

**A FACILE SYNTHESIS OF NEW PROSTAGLANDIN
ANALOGUES BY UTILIZING THE CHARACTERISTICS OF
THE 1,2,4-TRIAZOLE MOIETY**

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Abstract- Concise syntheses of some new prostaglandin analogues bearing the 1,5-disubstituted 1,2,4-triazole moiety were achieved by utilizing the characteristics of N2-substituted 3-nitro-1,2,4-triazole and/or N1-substituted 1,2,4-triazole derivatives.

We have recently provided a useful information on the development of new hypoxic cell radiosensitizers having the 3-nitro-1,2,4-triazole (3-NTR) moiety in the radiotherapy.^{1,2} Namely, N1-substituted 3-NTR derivatives (1) proved to be more promising radiosensitizers to hypoxic cancer cells *in vivo* than the corresponding N2-substituted ones (3). In the course of this study, we have recognized that N2-substituted 3-NTR (3) and N1-substituted 1,2,4-triazole (1,2,4-TR) derivatives (6) are synthetically available as the following synthons. The former (3) can be utilized as the cationic synthons (2) *via* addition of a suitable nucleophile (Nu^{\ominus}) with releasing NO_2^- to give compounds (4) [Eq. (1)].² On the other hand, the latter (6) can be readily employed as the anionic synthons (5) by treatment with some base.^{2,3} The resultant anion (5) should react with a suitable electrophile (E^{\oplus}) to afford compounds (7) [Eq. (2)]. Previously, the prostaglandin analogues bearing the 1,2-disubstituted imidazole moiety were disclosed by Matthias and Hans.⁴ Amino and his colleagues reported platelet aggregation inhibitory activity of the prostaglandin analogues bearing the 1,5-disubstituted imidazole moiety.⁵ These led us to investigate a synthesis of new prostaglandin analogues bearing the 1,5-disubstituted 1,2,4-TR moiety as shown in Figure 1.

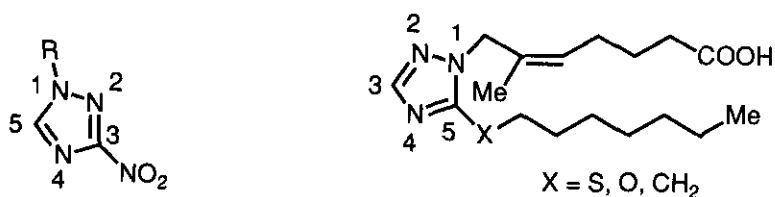
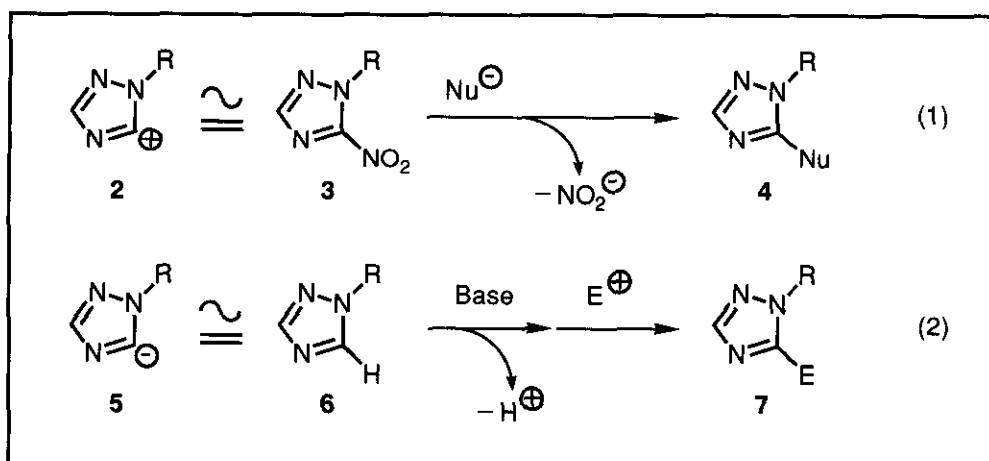
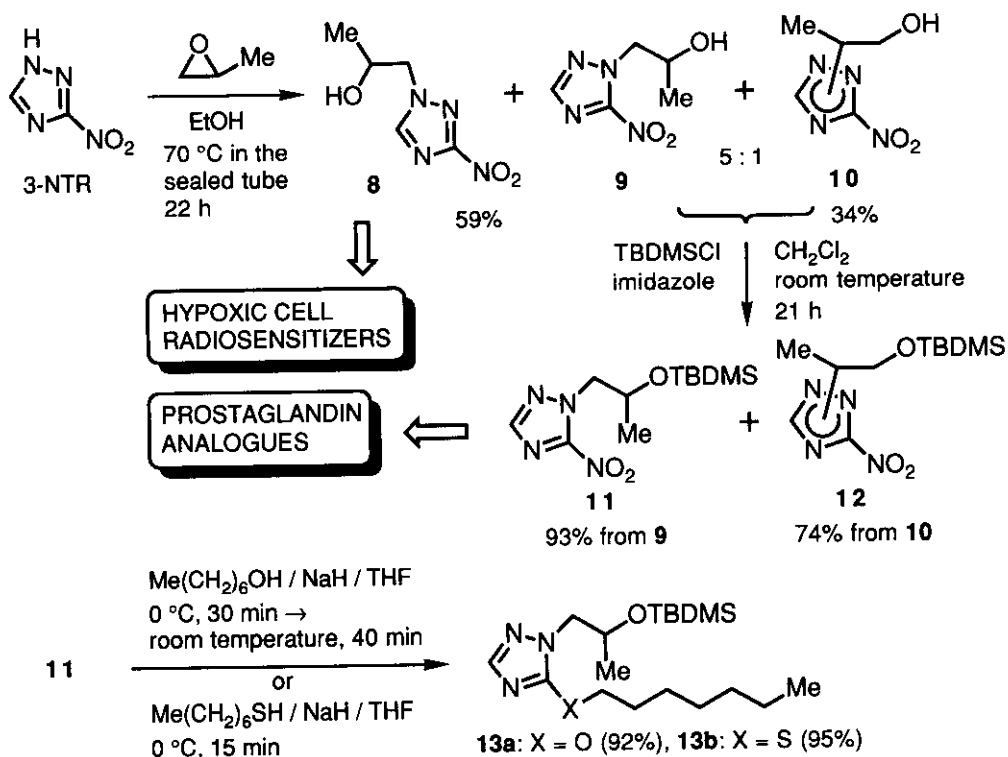


