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# A Simple and Convenient Method for Synthesis of Artemisinin Dimer through Aliphatic Nitro Compounds

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A simple way of synthesis of artemisinin dimer using nitro aliphatic compounds is reported. Herein, few artemisinin monomers and dimers have been synthesized with the help of linker nitroalkanes using iron catalyst supported on polymer (Fe/SBA-15). The synthesized artemisinin shows good anticancer and antimalarial activities.

**Keywords: Substituted aliphatic compounds, Polymer (Fe/SBA-15), Artemisinin dimer, Biological activities.**

## INTRODUCTION

In the modern methods of organic synthesis, it is found that nitro compounds are useful intermediates and building blocks [1-4]. Such nitro compounds are obtained easily can be conveniently used for the formation of carbon-carbon bond in basic medium and the nitro group can be converted to many desired functional groups. Such convertibility of nitro alkanes to various carbon-carbon bond formations and the criteria′s for such reactions have been explored by several researchers [5-8].

*Artemisia annua* [9] has active compound artemisinin and is very useful antimalarials drug in the case where *Plasmodium falciparum* is resistant to normal drugs for malaria. Besides antimalarial activity, artemisinin derivatives and derived dimers of artemisinin have been found to be significant anticancer drugs [10]. These reasons have made the quest for the exploration of newer synthetic routes for artemisinin dimers inevitable. In this research, a concept of nitroaliphatics in the synthesis of artesiminin dimer has been explored.

The artesiminin dimers are synthesized till now from ethers of dihydroartemisinin and are dimer at C-10 position. It is found that the non-acetal artemisin derivatives at C-10 are not easily hydrolyzed, have least toxicity [11] and longer half life. Several researchers have explored several approaches for the synthesis of C-10 carba analogues [12]. Atremisinin dimers can be synthesized from naturally occurring artemisitene bond formation at C-16 through Michael addition. Till date Michael addition at C-16 is less explored as far as literature is concerned. This C-16 position of artemisitene has been utilized for Michael addition by Ekthawatchai *et al*. [13] using dithiols and Grignard reagent for the synthesis of artemisinin dimer. Earlier researchers [14-21] have reported the importance of nitroaliphatics in the natural product synthesis. In this communication, dinitroailphatic compounds as linker at C-16 for the synthesis of artemisinin carbadimers are reported.

## EXPERIMENTAL

**Polymer support synthesis:** The polymer support SBA-15 was synthesized as per the process reported by Zhao *et al*. [22].

**Synthesis of catalyst:** Iron catalyst supported on polymer *i.e*. Fe/SBA-15 was synthesized by mixing 30 mL of $H_2O$, 0.03 mmol of $FeCl_3$ (4.835 mg) and 0.5 g of SBA-15 at ambient temperature for 24 h. The centrifugation of the solution was done for 5 min (4000 rpm). The liquid was decanted and solid remain was dried for 24 h at 100 ºC.

**Typical procedure:** A dry round bottom was charged with 0.6 mmol of artemisitene, 0.5 mmol of dinitro aliphatic compounds, 2.0 mL $CDCl_3$ and Fe/SBA-15 as catalyst. The entire components were mixed together at 50 ºC continuously upto 24 h. When the reaction got over the mixture was brought to 20 ºC and solid catalyst then removed through filtration.

**Characterization:** IR spectra of the compounds covering the range of 4000-200 $cm^{-1}$, was done on Bomem MB-FTIR machine and $^1H$ NMR spectra done at 400 MHz, $^{13}C$ NMR at 100 MHz both on Bruker Advance spectrometer in the solvent $CDCl_3$ with TMS as standard.

**(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6-dimethyl-9-[2',7'-dinitro octyl-8'-(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-octahydro-3,6-dimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one)]-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (3a):** White powder, yield 48%, m.p. 194-196 ºC; Elemental analysis of $C_{36}H_{52}N_2O_{14}$ calcd. (found) %: C 58.68 (58.70), H 7.11 (7.18), N 3.80 (3.76). IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 2942 (C-H *str.*), 1735 (C=O *str.*), 1547 (N-O, *asym. str.*), 1372 (br, s, C-O), 1230 (C-O), 700 ($CH_2$ rocking). $^1H$ NMR (δ ppm): 0.97 (6H, d, 6 Hz), 1.46 (6H, s), 1.6-1.98 (28H, m), 2.38-2.44 (6H, m), 3.03 (2H, m), 4.62-4.69 (1H, m), 5.02-5.23 (1H, m), 6.02 (1H, s), 6.29 (1H, s); $^{13}C$ NMR (δ ppm): 171.1, 170.4, 105.5, 105.2, 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; MS (*m/z*) = 759 [$M^+$+Na].

