, in the major isomer, a correlation between protons of the methoxy group and H-12, whereas in the minor isomer these protons correlate with H-9 (Scheme 2). Moreover, H, F hetero-NOE experiments revealed a correlation between the trifluoromethyl group

SCHEME 2. Assignment of the C-10 Configuration in 5a



SCHEME 3. Both Activation Pathway of Substitution Reaction of Bromide 4



and H-9 in the major isomer, whereas it correlates with both methyl-16 and H-12 in the minor one. On these bases, the major isomer with a ^{19}F signal at −75.9 ppm was assigned to be the isomer where the methoxy group is β (axial), whereas the minor one (δ ^{19}F = −75.5 ppm) was assigned to be the α isomer. Non ambiguous NOE effect indicated that methoxy in **5a**β is axial joint to X-ray data from a suitable crystal of **6**, clearly indicate that a chair conformation of D-ring is largely predominant.[8]

In these substitution reactions performed in the presence of a silver salt, since the reaction is not stereoselective it is reasonable to consider that reaction proceeds, at least in part, in a S_N1-type process providing an oxonium salt with both accessible faces (route a, Scheme 3). As usually observed in the DHA chemistry with Lewis acids, substitution and elimination are competitive pathways.[9]

Before extending the substitution to various nucleophiles, conditions had to be optimized in order to avoid the use of the nucleophile as solvent, which represents a real drawback in the case of expensive or high boiling point compounds. For this purpose, the choice of a good solvent could be crucial since we have previously demonstrated the great influence of solvent on the ratio elimination/substitution from DHA.[2b,10] Bromide **4** was thus placed in different solvents at room temperature and aliquots were taken at t = 1 and 8 h. The conversion into the glycal **7** was followed in ^{19}F NMR (δ $^{19}F_{\text{bromide 4}}$ = −78.1 ppm whereas δ $^{19}F_{\text{glycal 7}}$ = − 65.4 ppm) and compared to the conversion of **4** into **7** observed in MeOH as solvent (Table 1). From this study it appeared that bromide **4** was unstable in aprotic dipolar solvents such as DMSO or DMF, in which **4** was quickly converted into

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(10) Hoang, V. D.; Bonnet-Delpon, D.; Bégué, J. P. Unpublished results. The substitution of DHA with fluoro alcohols is dependent on the solvent used. A mixture of substitution/elimination compounds was obtained in Et_2O, whereas no elimination was observed when hexane was used as solvent.

TABLE 1. Stability of 4 in Different Solvents at Room Temperature

	DMSO		DMF		CH_3CN		hexane		CH_2Cl_2		MeOH[b]	
solvent	1 h	8 h	1 h	8 h	1 h	8 h	1 h	8 h	1 h	8 h	1 h	8 h
4 (%)[a]	41	4	68	45	91	77	>95	>95	>95	>95	14	0
7 (%)[a]	59	96	32	55	9	23	<5	<5	<5	<5	16	23

[a] ^{19}F NMR ratio. [b] **5a**α and **5a**β are the other products obtained. The **5a**α/**5a**β ratio was the same, 17/83, at 1 and 8 h.

glycal **7**. Conversely, it was stable in low or nonpolar ones such as CH_2Cl_2 or hexane (no elimination was observed in ^{19}F NMR after 8 h).

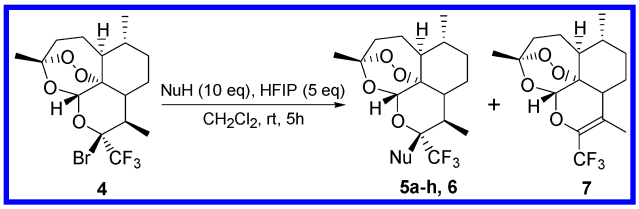
Surprisingly, in MeOH the reaction was complete in less than 2 h, and substitution compound **5a** was the major product accompanied with only 23% of glycal **7**. **5a** was obtained in a 17/83 ratio of α and β isomers.

The conclusion of these experiments on solvent effects is that the nucleophilic substitution of bromide **4** can occur without silver electrophilic assistance when using methanol as solvent. The diastereoisomer β was also predominantly formed (de = 66%) and a non negligible amount of elimination product was obtained. Addition of triethylamine or dimethylaminonaphthalin as proton sponge did not change the substitution/elimination ratio. Other alcohols such as ethanol or allylic alcohol used as solvents also allowed the substitution of **4**. It is postulated that in these cases the solvent is able to activate bromine through a hydrogen bond ($\alpha_{MeOH} = 0.98$).[11] Such a process, more or less concerted, could explain the low ratio of elimination and the better diastereoselection. However, unlike an S_N2 process, the substitution of **4** with MeOH occurred mainly with retention of configuration, similarly to an SNi process usually observed when the nucleophiles also play a role of activator (route b, Scheme 3).[12,13] The second point that this study highlighted, is that CH_2Cl_2 appears to be a solvent of choice for studying the substitution of **4** because no elimination was observed after 8 h and it solubilizes starting material better than hexane.

