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Short Note

(1*R*/*S*,7a*S*/*R*)-1-Benzyl-1-[2,8-bis(trifluoromethyl)quinolin-4-yl]-hexahydro-oxazolo[3,4-*a*]pyridin-3-one

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Abstract: An unexpected diastereoselective C-alkylation of a mefloquine derivative in up to 57% yield was the result of an attempted Williamson etherification of Boc-mefloquine. The domino reaction involved oxazolidinone ring closure, deprotonation, and stereoselective carbon–carbon bond formation. The structure was confirmed with 2D NMR experiments.

Keywords: mefloquine; oxazolidinone; C-alkylation; diastereoselectivity

1. Introduction

Mefloquine is a medicine used to prevent and treat malaria. Several derivatives of this 1,2-aminoalcohol have been obtained and assessed in a medicinal chemistry context [1]. Our studies on catalytic properties led us to explore its chemical space [2,3]. We attempted to obtain 11-*O*-benzyl mefloquine via Williamson etherification. However, the compound could not be obtained efficiently. To ensure preference for O-alkylation over N-alkylation, a series of protecting groups was introduced. Their subsequent reactivity led to the formation of the unique C-alkylated compound **1**.

2. Results and Discussion

2.1. Synthesis

Carbamate-protected mefloquine [4] was applied in the etherification reaction with benzyl bromide. The reaction was inefficient without a base, even at elevated temperatures. Conducting a similar reaction at room temperature but in the presence of KOH as a base resulted in an unexpected C-benzylated product **1** in a low yield (28%). Upon changing the base to sodium hydride, the same product **1** was obtained in moderate yield (57%, Figure 1, Table 1). The reaction with methyl iodide instead of benzyl bromide did not progress to incorporate a methyl group and instead delivered the known oxazolidinone **2** [5]. Oxazolidinone **2** was also formed in attempted Mitsunobu reactions of Boc-mefloquine.

2.2. Structure Elucidation

For the isolated product **1**, the 2D spectra (COSY, ^{1}H,^{13}C-HSQC, and HMBC experiments) clearly indicated three essential molecule fragments: a 2-substituted piperidine, a 4-substituted quinoline fragment, and a benzyl group (Figure 2). All of these fragments are merged by a single low-field quaternary carbon center (85 ppm), as indicated by the HMBC interaction between the quinoline 3C−H and benzyl CH_2 groups. The correlation between piperidine 12C−H is not visible due to the expected low $^{2}J_{C-H}$ coupling. However, $^{3}J_{C-H}$ couplings between this group and the benzyl CH_2 group as well as the quinoline C4 atom confirmed connectivity. The lack of a *tert*-butyl group but retained carbamate carbon atom (154 ppm) and an apparent elimination of tert-butanol, as evidenced in the mass spectrometry with no additional sp^2 atoms, indicated a ring closure reaction. These features can only be accommodated in the proposed structure: the incorporation of 11C−O and 13N

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in an oxazolinone ring and the formation of a bond between 11C and the pendant benzyl carbon atom. Further examination of through-space interactions in the NOESY experiment reveals a strong interaction between the benzyl CH_2 and piperidine 12C−H atoms but no other part of the piperidine ring. The magnitude of this interaction (10% relative to the intensity of the interaction within the benzyl CH_2 group) allows us to roughly estimate the interatomic distance at around 2.6 Å. This indicates that the benzyl group and the piperidine 12C−H atom are on the same face of the oxazolidinone ring, which is supported by a molecular model, where the relevant distances are 2.49 and 2.59 Å (Figure 2).