**(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6-dimethyl-9-[2',7'-dinitro decyl-8'-(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-octahydro-3,6-dimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one)]-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (3b):** Yellow sticky liquid, yield 52%; Elemental analysis of $C_{38}H_{56}N_2O_{14}$ calcd. (found) %: C 59.67 (59.49), H 7.38 (7.31), N 3.66 (3.75). IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 2945 (C-H *str.*), 1736 (C=O *str.*), 1546 (N-O, *asym. str.*), 1372 (br, s), 1230 (C-O), 708 ($CH_2$ rocking); $^1H$ NMR (δ ppm): 1.01-1.10 (6H, d), 1.29-1.37 (2H, m), 1.99 (6H, s), 2.20-2.28 (2H, m), 2.66-2.86 (22H, m), 3.02-3.18 (6H, m), 3.39-3.42 (6H, m), 4.02 (2H, m), 5.00-5.08 (2H, m), 6.05 (2H, s); $^{13}C$ NMR (δ ppm): 171, 105.4, 94.1, 87.8, 80.0, 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; MS (*m/z*) = 764.3 ($M^+$).

**(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6-dimethyl-9(2',7'-dinitro heptyl)-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (4):** Colourless liquid, yield 40%; $[\alpha]_D^{20}$ ($CHCl_3$, *c* 1.0) = + 29.8; Elemental analysis of $C_{21}H_{32}N_2O_9$ calcd. (found) %: C 55.25 (55.19), H 7.07 (7.10), N 6.14 (6.18). IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 2946 (C-H *str.*), 1735 (C=O *str.*), 1549 (N-O, *asym. str.*), 1370 (C-O br, s), 1232 (w, C-O), 710 ($CH_2$ rocking); $^1H$ NMR (δ ppm): 0.88 (3H, d, 5.8 Hz), 1.50 (3H, s), 2.36-2.60 (22H, m), 3.05 (2H, t, 7.0 Hz), 5.09-5.18 (1H, m), 6.03 (1H, s); $^{13}C$ NMR (δ ppm): 171.2, 105.4, 94.0, 87.3, 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; MS (*m/z*) = 456.1 ($M^+$).

**1,5-Dinitro-pentan-2-ol (5):** Yellow sticky liquid, yield 49%; Elemental analysis for $C_5H_{10}N_2O_5$ calcd. (found) %: C 33.71 (33.78), H 5.66 (5.70), N 15.73 (15.72). IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 3431 (O-H *str.*), 2928 (C-H *str.*), 1552 (N-O, *asym. str.*); $^1H$ NMR (δ ppm): 4.41-4.72 (5H, m, CHOH, $NO_2CH_2$), 2.12-2.29 (2H, m, $CH_2CH_2$-OH), 2.18 (1H, s, O-H); $^{13}C$ NMR (δ ppm): 81.0, 75.3, 67.9, 30.2, 25.2; MS(*m/z*) = 178 ($M^+$).

**2-(4-Nitro-1-nitromethyl-butoxy)tetrahydropyran (6):** Yellow sticky liquid, yield 68%; Elemental analysis of $C_{10}H_{18}N_2O_6$ calcd. (found) %: C 45.79 (45.74), H 6.92 (6.88), N 10.68 (10.72). IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 2952 (C-H *str.*), 1552 (N-O, *asym. str.*), 1131(C-O *str.*), 1034 ($CH_2$ twist), 981 (C-C-C); $^1H$ NMR (δ ppm): 1.28-1.81 (6H, m, $CH_2$THP), 2.18-2.32 (4H, m, $CH_2$), 3.62 (1H, m, HCO), 3.91 (2H, m, HCO, HCOTHP), 4.40-4.56 (4H, m, $NO_2CH_2$), 4.71-4.90 (1H, m, OCHO); $^{13}C$ NMR (δ ppm): 100.0, 79.1, 74.9, 73.8, 64.0, 30.9, 29.6, 25.0, 22.9, 20.2; MS (*m/z*)= 262 ($M^+$).

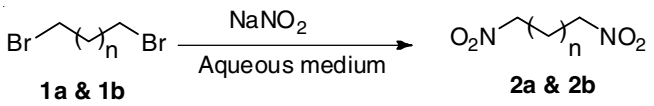
**(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6-diimethyl-9-[2',6'-dinitro-5-(2-tetrahydro-pyran)heptyl 7'-(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-octahydro-3,6-dimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one)]-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (7):** Pale yellow Sticky liquid, yield 51%; Elemental analysis of $C_{40}H_{58}N_2O_{16}$ calcd. (found) %: C 58.38 (58.31), H 7.10 (7.08), N 3.40 (3.45). IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 2942 (C-H *str.*), 1737 (C=O *str.*), 1550 (N-O, *asym. str.*), 1372 (br, s), 1230 (C-O), 700 ($CH_2$ rocking); $^1H$ NMR (δ ppm): 0.78 (3H, d, 6 Hz), 0.94 (3H, d, 6 Hz), 1.07 (6H, s), 1.98-2.18 ( 36H, m), 3.01 (2H, m), 2.28 (1H, m), 3.96 (1H, m), 4.30-4.36 (3H, m), 4.99-5.26 (1H, m), 6.03 (1H, s), 6.19 (1H, s); $^{13}C$ NMR (δ ppm): 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; MS (*m/z*) = 734.8 ($M^+$-THP).