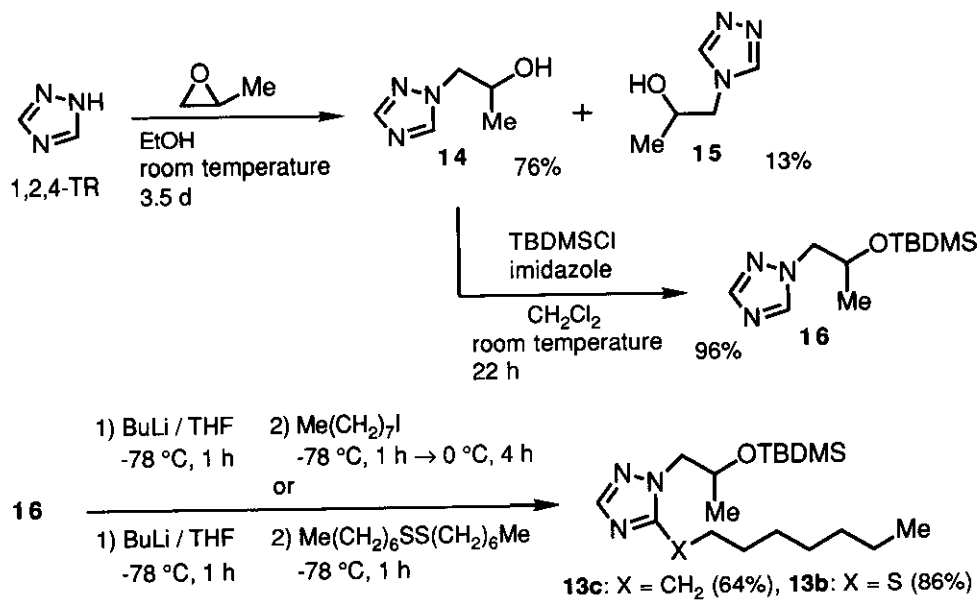
Figure 1. Prostaglandin analogues bearing the 1,5-disubstituted 1,2,4-TR moiety



