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

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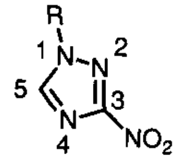
Abstract- Concise syntheses of some new prostaglandin analogues bearing the 1,5-disubstituted 1,2,4-triazole moiety were achieved by utilizing the characteristics of N2-substituted 3-nitro-1,2,4-triazole and/or N1-substituted 1,2,4-triazole derivatives.

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.



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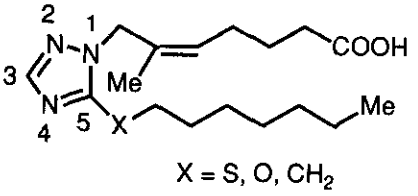
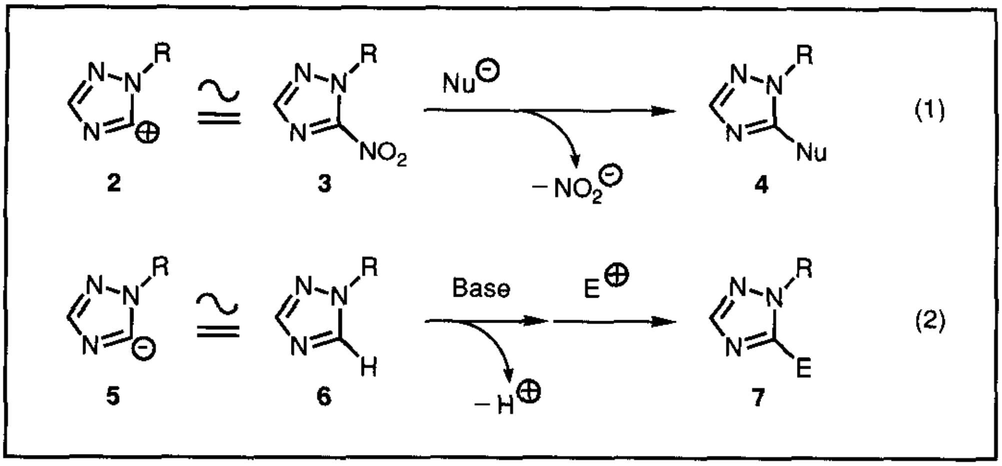
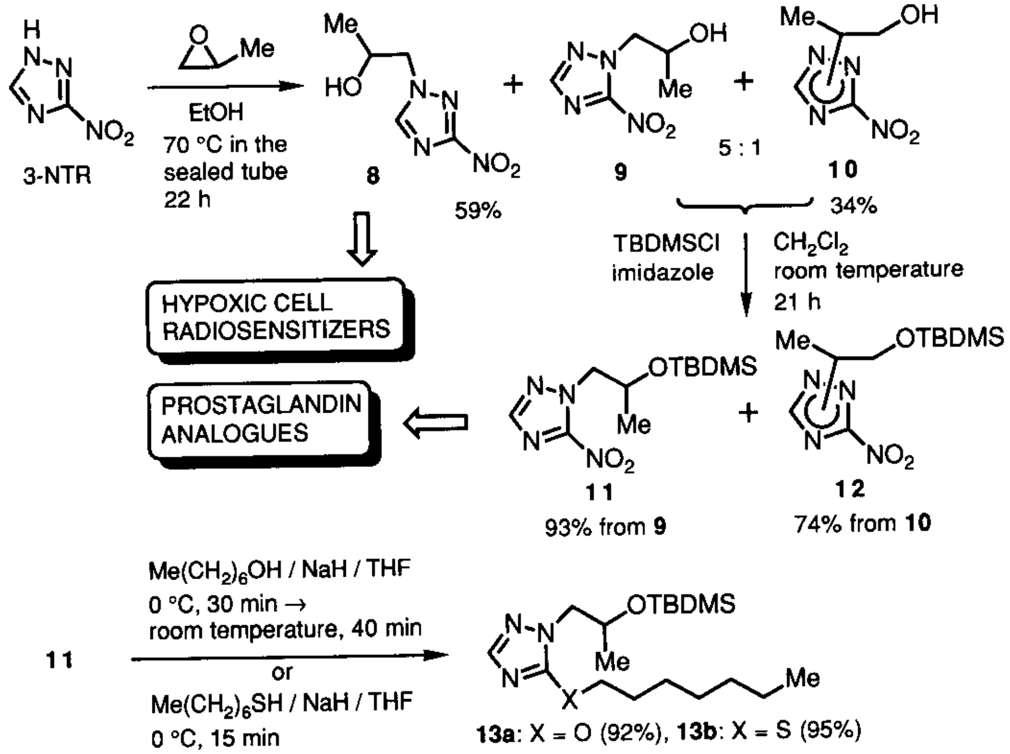