Bromide **4** was thus placed in CH_2Cl_2 with 10 equiv of MeOH at room temperature. The substitution reaction was slowed (72% conversion after 15 h). Nevertheless, it is interesting to note that the diastereoselection was improved (**5a**α/**5a**β = 8:92) compared to the reaction performed with MeOH as solvent (**5a**α/**5a**β = 17:83). Moreover, under these conditions the elimination process into glycal **7** could be reduced to 3%.

With the hypothesis that the slower reaction rate was due to the weaker activation process of bromide **4** by MeOH as represented in Scheme 3, we thought to reinforce this activation using a stronger hydrogen bond donor but less electrophilic than a silver salt. A good candidate was 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), which possesses a low nucleophilicity, a high ionizing power, and a high hydrogen bond donor ability (α = 1.96).[11] All these properties contribute to modify the

TABLE 2. Substitution of Bromide 4 with Various Nucleophiles



4 **5a-h, 6** **7**

nucleophile	compd	yield[a] (%)	olefin **7**[b] (%)
H_2O	**6**	87	12
MeOH	**5a**	79	5
EtOH	**5b**	76	6
4-$(MeO_2C)C_6H_4CH_2OH$	**5c**	76[b]	6
$CH_2{=}CHCH_2OH$	**5d**	73	5
$HOCH_2CH_2OH$	**5e**	89	2
CF_3CH_2OH [c]	**5f**	46	12
H_2O_2 (UHP)[d]	**5g**	83	0
$HO_2C(CH_2)_2CO_2H$[d,e]	**5h**	68	5

[a] Isolated yield. [b] NMR ratio of the crude. [c] Used as solvent, and with addition of Et_3N. [d] In a mixture 1:1 CH_2Cl_2/HFIP. [e] In the presence of 5 equiv of Et_3N.

course and the rate of solvolysis reactions when HFIP is used as solvent.[14] They have also been exploited in various other reactions, such as hydrogen peroxide activation, oxirane ring opening,[15] Nazarov cyclization,[16] or Michael reaction.[17]

Experiments under various conditions using different ratios of HFIP/MeOH or HFIP/CH_2Cl_2/MeOH allowed selecting the following best conditions for the reaction of **4** with MeOH: 10 equiv of MeOH and 5 equiv of HFIP in a dichloromethane solution at room temperature. Under these conditions, the reaction was complete in less than 5 h, instead of more than 1 day without HFIP. Moreover, the reaction was still chemoselective, with only 5% of glycal **7** formed, and stereoselective: the α stereoisomer was not detected in NMR. However, an excess of nucleophile was still required for the reaction. When the nucleophile was used in stoichiometric amount, degradation of the starting material was observed.

These conditions have been applied to other nucleophiles in order to obtain artemisinin derivatives with better solubility in either oil or water. Treatment of **4** with various alcohols in the presence of HFIP gave **5a**−**e** in good isolated yields ranging from 73 to 89% (Table 2). They were accompanied with a small amount of glycal **7** (2−6%). When products could not be separated from glycal **7** by chromatography because of their close polarity (**5a** and **5b**), **7** was oxidized into a polar diol with RuO_4 generated in situ from $RuCl_3$ and $NaIO_4$. After substitution of **4** with methyl 4-(hydroxymethyl)benzoate, a fast purification on silica gel allowed the recycling of the excess of reagent (90% were recovered). The product **5c** was then hydrolyzed under basic conditions to afford the corresponding carboxylic acid **5c′** in 53% yield from **4**.

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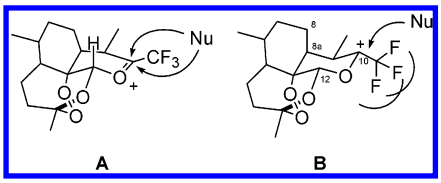
SCHEME 4. Conformation of Artemisinin Rings in Different Activation Methods



In all cases, the reaction was stereoselective. Configuration of C-10 was assigned by NMR for compound **5a** (β OMe). Interestingly, substitution of **4** with water also occurred and gave back the β isomer of the ketal **6** in 87% yield, thus confirming the stereochemical assignments.[18] All other products were hence supposed to be the β isomers.

