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FULL-LENGTH PAPER

A facile and one pot synthesis of 1,4-disubstituted-1H-1,2,3-triazoles from terminal alkynes and phenacyl azides prepared from styrenes by CAN oxidant and sodium azide

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Abstract A facile and green synthesis of 1,4-disubstituted-1H-1,2,3-triazoles is reported. The reaction of α-azido ketones and terminal alkynes in the presence of [$CuSO_4(H_2O)_5$/sodium ascorbate] in a mixture of H_2O/polyethylene glycol 400 as solvent afforded the corresponding 1,4-disubstituted triazoles at ambient temperature with short reaction times and at high yields. The corresponding α-azido ketones were directly prepared in situ from various substituted styrenes using the oxidant cerium ammonium nitrate and sodium azide in oxygen-saturated methanol.

Keywords Click chemistry · Styrene · Regioselective · Sodium azide · Triazole

Introduction

1,3-Dipolar cycloadditions between organic azides and a variety of terminal alkynes provide a fulfilling method for the direct synthesis of substituted triazoles [1–3]. However, because of the high activation energy involved, these cycloadditions are often very slow even at elevated temperatures (80–120 °C for 12–24 h) and produced mixtures of regioisomers until Sharpless introduced Cu(I) as catalyst for this cyclization [4]. Copper(I)-catalyzed azide-alkyne cycloaddition is best known as "click" reaction and has been termed the "cream of the crop" of click reactions. This cycloaddition has been applied in various ways in drug discovery, chemical biology and medicinal chemistry [4–8]. Heteroaromatic 1,2,3-triazoles have several biological traits giving them, for example, anti-allergic, anti-microbial, and anti-HIV properties [7–11]. Many 1,2,3-triazoles are also used as dyes, agrochemicals, optical brighteners, corrosion inhibitors, and photographic materials [12–16]. The synthesis of substituted 1,2,3-triazoles by the direct alkylation of 1,2,3-triazoles is generally not preferred because of poor regioselectivity. The click reaction between α-azido ketones and terminal alkynes in the presence of Cu(I) catalyst can be used in the synthesis of 1,4-disubstituted triazoles. Since α-azido ketones are often unstable to heat and light, their in situ preparation offers a great alternative to their use and handling. α-Azido ketones can be prepared in situ directly or indirectly. The indirect approach to α-azido ketones involves the reaction of α-halo ketones [17,18] and α-tosyloxy ketones (obtained from enolizable ketones using Koser's reagent, [hydroxy(tosyloxy)iodo]benzene) [19] with sodium azide. The direct preparation of α-azido ketones can be achieved by the reaction of various styrene derivatives with sodium azide and cerium ammonium nitrate (CAN) in oxygen-saturated methanol [20]. Only two methods have been reported for the preparation of 1,4-disubstituted 1,2,3-triazoles from α-azido ketones: multi-component reactions of α-tosyloxy ketones or α-halo ketones with sodium azide and terminal alkynes [21,22]. These two methods are based on the indirect preparation of α-azido ketones using enolizable ketones where the first step converts the enolizable ketones into α-tosyloxy or α-halo ketones.

Although it is reported that the multi-component reaction of α-halo ketones with sodium azide and terminal alkynes produce 1,4-disubstituted triazoles [22], this method is problematic because the reaction is often not complete and the α-halo ketones are highly eye-irritant [23,24]. A new and shorter procedure is hereby reported for the synthesis of 1,4-disubstituted 1,2,3-triazoles from the click reaction of terminal alkynes and directly prepared phenacyl azides.

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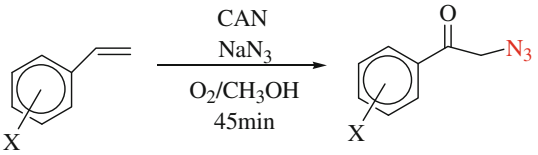

X= Br, Me,OMe, H,

Scheme 1 Direct preparation of phenacyl azides from styrenes

Experimental

All of the triazole derivatives were prepared by our procedure; their spectroscopic and physical data were compared with those of authentic samples. NMR spectra were recorded in DMSO-d6 or CDCl3 on a Bruker Advanced DPX 500 and 400 MHz instrument spectrometers using TMS as internal standard. IR spectra were recorded on a BOMEMMB-Series 1998 FT-IR spectrometer.