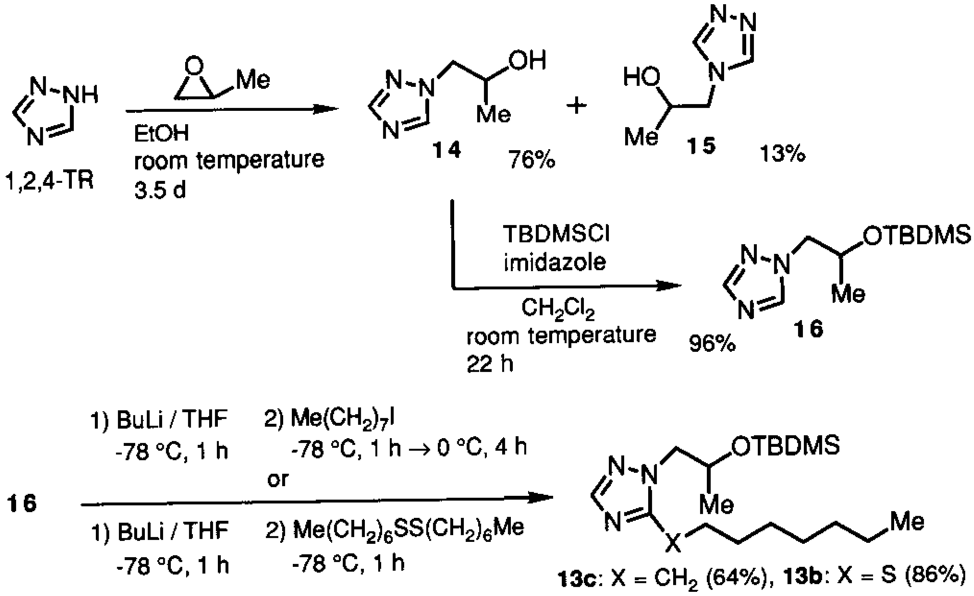
Figure 1. Prostaglandin analogues bearing the 1,5-disubstituted 1,2,4-TR moiety



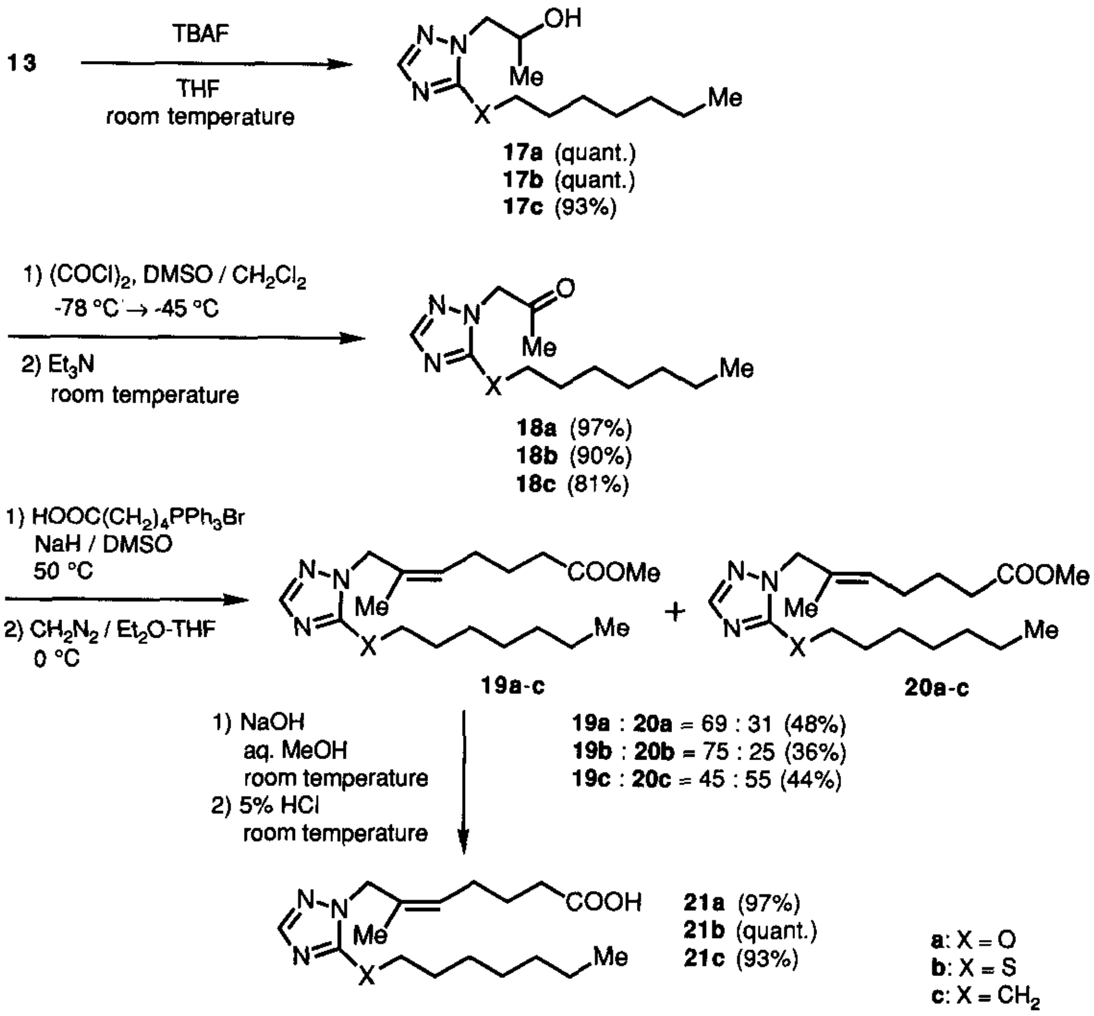
First, a synthetic procedure illustrated in Scheme 1 was examined adopting the methodology Eq. (1). Thus, a mixture of 3-NTR and large excess propylene oxide was heated at 70 °C in the sealed tube to give alcohol (**8**) and an inseparable mixture of alcohols (**9**) and (**10**). The compound (**8**) 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 CH_2Cl_2 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 heptanolate 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 °C - 0 °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 oxidation[7] to produce the desired ketones (**18a-c**) in excellent yields (81-97%), respectively. The Wittig reaction[8] of compounds (**18a-c**) with the ylide prepared from 4 mol equiv of (4-carboxybutyl)triphenylphosphonium bromide and 8 mol equiv of dimsyl 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.

REFERENCES AND NOTES

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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 deuteriation 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 $C_{17}H_{29}N_3O_3$ 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 $C_{17}H_{29}N_3O2S$ 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 $C_{18}H_{31}N_3O_2$ MW 321.2415, found *m/z* 321.2412 (M^+).

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