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FULL-LENGTH PAPER

Dinitroaliphatics as linkers: application in the synthesis of novel artemisinin carba-dimer

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Abstract The versatility of nitroaliphatics is demonstrated by using it in the syntheses of artemisinin derived dimers. A few novel artemisinin derived dimer and monomer have been synthesized using nitroalkane as linker.

Keywords Artemisinin · *Artemisia annua* · Nitroaliphatics · Artemisinin derivatives · Artemisinin dimer

Introduction

In recent years aliphatic nitro compounds are emerging as versatile building blocks and intermediates in organic synthesis [1–4]. This is primarily due to the fact that they are easily available, they undergo a variety of carbon–carbon bond forming processes in presence of a suitable base and the nitro group can be converted into many other functional groups. The mechanism and factors influencing the carbon–carbon bond forming reactions of nitroalkanes have been studied extensively by several groups [5–8].

Artemisinin, the active ingredient of *Artemisia annua* [9] and their derivatives are currently recommended as frontline antimalarials for regions experiencing *Plasmodium falciparum* resistance to traditional antimalarial drugs. In addition to their well known antimalarial activity, artemisinin derivatives and more importantly artemisinin derived dimers have recently been known to posses potency to kill various cancerous cell [10]. Therefore, search for new routes towards synthesis of artemisinin dimers has been a growing area for the last few years.

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In continuation of our interest in both nitroaliphatics and artemisinin chemistry, we focussed our attention on using nitroaliphatics in the synthesis of artemisinin dimers (Scheme 1).

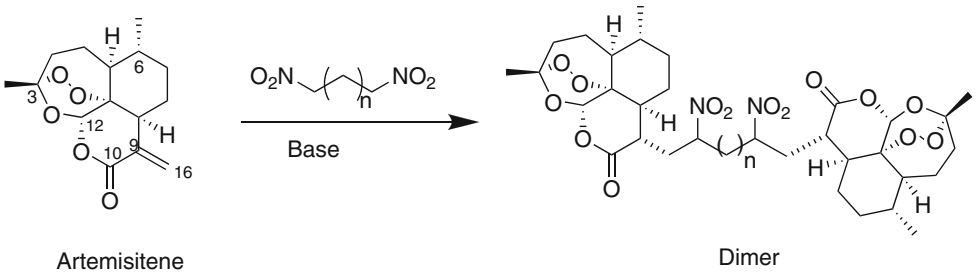
Most of the dimers synthesized so far are dimer at C-10 and are derived from ethers of dihydroartemisinin. It has been noted that the C-10 non-acetal type artemisinin derivatives are not only more hydrolytically stable, they also have longer half-life and potentially lower toxicity [11,12]. Consequently, several groups have developed synthetic and semi-synthetic approaches to C-10 carba analogues [13]. Michael addition reaction at C-16 of naturally occurring artemisitene is another familiar pathway for synthesizing artemisinin dimers. So far, only a few reports of Michael addition at C-16 are available in literature. Ekthawatchai et al. [14] have reported synthesis of artemisinin dimers by carrying out Michael addition at C-16 of artemisitene with the help of bis-Grignard reagent and dithiols. Herein, we report synthesis of artemisinin carbadimers at C-16 by using dinitroaliphatics as linkers. Investigations in our laboratory over the past few years have demonstrated the utility of nitroaliphatics [15–21] as readily available, cheap building block in the synthesis of pharmacologically important natural products. In this context and as a part of our ongoing programme on value addition to phytochemicals [22], we have introduced a novel synthetic route towards generating artemisinin dimers using dinitroalkane as linker.

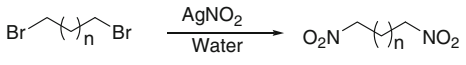
Experimental section

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 NMR machine. IR spectra were recorded

Scheme 1 General scheme for the synthesis of C-16 artemisinin carbadimers





1a-b **2a-b**

1a, n=4 **2a**, n=4 (51%)

1b, n=6 **2b**, n=6 (60%)

Scheme 2 Synthesis of aliphatic dinitro compounds from aliphatic dihalides

on a Perkin-Elmer 1640 FT-IR spectrometer. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. Mass spectra were recorded on a Bruker Daltonic Data Analysis 2.0 spectrometer. Melting points are uncorrected and recorded on Buchi B-540 melting point apparatus. Column chromatography was performed with Merck silica gel (100–200 mesh) and preparative TLC was carried out on plates prepared with Merck Silica gel G. Moisture sensitive reactions were conducted under a dry nitrogen atmosphere. THF was distilled from benzophenone ketyl prior to use. All solvents were distilled at their boiling point and other commercially available reagents were used as received, unless otherwise stated.