General procedure for the preparation of phenacyl azides

Oxygen was purged into a two-neck round-bottom flask containing a solution of methanol (10 mL), styrene (Table 1, 1a–12a, 1.3 mmol) and sodium azide (2 mmol). After 5 min, a methanol solution of CAN (1.26 g, 2.3 mmol of CAN dissolved in 15 mL of methanol) was added drop-wise to the flask at ice-cold temperature, while the reaction mixture was continuously being purged with oxygen. After 45 min, the reaction mixture was diluted with distilled water (50 mL), extracted with dichloromethane (2 × 25 mL), washed with saturated brine, and dried over anhydrous sodium sulfate. Evaporation of solvent afforded corresponding phenacyl azides which were purified by column chromatography (ethyl acetate/*n*-hexane, 5:1 as eluting solvent). Their structures were confirmed by infra-red (IR) and ^{1}H-NMR spectroscopy, (Scheme 1).

General procedure for the synthesis
of 1,4-disubstituted-1H-1,2,3-triazoles (1c–12c)

Sodium ascorbate (0.050 g) and $CuSO_4(H_2O)_5$ (0.050 g) were added to a mixture of phenacyl azide (1 mmol), alkeyne (Table 1, 1b–12b, 1.1 mmol) in H_2O/PEG (1:1) as solvent. The mixture was stirred for 15 min. The organic phase was extracted with ethyl acetate (20 mL), dried over sodium sulfate, and filtered. The resulting solid residue was washed with diethyl ether and dissolved in minimum amount of ethyl acetate. *N*-hexane was added drop-wise to give pure crystal, (Scheme 2) and (Table 1 1c–12c).

1c: IR (KBr): 1697 (CO) cm^{-1}. ^{1}H NMR(400 MHz, DMSO-d$_6$): 8.53(1 H, s), 8.12–8.10(2 H, d; $j = 8.15$), 7.89–7.87(2H, d; $j = 8.15$), 78–7.74 (1 H, m), 7.65– 7.61 (2 H, t; $j = 7.7$), 7.49–7.45 (2 H, t; $j = 7.7$ Hz), 7.37–7.33 (1 H, m), 6.27 (2 H, s). ^{13}C NMR(100 MHz, DMSO-d$_6$): δ = 195.0 (CO), 152.4, 139.0, 138.2, 134.5, 133.5, 133.2, 132.7, 132.5, 130.1, 126.4, 59.9.

2c: IR (KBr): 1709(CO) cm^{-1}. ^{1}H NMR(400 MHz, DMSO-d$_6$): 8.19(1H, s), 8.08–8.06 (2H, m), 7.88–7.86 (2H, m), 7.71–7.68 (1H, m), 7.61–7.57 (2H, m), 7.46–7.42 (m, 2H), 7.31–7.38 (m, 1H), 6.08(s, 2H). ^{13}C NMR(100 MHz, DMSO-d$_6$): δ = 192.1 (CO), 146.7, 133.58, 132.57, 131.1, 130.7, 129.4, 128.9, 128.3, 125.6, 123.5, 56.4.

3c: IR (KBr): 1697(CO) cm^{-1}. ^{1}H-NMR(500 MHz, DMSO-d$_6$): δ = 8.52 ppm (1H, s), 8.09–8.08 (2H, d; $j = 8.4$ Hz), 7.89–7.87 (2H, d; $j = 8.4$ Hz), 7.49–7.46 (2H, t; $j = 7.6$ Hz), 7.37–7.34 (1H, t; $j = 7$ Hz), 7.15–7.146 (2H, d; $j = 8.5$ Hz), 6.19 ppm (s; 2H), 3.9 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 194.95, 162.12, 141.9, 134.5, 131.66, 131.51, 129.82, 128.71, 126, 123.96, 115.13, 56.58, 56.49.

4c:IR (KBr): 1698(CO) cm^{-1}.^{1}H-NMR(500 MHz, DM SO-d$_6$): δ = 8.53 ppm (1H, s), 8.02–8 (2H, d; $j = 8.29$ Hz), 7.89–7.87 (2H, d; $j = 8.29$ Hz), 7.49–7.43 (4H, m), 7.37–7.34 (1H, t; $j = 7.5$ Hz), 6.22 (2H, s), 2.43 (3H, s). ^{13}C-NMR(125 MHz, DMSO-d$_6$): δ = 192.5, 147.14, 145.78, 139.4, 132.5, 131.6, 129.8, 129.2, 128.7, 126, 123.9, 56.7, 22.1.