The reaction was also performed with the poor nucleophile alcohol 2,2,2-trifluoroethanol (TFE), but the substitution did not occur and degradation of starting bromide was observed. When TFE was used as solvent, **5f** (β isomer as determined by NOE experiments) was obtained in a poor yield (23%), which could be improved to 46% when Et_3N was added to the mixture. Substitution of **4** with hydrogen peroxide was also investigated in view to obtain compound with two peroxide functionalities. To avoid the competition between water and hydrogen peroxide substitution, H_2O_2 was delivered through urea hydrogen peroxide (UHP) which is a safe source of anhydrous hydrogen peroxide.[19] UHP is commercially available, stable, and can be handled without the need of specific precautions. Moreover, we have recently reported that this stable complex could easily release hydrogen peroxide when HFIP was used as solvent or as cosolvent.[20] Reaction of **4** with UHP in a 1:1 v/v mixture of CH_2Cl_2/HFIP was thus investigated, and it was revealed that substitution quickly occurred in less than 2.5 h and was selective. No traces of glycal **7** were detected. The resulting adduct was stable enough to be purified on silica gel. **5g** (β) was isolated in 83% yield.

Carboxylic acids were also engaged in substitution reaction of **4**. Reaction with carboxylate generated in situ from succinic acid and triethylamine (5 equiv), in the presence of HFIP as a cosolvent (1:1 v/v CH_2Cl_2/HFIP), provided **5h** which could be isolated after purification in 68% yield (Table 2).

The high selectivity of the substitution reaction with retention of configuration is very striking. The comparison of the reaction performed with MeOH/CH_2Cl_2 and MeOH/CH_2Cl_2/HFIP clearly shows that HFIP favors the cleavage of the C−Br bond. However, in this case the hypothesis of an SNi-type reaction is ruled out since the activator, HFIP, and the nucleophile are two different molecules. Moreover, if a planar oxonium salt (intermediate **A**, Scheme 4) was formed, a mixture of α and β isomers would be expected as obtained in reactions in methanol in the presence of silver salts. The predominant β attack could be ascribed to a substitution reaction involving an intermediate pyramidal alkoxy carbenium ion (**B,** Scheme 4). The α approach of the nucleophile is electronically and sterically disfavored, because of the presence of the bulky trifluoromethyl moiety (usually compared to an isopropyl group) and the oxygen lone pairs, while the β face is only hindered by the C8a−C8 axial bond. It is assumed that due to the non polar medium (CH_2Cl_2 is the major solvent) and to a different counterion, the alkoxy carbenium ion, after ionization of the C−Br bond, does not undergo the isomerization of **B** into the planar oxonium salt **A**.

Conclusion

This study allowed us to highlight the importance of two cosolvents in the substitution reactions of α trifluoromethyl bromide **4** derived from artemisinin. The first one, dichloromethane, allowed a decrease in the formation of the elimination product **7** (less than 10%) and thus an increase in the chemoselectivity of the reaction. The second, the hexafluoro-2-propanol, could both activate the reaction and allow a complete diastereoselectivity (up to 95%).

The substitution of bromide **4** with various nucleophiles under mild conditions gave an access to new C-10 fluorinated analogues of artemisinin such as trifluoromethyl analogues of artemether, arteether, and artesunic acid.

This new process constitutes an easy substitution reaction on a center bearing a trifluoromethyl group which could be extended to other substrates. Biological properties against malaria of these new compounds are under investigation.

Experimental Section

Typical Procedure for the Substitution of 4. Bromide **4** (353 mg, 0.85 mmol) was dissolved in CH_2Cl_2 (5 mL). The solution was stirred under Ar stream at room temperature, and ethylene glycol (475 μL, 8.5 mmol) and HFIP (440 μL, 4.2 mmol) were successively added. After being stirred for 5 h, the mixture was diluted with ethyl acetate, washed with a saturated aqueous solution of $NaHCO_3$, and dried over $MgSO_4$. Evaporation of the solvent afforded the crude product which was purified on a SiO_2 column (7:3 petroleum ether/AcOEt). Compound **5e** was obtained (299 mg, 89%) as white crystals: mp 92°C (petroleum ether/AcOEt).

Acknowledgment. We thank MENRT for financial support (PAL+ program) and a fellowship (G.M.) and CNRS (GDR Etude des protozoaires pathogènes: cibles thérapeutiques et vaccinales) for financial support. We are grateful to Dr. V. D. Hoang, P. G. Dien, and N. V. Hung at the Institute of Natural Products (CNST, Hanoi, Vietnam) for supplying of artemisinin and Central glass for supplying HFIP. We thank Sophie Mairesse-Lebrun at the Microanalysis service of BIOCIS for elementary analysis.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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