General procedure for synthesis of **2a**, **2b** and their characterization data

Silver nitrite (2.7 mmol) was added to a stirred solution of dibromoalkane (1.22 mmol) in water and the reaction flask was wrapped with carbon paper to keep away from light. After being stirred for overnight, the reaction mixture was filtered and the filtrate was extracted with diethyl ether, dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product. Purification was done by column chromatography (5% EtOAc in hexane) to afford **2a** (51%) and **2b** (60%) as a colorless liquids.

Compound **2a**

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (t, 4H, CH_2NO_2, J = 6 Hz), 2.08–1.99 (m, 4H, $CH_2CH_2NO_2$), 1.52–1.25 (m, 4H, aliphatic CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.7, 27.3, 26; IR ($CHCl_3$) ν : 2932, 1551 cm^{-1}; MS (ESI) m/z 176.1 (M^+). Analysis calculated for $C_6H_{12}N_2O_4$ C 40.92, H 6.87, N 15.90. Found C 40.87, H 6.94, N 16.15.

Compound **2b**

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (t, 4H, J = 6 Hz, CH_2NO_2), 2.05–1.96 (m, 4H, $CH_2CH_2NO_2$), 1.37–1.36 (m, 8H, aliphatic CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.6, 28.4, 27.2, 26.0; IR ($CHCl_3$) ν : 2930, 1551 cm^{-1}; MS (ESI) m/z 204.1 (M^+). Analysis calculated for $C_8H_{16}N_2O_4$ C 47.05, H 7.90, N 13.72. Found C 47.13, H 7.55, N 13.85.

General procedure for synthesis of **3a**, **4**, and **3b** and their characterization data

To a stirred solution of the dinitroalkane (0.46 mmol) in dry THF, artemisitene (1.15 mmol) and KF–basic alumina (0.46 g per mmol) was added. The reaction mixture was stirred at 50 °C overnight, then filtered and the filtrate was evaporated to give the crude product. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford **3a** (40%), **4** (30%), and **3b** (46%).

Compound **3a**

White solid. mp = 195.4 °C. $[\alpha]_D^{20}$ (c3.8, $CHCl_3$) = +53.8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (s,1H, H-12), 5.92 (s,1H, H-12$^/$), 5.08–5.03 (m, 1H, $CHNO_2$), 4.69–4.62 (m, 1H, $CHNO_2$), 2.73 (m, 2H, H-9, H-9$^/$), 2.44–2.38 (m,8H, aliphatic CH_2), 2.1–1.6 (m, 26H, arte CH_2), 1.46 (s, 6H, H-3, H-3$^/$), 1.0 (d, 6H, J = 6 Hz, H-6, H-6$^/$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.3, 105.5, 105.4, 94.0, 93.1, 87.6, 87.5, 85.6, 80.2, 80.1, 50.2, 45.8, 45.7, 41.9, 41.5, 41.4, 39.6, 37.9, 37.4, 35.8, 34.0, 33.8 33.7, 30.9, 30.7, 25.4, 25.3, 24.9, 24.6, 19.8. IR ($CHCl_3$) ν : 1735, 1547 cm^{-1}. MS (ESI) m/z 759 (M^++Na). Analysis calculated for $C_{36}H_{52}N_2O_{14}$ C 58.68, H 7.11, N 3.80. Found C 58.76, H 7.23, N 3.85.

Compound **4**

Colourless liquid. $[\alpha]_D^{20}$ (c1.0, $CHCl_3$) = + 29.8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 1H, H-12), 5.12–5.04 (m, 1H, $CHNO_2$), 4.40 (t, 2H, J = 6.9 Hz, CH_2NO_2), 2.44–2.39 (m, 1H, H-9), 2.09–2.05 (m, 8H, aliphatic CH_2), 1.60 (m, 13H, arte CH_2), 1.46 (s, 3H, H-3), 1.0 (d, 3H, J = 6 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 105.5, 94.0, 87.5, 80.1, 75.3, 66.8, 50.2, 45.9, 41.5, 39.7, 37.5, 35.8, 34.0, 33.7, 30.7, 26.9, 25.6, 25.4, 24.9, 19.8. IR ($CHCl_3$) ν : 1735, 1549 cm^{-1}. MS (ESI) m/z 456.2 (M^+). Analysis calculated for $C_{21}H_{32}N_2O_9$ C 55.25, H 7.07, N 6.14. Found C 55.34, H 7.03, N 6.25.