5c: IR (KBr): 3420 and 3338(NH$_2$)cm^{-1}, 1701(CO) cm^{-1}. ^{1}H-NMR(500 MHz, DMSO-d$_6$): δ = 8.35 ppm (1H, s), 8.11–8.10 (2H, d; $j = 7.46$ Hz), 7.75–7.74 (1H, t; $j = 7$ Hz), 7.64–7.61 (2H, t; $j = 7.32$ Hz), 7.15 (1H, s), 7.10–7.08 (1H, t; $j = 7.6$ Hz), 6.98–6.97 (1H, d; $j = 7.5$ Hz), 6.56–6.55 (1H, d; $j = 7.5$ Hz), 6.22 (2H, s), 5.22 (2H, s). ^{13}C-NMR(125 MHz, DMSO-d$_6$): δ = 193.1(CO), 149.9, 147.85, 135.13, 135.02, 132.09, 130.27, 129.88, 129.8, 123.46, 114.48, 113.9, 111.38, 56.78.

7c: IR (KBr): 3424 and 3332(NH$_2$)cm^{-1}, 1695(CO) cm^{-1}.^{1}H-NMR(500 MHz, DMSO-d$_6$): δ = 8.34 ppm (s, 1H), 8.09–8.07 (d; $j = 8.9$, 2H), 7.15–7.13 (d; $j = 8.9$, 3H), 7.13(s, 1H), 7.10–7.07 (t; $j = 7.74$, 1H), 6.97–6.95 (1H, m), 6.55–6.53 (1H, m), 6.14 (2H, s), 5.18 (2H, s), 3.89 (3H, s). ^{13}C-NMR(125 MHz, DMSO-d$_6$): δ = 191.3, 164.8, 149.9, 147.78, 132.12, 131.48, 130.24, 127.89, 123.48, 115.12, 114.42, 113.85, 111.34, 56.57, 56.40.

8c: IR (KBr): 3420 and 3336(NH$_2$)cm^{-1}, 1690(CO) cm^{-1}. ^{1}H-NMR(500 MHz, DMSO-d$_6$): δ = 8.53 ppm (1H, s), 8.02–8 (2H, d; $j = 8.26$), 7.89–7.87 (2H, d; $j = 8.26$), 7.15 (1H, s), 7.10–7.08 (1H, t; $j = 7.6$ Hz), 6.98–6.97 (1H, d; $j = 7.5$ Hz), 6.56–6.55 (1H, d; $j = 7.5$ Hz), 6.12 (2H, s), 5.19(2H, s), 2.45 (3H, s).^{13}C-NMR(125 MHz, DMSO-d$_6$): δ = 191.5, 148.5, 147.1, 145.78, 132.5, 139.4, 131.6, 129.8, 129.2, 128.7, 126, 115.1, 114.2, 56.7, 22.1.

9c: 1696(CO) cm^{-1}.^{1}H-NMR(500 MHz, DMSO-d$_6$): δ = 8.64 ppm (2H, s), 8.43 (1H, s), 8.11–8.13 (4H, d; $j = 8.3$ Hz), 7.8 (1H, d; $j = 1.6$), 7.86 (1H, d; $j = 1.6$ Hz), 7.76 (2H, t; $j = 7.7$ Hz), 7.6 (4H, t; $j = 8.3$ Hz), 7.58 (1H, t; $j = 7.7$