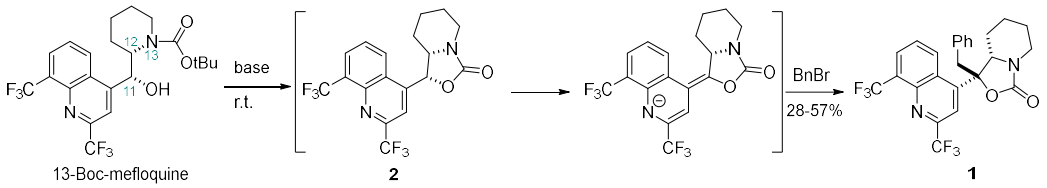
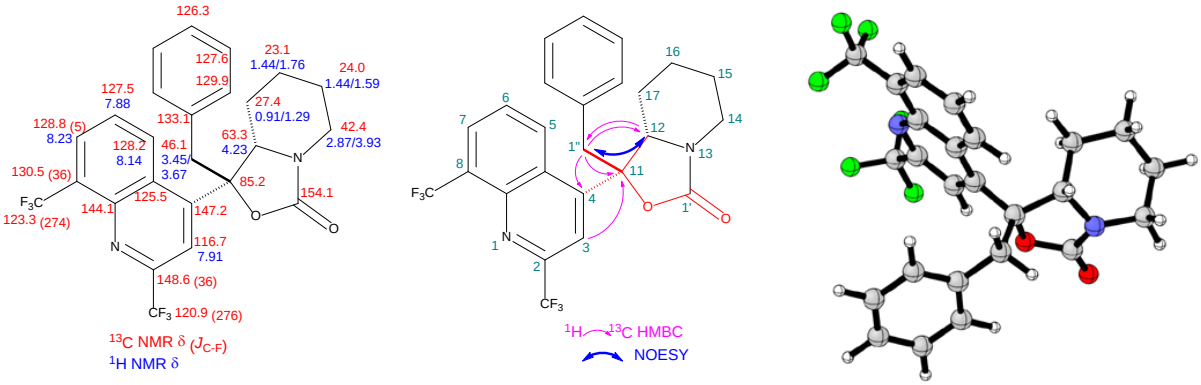


Figure 1. Reaction of Boc-mefloquine with alkyl halides under basic conditions.

Table 1. Reactions of Boc-mefloquine.

Entry	Alkyl Halide	Base/Reaction Conditions	Product, Yield %
1	BnBr	None, r.t to 70 °C	0
2	BnBr	KOH, r.t.	**1**, 28
3	BnBr	NaH, r.t.	**1**, 57
4	MeI	NaH, r.t.	**2**, 17
5	MeI	KOH, r.t,	**2**, 42
6	none [1]	PPh_3, DIAD, HN_3, r.t.	**2**, 68

[1] Attempted synthesis of 11-azidomefloquine derivative.



(**a**) (**b**) (**c**)

Figure 2. (**a**) NMR spectral assignment; (**b**) non-trivial ^{1}H,^{13}C HMBC and NOESY correlations and atom numbering scheme of parent mefloquine; (**c**) DFT/B3LYP/6-31G(d,p) molecular model for compound **1**.

3. Discussion

The formation of product 1 must involve intramolecular substitution of tert-butoxide with the 11-alkoxide group to form oxazolidinone **2**. This cyclization, though common [6], is not consistently observed as a side reaction of Boc-1,2-aminoalcohols under basic conditions [7–10]. The subsequent step likely involves the deprotonation of oxazolidinone due to the strongly electron-withdrawing effect of trifluoromethyl-substituted quinoline [2]. Deprotonation of lepidine under relatively mild conditions is long known to initiate addition to electophiles [11]. Finally, the reaction with an electrophile such as benzyl bromide gives the C-alkylated product. Alkylation of oxazolidinone at this position has only been reported once, involving coupling with transition metal organometallics [12]. On the other

hand, coupling reactions of lithiated 4-picoline are better known and proceed more efficiently at a more substituted center with benzyl bromide than with methyl iodide [13]. Since compound **1** is obtained as a single diastereomer, the approach of the benzyl group must have occurred stereoselectively. To explain the diastereoselectivity, we devised a molecular model of the intermediate anion at the DFT/B3LYP/6-31G(d,p) level. Assuming a 12*S* configuration, the model demonstrates a nearly flat alignment of the piperidine and oxazolidinone rings, with the remaining part of the piperidine ring protruding from the *Re*-face. Thus, the preferrable sterically unobstructed trajectory from the *Si*-face would deliver the observed *erythro* product **1** (Figure 3).