Compound **3b**

Yellowish gum. $[\alpha]_D^{20}$ (c0.7, $CHCl_3$) = +19.9. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.9 (s, 2H, H-12, H-12$^/$), 5.08–5.0 (m, 2H, $CHNO_2$), 2.48 (m, 2H, H-9, H-9$^/$), 2.42–2.05 (m, 12H, aliphatic CH_2), 1.73– 1.29 (m, 26H, arte CH_2), 1.45 (s, 6H, H-3, H-3$^/$), 1.0–0.98 (d, 6H, J = 6 Hz, H-6, H-6$^/$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171, 105.4, 94.0, 87.8, 80.1, 50.2, 45.8, 41.6, 39.7, 37.5, 37.1, 35.8, 34.4, 33.7, 32.7, 31.9, 30.7, 30.0, 29.7, 29.4, 28.6, 25.4, 25.3, 24.6, 22.7, 19.8, 14.1; IR ($CHCl_3$) ν : 1736, 1546 cm^{-1}; MS (ESI) m/z 787.3 (M^+ + Na). Analysis calculated for $C_{38}H_{56}N_2O_{14}$ C 59.67, H 7.38, N 3.66. Found C 59.53, H 7.25, N 3.71.

Synthesis of **5** and its characterization data

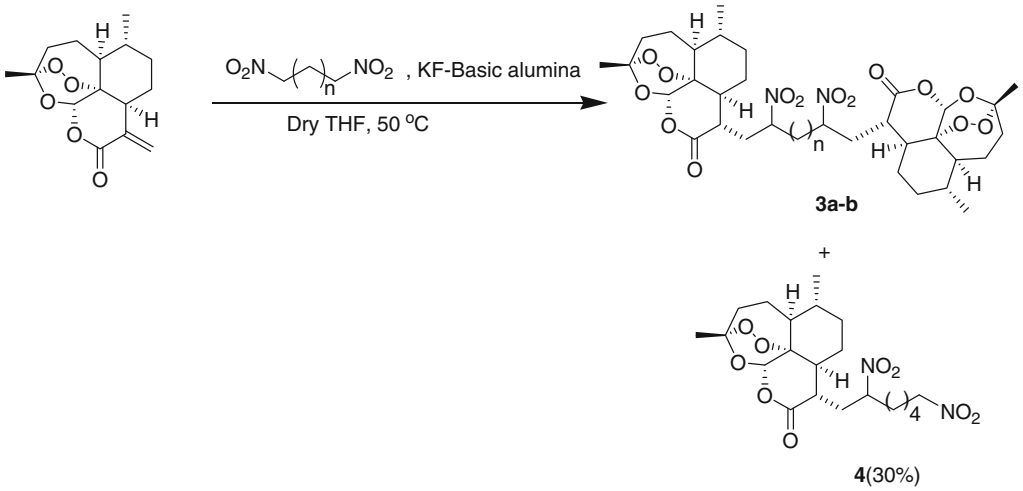
To a stirred solution of acrolein (0.5 g, 8.9 mmol) at 0 °C in nitromethane, Amberlyst A-21 (4 g) was added and stirred for 3 h. The reaction mixture was filtered and solvent was removed under reduced pressure. The crude product was purified by column chromatography (10% EtOAc in hexane) to give **5** as a gum (0.7 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67–4.35 (m, 5H, CH_2NO_2, *CH*OH), 2.30–2.15 (m, 2H, *C H*$_2$CH$_2$NO$_2$), 2.13 (br s, 1H, OH), 1.65–1.57 (m, 2H, *C H*$_2$CHOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.9, 75.4, 68.3, 30.2, 25.2; IR ($CHCl_3$) ν : 3429, 2931, 1549 cm^{-1}; MS (ESI) m/z 178 (M^+). Analysis calculated for $C_5H_{10}N_2O_5$ C 33.71, H 5.66, N 15.73. Found C 33.57, H 5.64, N 15.93.

Synthesis of **6** and its characterization data

To a stirred solution of **5** (0.2 g, 1.12 mmol) in dichloromethane Montmorrilonite KSF (0.028 g) was added. After subsequent dropwise addition of dihydropyran (0.115 g, 1.3 mmol), the mixture was stirred at room temperature for 2 h. The reaction mass was filtered, concentrated, and purified by column chromatography to give **6** as a gum (0.18 g, 61.3%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87–4.68 (m, 1H, OCHO), 4.49–4.36 (m, 4H, CH_2NO_2), 3.8 (m, 2H, HCOTHP, HCO), 3.5 (m, 1H, HCO), 2.2–2.13 (m, 4H, aliphatic CH_2), 1.77–1.3 (m, 6H, CH_2 THP). ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.0, 79.0, 74.9, 73.8, 64.0, 30.9, 29.6, 25.0, 22.9, 20.2; IR ($CHCl_3$) ν : 2945, 1553 cm^{-1}; MS (ESI) m/z 262 (M^+). Analysis calculated for $C_{10}H_{18}N_2O_6$C 45.8, H 6.92, N 10.68. Found C 45.74, H 6.85, N 10.71.