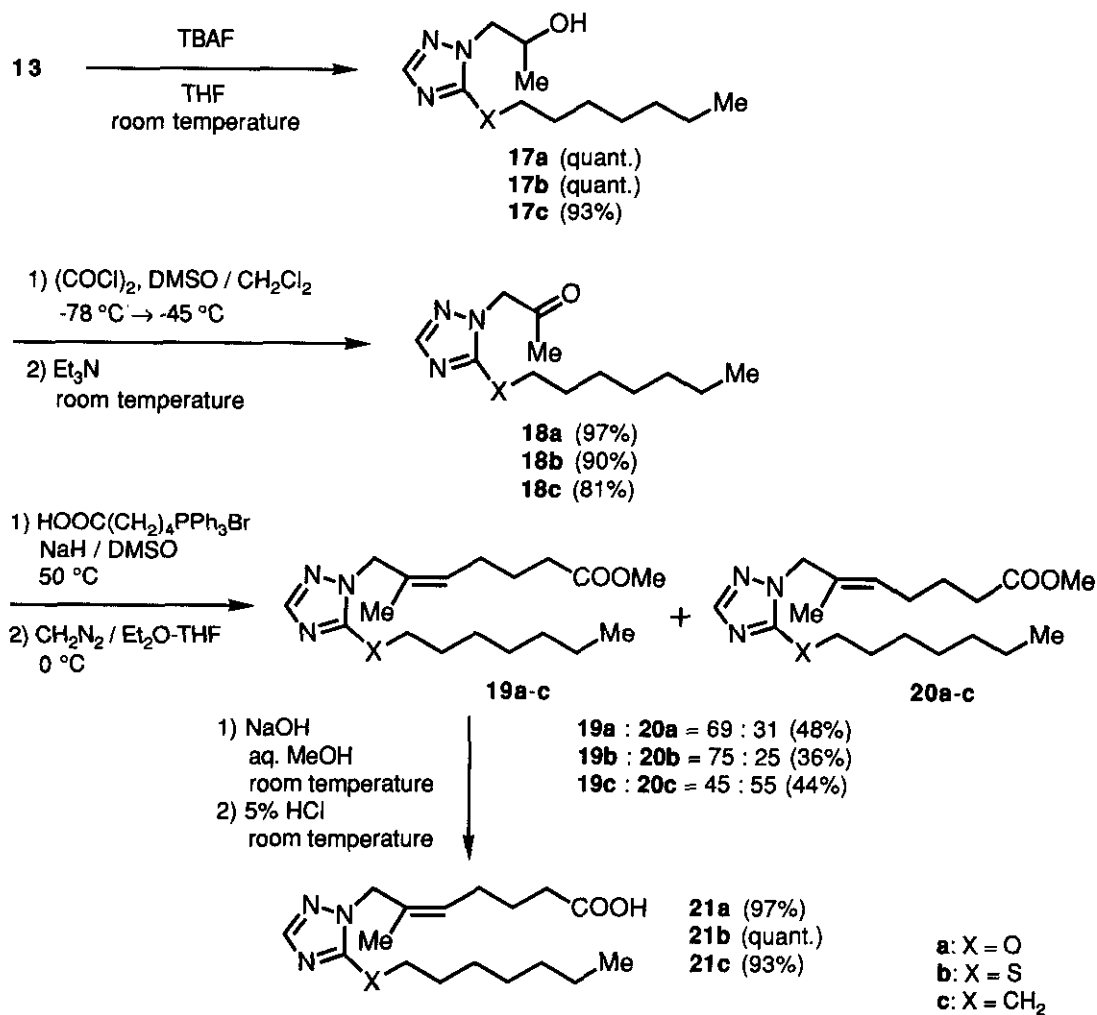
First, a synthetic procedure illustrated in Scheme 1 was examined adopting the methodology Eq. (1). Thus, a mixture of 3-NTR and large excess propylene oxide was heated at 70 °C in the sealed tube to give alcohol (8) and an inseparable mixture of alcohols (9) and (10). The compound (8) was converted to the fluorinated derivatives which exhibited strong radiosensitizing effect on the hypoxic cancer cells *in vivo*.⁶ Treatment of the mixture of 9 and 10 with 1.2 mol equiv of *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of 2.4 mol equiv of imidazole in CH₂Cl₂ followed by chromatographic separation of the resultant two silyl ethers on a silica gel column gave the desired pure compound (11) in 93% yield and compound (12) in 74% yield, respectively (Scheme 1). The silyl ether (11) was successfully exploited for the synthesis of new prostaglandin analogues as follows. The compound (11) was treated with 1.5 mol equiv of sodium heptanoate or 1.5 mol equiv of sodium heptanethiolate in THF at 0 °C - room temperature to give each corresponding C5-heptyloxy (13a, colorless oil, 92% yield) or C5-heptylthio derivative (13b, colorless oil, 95% yield).



Scheme 1



Scheme 2



Scheme 3

Subsequently, we investigated another synthetic procedure shown in Scheme 2 according to the methodology Eq. (2). A treatment of 1,2,4-TR with large excess propylene oxide at room temperature furnished oily alcohols (**14**) and (**15**) in 76% and 13% yields, respectively. Conventional silylation of **14** with TBDMSCl (1.2 mol equiv) and imidazole (2.4 mol equiv) gave silyl ether (**16**, colorless oil, 96% yield), which was treated with 1.1 mol equiv of *n*-butyllithium (1.6 M soln of *n*-hexane) in anhydrous THF at -78°C for 1 h. The resultant 5-lithio-**16** was allowed to react with 1.1 mol equiv of *n*-heptyl iodide or 1.1 mol equiv of di-*n*-heptyl disulfide at $-78^\circ\text{C} - 0^\circ\text{C}$ to give the corresponding products (**13c**, colorless oil, 64% yield) and (**13b**, colorless oil, 86% yield), respectively. All physical and spectroscopic data of the compound (**13b**) obtained from **16** were

identical with those of the same compound from **11**. Thus, we demonstrated that the methodology Eq. (1) should be efficient for the preparation of **13a** and the methodology Eq. (2) for **13c**.