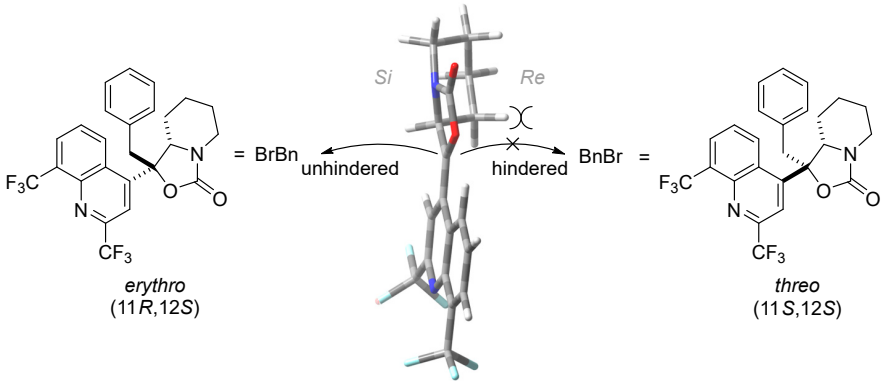


Figure 3. Proposed rationale for the observed (*erythro*) selectivity, including the DFT/B3LYP/6-31G(d,p) computed model of the intermediate anion.

4. Materials and Methods

NMR spectra were collected on a 600 MHz Bruker Avance II instrument. Spectra were internally referenced to tetramethylsilane (TMS $\delta_C = 0$ and $\delta_H = 0$). Electrospray (ESI) MS and HRMS spectra were recorded on a Waters LCT Premier XE apparatus with a TOF analyzer. Flash chromatography was performed on standard silica gel 230–400 mesh (Merck, Darmstad, Germany). Automated flash-chromatography system CombiFlash NextGen 300 (ISCO Teledyne, Lincoln NE, USA) was used in some isolations.

Boc-Mefloquine was prepared according to a published protocol [4], first described in reference [14]. All other reagents and solvents were purchased from commercial suppliers and used as received.

*4.1. (1R/S,7aS/R)-1-Benzyl-1-[2,8-bis(trifluoromethyl)quinolin-4-yl]-hexahydro-oxazolo[3,4-a]pyridin-3-one (**1**)*

(*rac*)-*erythro*-13-*tert*-Butoxycarbonyl-mefloquine [14] (103 mg, 0.215 mmol) was dissolved in freshly distilled THF (1.5 mL), and the solution was cooled to 0 °C. Next, NaH (13 mg, 60% dispersion in paraffin liquid, 0.323 mmol, 1.5 equiv) and benzyl bromide (64 µL, 92 mg, 0.538 mmol, 2.5 equiv) were added under an argon atmosphere in a sequence. The mixture was stirred at rt for 18 h, diluted with DCM (15 mL), and washed with NH_4Cl-saturated solution (2 × 5 mL) and brine (5 mL). Then, the organic phase was dried over $MgSO_4$ and purified using column chromatography on silica gel (100% EtOAc), giving the product (60.7 mg) as an off-white solid (57%).

m.p. = 186−188 °C. ^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ = 8.24 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.91 (s, 1H), 7.88 (t, J = 7.9 Hz, 1H), 7.07–7.16 (m, 3H), 6.79–6.84 (m, 2H), 4.23 (dd, J = 12.1 Hz, 3.1 Hz, 1H), 3.89–3.96 (m, 1H), 3.67 (d, J = 14.2 Hz, 1H), 3.45 (d, J = 14.2 Hz, 1H), 2.83–2.90 (m, 1H), 1.72–1.79 (m, 1H), 1.56–1.61 (m, 1H), 1.37–1.50 (m, 2H), 1.26–1.31 (m, 1H), 0.87–0.95 (m, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, TMS) δ = 154.1, 148.6 (q, J = 35.9 Hz), 147.2, 144.1, 133.1, 130.5 (q, J = 35.9 Hz), 129.9, 128.8 (q, J = 4.7 Hz), 128.2, 127.57, 127.54, 126.3, 125.5, 123.3 (q, J = 273.7 Hz), 120.9 (q, J = 275.8 Hz), 116.7, 85.2, 63.3, 46.1, 42.4, 27.4, 24.0, 23.1 ppm. HRMS (ESI-TOF) $[C_{25}H_{20}F_6N_2O_2+H]^+$ calcd.: 495.1502, found: 495.1482.