Synthesis of **7** and **8** and characterization data

To a stirred solution of artemisitene (0.32 g, 1.15 mmol) in dry THF, **6** (0.15 g, 0.57 mmol) and KF–basic alumina (0.262 g)



3a, n=4 (40%)

3b, n=6 (46%)

Scheme 3 Synthesis of C-16 artemisinin carbadimers

were added and the reaction mixture was stirred at 50 °C overnight, filtered, and the filtrate was concentrated. The resulting crude product was purified by column chromatography (20% EtOAc in hexane) to afford **7** (0.187 g, 40% yield) and **8** (0.129, 42% yield) as gummy liquids.

Compound **7**

$[\alpha]_D^{20}$ (*c*0.4, $CHCl_3$) = +15.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (s,1H, H-12), 5.23 (s, 1H, H-12′), 4.59–4.56 (m, 1H, $CHNO_2$), 4.36–4.25 (m, 3H, $CHNO_2$, OCHO, HCOTHP), 3.8 (m, 1H, HCO), 3.41 (m,1H, HCO), 2.31 (m, 2H, H-9, H-9′), 2.18–2.03 (m, 4H, aliphatic CH_2), 1.98–1.71 (m, 26H, CH_2 arte), 1.70–1.32 (m, 6H, CH_2 THP), 1.18 (s, 6H, H-3, H-3′), 0.93 (d, 3H, J = 6 Hz, H-6), 0.83 (d, 3H, J = 6 Hz, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.8, 105.4, 99.3, 99.2, 94.1, 94.0, 87.3, 87.1, 80.1, 80.0, 79.0, 78.9, 73.7, 73.3, 62.9, 50.2, 45.8, 41.5, 39.7, 39.6, 37.4, 35.8, 33.7, 30.9, 30.7, 30.6, 29.8, 29.6, 27.9, 25.4, 25.0, 24.6, 20.4, 19.7, 19.5; IR ($CHCl_3$) ν : 1737, 1550 cm^{-1}; MS (ESI) *m*/*z* 734.9 (M^+-THP). Analysis calculated for $C_{40}H_{58}N_2O_{16}$ C 58.38, H 7.10, N 3.40. Found C 58.42, H 7.19, N 3.39.