**(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6-dimethyl-9-[2',6'-dinitro-5-(2-tetrahydro-pyran)hexyl]-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (8):** Light yellow sticky liquid, yield 55%; Elemental analysis for $C_{25}H_{38}N_2O_{11}$ calcd. (found) %: C 55.34 (55.29), H 7.06 (7.03), N 5.16 (5.19). IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 2942 (C-H *str.*), 1737 (C=O *str.*), 1550 (N-O, *asym. str.*), 1208 (C-O *str.*), 1034 ($CH_2$ twist); $^1H$ NMR (δ ppm): 1.02 (3H, d, 6 Hz), 1.19 (3H, s), 1.28-1.37 (23H, m), 2.79 (2H, m), 3.03 (1H, m), 3.80 (1H, m), 3.98-4.12 (2H, m), 5.05-5.23 (2H, m), 5.96 (1H, s); $^{13}C$ NMR (δ ppm): 170.4, 170.8, 104.5, 100.2, 99.1, 93.9, 87.3, 80.2, 79.0, 73.8, 73.1, 63.0, 50.1, 46.0, 41.6, 40.1, 39.6, 37.4, 36.0, 33.7, 31.0, 30.7, 30.5, 30.0, 29.6, 28.1, 25.4, 25.1, 24.8, 20.2, 19.8, 19.1; MS (*m/z*) = 541.9 ($M^+$).

## RESULTS AND DISCUSSION

In first step, open chain aliphatic dihalides was treated with sodium nitrite which led to the formation of open chain dinitro compounds (**Scheme-I**) [22]. Open chain dibromo-aliphatic compounds **1a** (n=4) and **1b** (n=6) were treated with sodium nitrite in aqueous medium yielded dinitrohexane **2a** (n=4) and **2b** (n=6), respectively in 60-70% yield after 36 h.

In next step, an increment of C-C bond at α,β-unsaturated lactone moiety through Michael addition in artemisitene was




**Scheme-I**

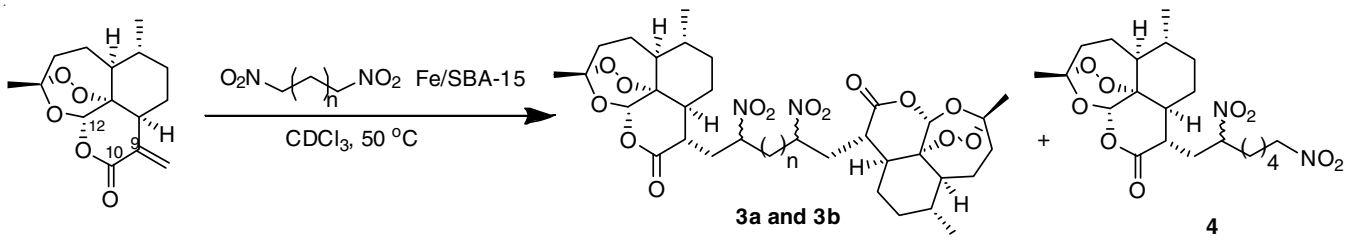
achieved in the presence of Lewis acid like $AlCl_3$, $FeCl_3$, *etc*. In present work, iron impregnated polymer was used as a catalysts, where artemisitene undergoes Michael addition reaction with open chain dinitro compounds whose terminal H was substituted with nitro group (**2a** and **2b)** in the presence of polymer based catalyst Fe/SBA-15 at 50 ºC to generate artemisinin dimers **3a (n = 4)** and **3b (n = 6)** as shown in **Scheme-II**.

Substituted artemisinin with dinitro group (**4)** and the dimer **3a** can be easily isolated in case of 1,6-dinitrohexane. Among the various Lewis acids like $AlCl_3$, $SiCl_4$, and the bases like sodium hydride, triethyl amine, DBU, *etc*. none was able to perform the Michael addition reaction on artemisitene with these nitroaliphatics. But SBA-15 supported $FeCl_3$ gave the reaction fast and with better yield. A stereochemistry at C-9 of artemisinin is assigned because, the peak for C-9 proton in artemisinin ($\delta$ = 3.46 ppm) was found to be shifting upfield with $\delta$ < 3.0 ppm in the NMR spectra of compounds **3a**, **3b** and **4**, which is verified with the documented $^1$H NMR data of artemisinin molecule along with its analogues and thus confirmed that a stereochemistry associated with C-9 proton.