Desilylation of compounds (**13a-c**) with tetra-*n*-butylammonium fluoride (TBAF) in THF gave the corresponding alcohols (**17a-c**) which were submitted to the Swern oxidation⁷ to produce the desired ketones (**18a-c**) in excellent yields (81-97%), respectively. The Wittig reaction⁸ of compounds (**18a-c**) with the ylide prepared from 4 mol equiv of (4-carboxybutyl)triphenylphosphonium bromide and 8 mol equiv of dimethyl sodium in DMSO followed by methylation with diazomethane afforded a mixture of olefinic products (**19a-c** and **20a-c**)⁹ in 36-48% yields from **18a-c**. Compound (**19a**), obtained by chromatographic separation of the mixture of **19a** and **20a** on a silica gel column, was submitted to hydrolysis in aqueous MeOH solution containing NaOH at ambient temperature to give the desired carboxylic acid (**21a**)¹⁰ in 97% yield after acidification. Other desired carboxylic acids (**21b** and **21c**)¹⁰ were similarly obtained in quantitative and 93% yields from the corresponding pure compounds (**19b** and **19c**). Biological and pharmacological tests of new prostaglandin analogues (**21a-c**) are now undertaken.

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3. The possibility of regioselective anion formation of **6** under the basic conditions can be readily anticipated from the viewpoints of deuteration experiment of some N1-substituted 1,2,4-triazoles.²
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9. The geometry of **19a-c** was assigned to be Z-type by means of their ^1H - ^1H NOE (400 MHz, CDCl_3) experiments. Irradiation of the olefinic-H resonance signal leads to some clear enhancement of the signal due to allylic Me-protons, whereas any similar enhancement is not observed at all in the case of the corresponding E-isomer (**20a-c**).
10. Compound (**21a**): Colorless oil; ^1H nmr (400 MHz, CDCl_3) δ 0.89 (3 H, t, $J = 6.8$ Hz), 1.23-1.46 (8 H, m), 1.61 (3 H, d, $J = 1.0$ Hz), 1.70-1.83 (4 H, m), 2.23 (2 H, dt, $J = 7.3, 7.3$ Hz), 2.38 (2 H, t, $J = 7.3$ Hz), 4.40 (2 H, t, $J = 6.6$ Hz), 4.52 (2 H, s), 5.39 (1 H, br t), 7.53 (1 H, s), >9.0 (1 H, br s); ir (CHCl_3) 3600-2400, 1710, 1555, 1525, 1435, 1380, 1275, 1120 cm^{-1} ; HRms calcd for $\text{C}_{17}\text{H}_{29}\text{N}_3\text{O}_3$ MW 323.2209, found m/z 323.2211 (M^+).
- Compound (**21b**): Colorless oil; ^1H nmr (400 MHz, CDCl_3) δ 0.88 (3 H, t, $J = 6.8$ Hz), 1.20-1.36 (6 H, m), 1.36-1.47 (2 H, m), 1.57 (3 H, s), 1.67-1.82 (4 H, m), 2.27 (2 H, dt, $J = 7.8, 7.3$ Hz), 2.41 (2 H, t, $J = 7.3$ Hz), 3.21 (2 H, t, $J = 7.3$ Hz), 4.68 (2 H, s), 5.42 (1 H, br t), 7.87 (1 H, s), >9.0 (1 H, br s); ir (CHCl_3) 3600-2400, 1710, 1475, 1455, 1420, 1355, 1270 cm^{-1} ; HRms calcd for $\text{C}_{17}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$ MW 339.1980, found m/z 339.1985 (M^+).
- Compound (**21c**): Colorless oil; ^1H nmr (400 MHz, CDCl_3) δ 0.87 (3 H, t, $J = 6.8$ Hz), 1.19-1.41 (10 H, m), 1.54 (3 H, d, $J = 1.0$ Hz), 1.68-1.82 (4 H, m), 2.25 (2 H, dt, $J = 7.3, 7.3$ Hz), 2.40 (2 H, t, $J = 7.3$ Hz), 2.71 (2 H, t, $J = 7.8$ Hz), 4.72 (2 H, s), 5.44 (1 H, br t), 7.85 (1 H, s), 9.00 (1 H, br s); ir (CHCl_3) 3600-2400, 1710, 1490, 1455, 1400, 1280 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{31}\text{N}_3\text{O}_2$ MW 321.2415, found m/z 321.2412 (M^+).

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