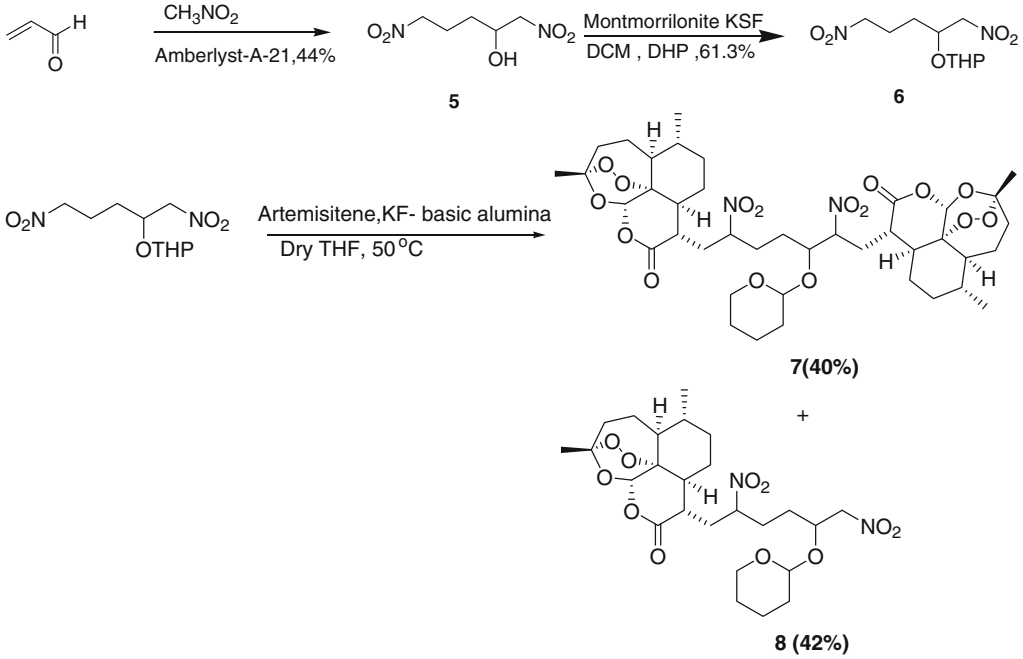
Compound **8**

$[\alpha]_D^{20}$ (*c*2.75, $CHCl_3$) = +31.2; ^{1}H NMR (300 MHz, $CDCl_3$) 5.92 (s,1H, H-12), 4.85–4.63 (m, 2H, CH_2NO_2), 4.42–4.35 (m, 3H, $CHNO_2$, OCHO, HCOTHP), 3.8 (m, 1H, HCO), 3.48 (m, 1H, HCO), 2.74 (m, 1H, H-9), 2.37–1.28 (m, 23H, CH_2 arte, CH_2 THP), 1.25 (s, 3H, H-3), 1.02 (d, 3H, J = 6 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) 170.2, 105.5, 99.3, 94.0, 93.8, 85.6, 80.1, 79.0, 73.5, 63.0, 50.3, 42.0, 41.4, 37.9, 35.8, 33.8, 31.9, 30.9, 29.3, 28.8, 25.3, 24.6, 22.6, 19.8, 14.1; IR ($CHCl_3$) ν : 1737, 1550 cm^{-1}. MS (ESI) *m*/*z* 542.2 (M^+). Analysis calculated for $C_{25}H_{38}N_2O_{11}$C 55.34, H 7.06, N 5.16. Found C 55.23, H 7.14, N 5.25.

Results and discussion

Our synthetic strategy commences with the synthesis of dinitroaliphatic compounds from commercially available aliphatic dihalides (Scheme 2) [23]. Treatment of the dibromoaliphatic compound **1a**–**b** with silver nitrite in water furnished the desired dinitroaliphatics **2a**–**b** in 50–60% isolated yield after 2 days.

Presence of α, β-unsaturated lactone moiety in artemisitene, which co-occurs with artemisinin in *Artemisia annua* makes it an obvious candidate for Michael addition reaction. We made several failed attempts with bases like Amberlyst A-21, DBU, triethyl amine, sodium hydride, etc., to induce this Michael addition with dinitroaliphatics. However, to our delight, basic alumina supported potassium fluoride was able to trigger the reaction. Adsorbing KF on alumina enhances the basic property of the catalyst and thus enables it for promoting Michael addition between nitroparaffins and reactive Michael acceptors [24]. The dinitro aliphatic compounds **2a**–**b** in presence of KF– Al_2O_3 undergoes Michael addition reaction with artemisitene at slightly elevated temperature (50°C) to generate artemisinin dimers **3a**–**b** (Scheme 3).



Scheme 4 Synthesis of C-16 artemisinin carbadimer using protected dinitro alcohol as linker

In the case of 1,6-dinitrohexane we were able to isolate one dinitro artemisinin derivative **4** along with dimer **3a**. The α stereochemistry at C-9 of the compounds **3a–b** and **4** was attributed to the fact that the multiplet of C-9 α oriented proton of artemisinin at δ 3.46 was seen shifting further upfield beyond δ 3.0 in the NMR spectra of these compounds. This is in consonance with documented NMR data of artemisinin molecule and many of its analogues, and therefore, we assigned β stereochemistry to the C-9 proton [14].

With an objective to introduce alchohol functionality in the dinitroaliphatic linker we employed a different strategy starting from acrolein. Treatment of acrolein with Amberlyst A-21 in nitromethane resulted in the formation of the dinitroaliphatic compound **5**. Nitromethane, in presence of the base underwent tandem Michael and Henry reaction to furnish compound **5**. Surprisingly, the dinitro compound **5** having the alchohol functionality did not give the Michael adduct with artemisitene even after stirring for several days. However, the THP protected dinitrocompound smoothly underwent Michael addition to artemisitene to furnish compound **7** and **8** (Scheme 4). Probably the competitive oxy-Michael addition could be avoided by protecting the alcohol group with THP. However, no definite conclusion can be made at this stage. Further, it is also known that 2-nitroalcohols are prone to undergo retro-Henry cleavage under variety of conditions [25,26].

The α stereochemistry at C-9 of compounds **7** and **8** was assigned on similar grounds as the previous ones. Extensive biological study of these artemisinin analogues and the dimers are currently underway and will be reported elsewhere in due course of time.

Conclusion

In conclusion, we have introduced an efficient process for synthesizing artemisinin dimers using nitroaliphatics as cheap and readily available linkers. The noteworthy feature of these dimers is the linker with two nitro functionalities. These nitro groups offer further access for making libraries of new derivatives of these artemisinin derived dimers for pharmacological evaluation.

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