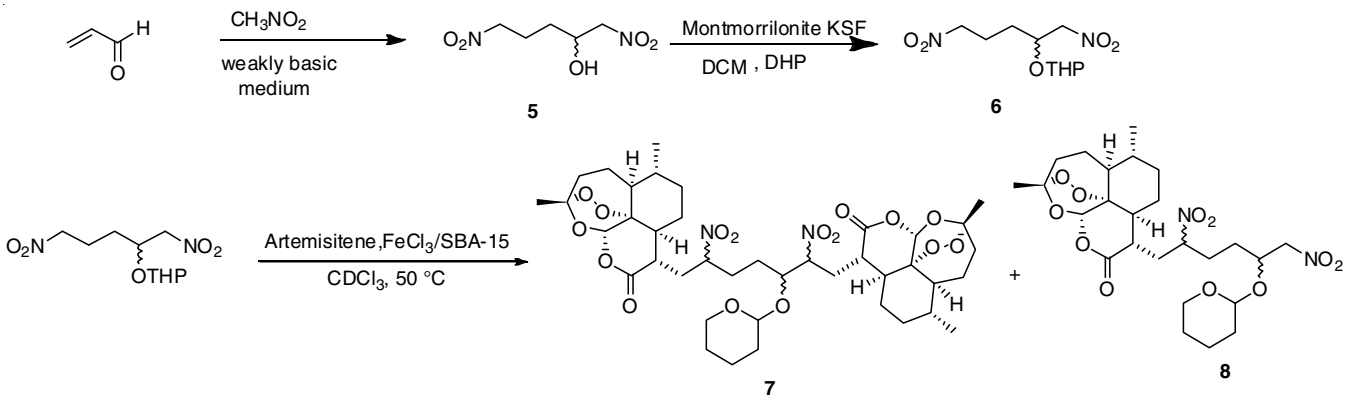
In order to find the effect of alcohol group in the dinitroaliphatic linker, reaction of acraldehyde with nitromethane in the presence of weak base yielded dinitroaliphatic compound **5**. Nitromethane in mild base basic conditions using Tandem Michael-Henry reaction to yield compound **6**. In present experiment, it was found that alcohol functionality in dinitro compound **5**, no Michael adduct was obtained with artemisitene. If the alcoholic group is 2-tetrahydropyranyl (THP) protected in dinitro compound then the Michael addition in artemisitene easily yielded derivatives **7** and **8** (**Scheme-III**).

On similar analogy as stated above, the C-9 position of dimer **7** was found to have a stereochemistry. The stereochemistry of nitro group of compounds **3a** and **3b** as well as of compound **8** was not studied.

**Anticancer and antimalarial activities:** The preliminary *in vitro* screening of these C-16 artemisinin dimers and derivatives were studied for their proliferation inhibitory effect against various cancer cell lines. These results are given in the Table-1. It was found that some of these dimers show notable anticancer activities. The antimalarial screening results of some




**Scheme-II**




**Scheme-III**

TABLE-1
INHIBITION OF PROLIFERATION OF DIFFERENT CANCER CELL LINES

| Compounds | Conc. (M) | Lung | CNS | Prostrate | Leukemia | Colon |
|---|---|---|---|---|---|---|
| | | A-549 | SF-295 | PC-3 | THP-1 | Colo-205 |
| **3a** | 10 | 2 | 3 | 0 | 7 | 18 |
| **7** | 10 | 14 | 24 | 9 | 40 | 25 |
| **4** | 10 | 0 | 0 | 6 | 10 | 9 |
| Adriamycin | 1 | NA | 70 | NA | NA | NA |
| Paclitaxel | 10 | 65 | NA | NA | NA | NA |
| Mitomycin | 10 | NA | NA | 68 | NA | |
| 5-Fluorouracil | 20 | | NA | NA | 70 | 55 |

NA = Compounds not exposed to cancer cell lines.

of these compounds against chloroquine sensitive *P. falciparum* strain were also found comparable to that of artemisinin (Table-2).

TABLE-2
ANTIMALARIAL ACTIVITY OF COMPOUNDS **3a**, **4**, **7** AND **8**

| Compounds | Dosage (μg/mL) | % Dead rings + schizonts (mean of three replicates) |
|---|---|---|
| **3a** | 0.1 | 22.4 |
| **4** | 0.1 | 10.1 |
| **7** | 0.1 | 40.0 |
| **8** | 0.1 | 12.0 |
| Artemisinin | 0.1 | 58.2 |

## Conclusion

A novel simple and greener synthetic method for synthesizing artemisinin dimers by employing nitroaliphatics as linkers containing two nitro groups is successfully accomplished. The process may be further employed for making artemisinin derivatives.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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