*4.2. (1R/S,7aS/R)-1-[2,8-Bis(trifluoromethyl)quinolin-4-yl]-hexahydro-oxazolo[3,4-a]pyridin-3-one (**2**) [6]*

Method A: (*rac*)-*erythro*-13-Benzyloxycarbonylmefloquine [15,16] (108 mg, 0.218 mmol) was dissolved in freshly distilled THF (2 mL). Next, iodomethane (36 µL, 82.1 mg, 0.578 mmol, 2.65 equiv) and KOH were added (27.5 mg, 0.491 mmol, 2.25 equiv). After two hours, the substrate was consumed, and the solvent was evaporated. The residue was diluted with DCM (15 mL) and washed with water (3 × 5 mL) and brine (5 mL). Then the organic phase was dried over $MgSO_4$ and purified using column chromatography on silica gel (EtOAc/hexane, 3:2), giving product **2** (36.7 mg) as an off-white solid (42%).

Method B: (*rac*)-*erythro*-13-*tert*-Butoxycarbonylmefloquine [4] (125 mg, 0.262 mmol) was dissolved in freshly distilled THF (1.7 mL). A solution of hydrazoic acid in benzene (1.6 M, 0.25 mL, 0.40 mmol, 1.53 equiv) was added, and the mixture was cooled to 0 °C. In another flask, triphenylphosphine (60.4 mg, 0.230 mmol, 0.88 equiv) was dissolved in freshly distilled THF (0.8 mL), and the solution was cooled to 0 °C. Then, diisopropyl azadicarboxylate (DIAD, 45 µL, 46.4 mg, 0.230 mmol, 0.88 equiv) was added dropwise and stirred for 10 min until a precipitate was formed. The suspension was added to the previously prepared solution of the substrate and stirred for 3 days at room temperature. The mixture was concentrated and purified using column chromatography on silica gel (EtOAc/hexane, 3:2), giving product **2** (63.5 mg) as an off-white solid (68%).

^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ = 8.24 (d, J = 7.2 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 5.83 (d, J = 5.6 Hz, 1H), 3.96–4.01 (m, 1H), 3.51–3.56 (m, 1H), 2.86 (td, J = 13.0 Hz, 3.4 Hz, 1H), 2.15–2.20 (m, 1H), 2.01–2.07 (m, 1H), 1.72–1.79 (m, 2H), 1.52–1.60 (m, 1H), 1.37–1.47 (m, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 155.6, 148.8 (q, J = 35.7 Hz), 146.6, 143.9, 130.2 (q, J = 30.7 Hz), 129.2 (q, J = 5.4 Hz), 128.0, 126.3, 125.9, 123.3 (q, J = 273.9 Hz), 120.9 (q, J = 275.7 Hz), 118.2, 76.8, 61.7, 41.9, 30.8, 24.1, 22.7 ppm. HRMS (ESI-TOF) $[C_{18}H_{14}F_6N_2O_2+H]^+$ calcd.: 405.1032, found: 405.1031.

5. Conclusions

A unique diastereoselective C-alkylation at the mildly acidic position of the oxazolidinone occurred. The findings expand the understanding of mefloquine reactivity, highlight the role of electron-deficient quinoline residues, and open avenues for further exploration of diastereoselective C-benzylations in similar contexts.

Supplementary Materials: The following supporting information can be downloaded: plots of NMR spectra and experimental details for compound **2**.

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