Table 1 Synthesis of 1,4-disubstituted-1H-1,2,3-triazoles

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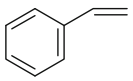
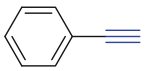
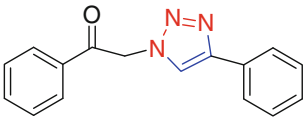
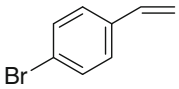
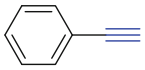
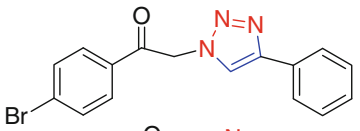
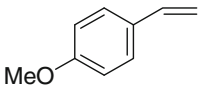
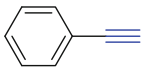
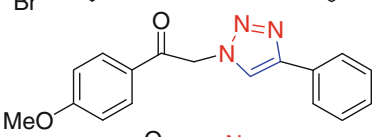
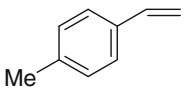
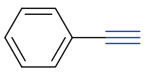
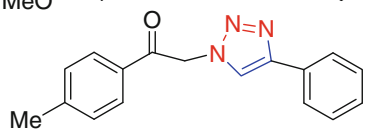
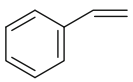
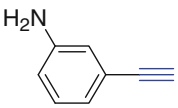
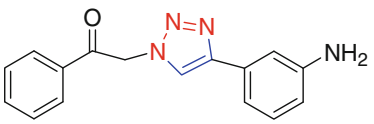
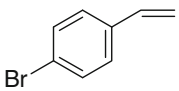
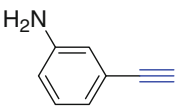
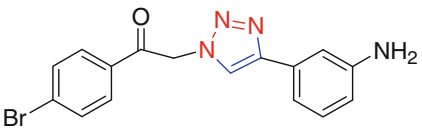
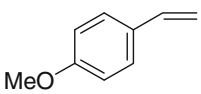
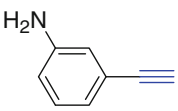
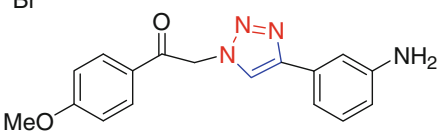
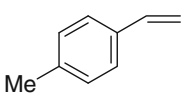
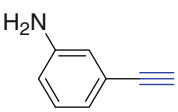
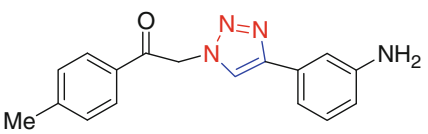
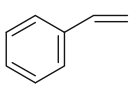
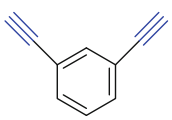
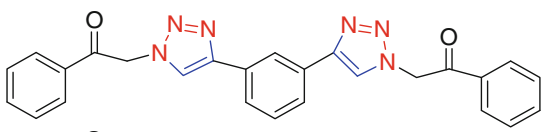
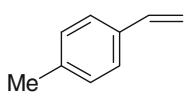
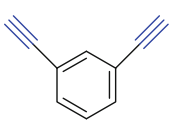
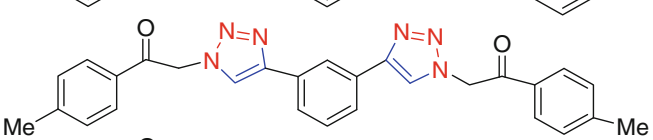
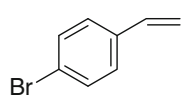
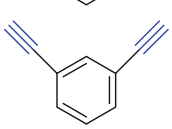
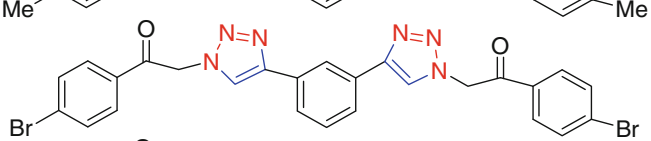
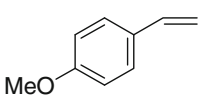
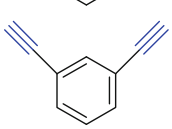
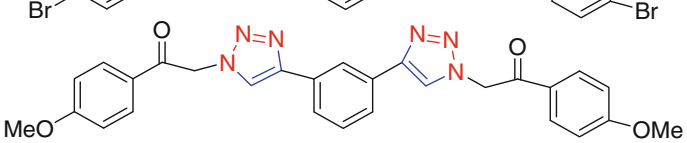
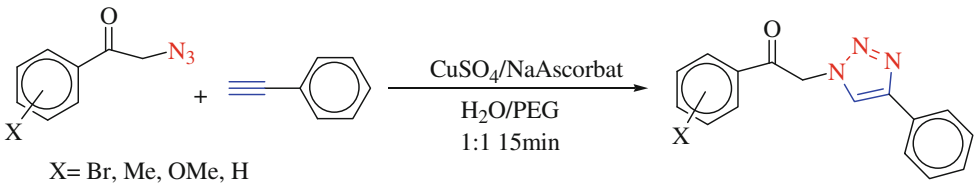
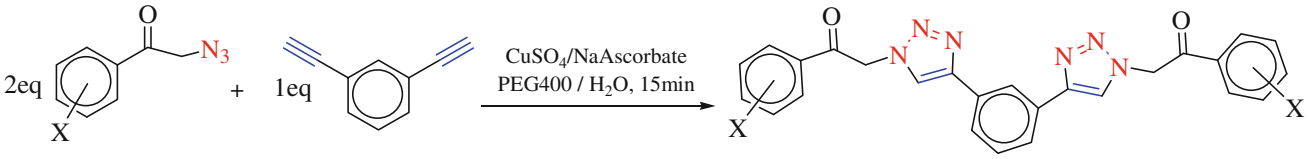
1				85
2				83
3				80
4				79
5				78
6				80
7				76
8				80
9				82
10				82
11				85
12				85

[d] Yield refer to pure and isolated products

Scheme 2 Synthesis of 1,4-disubstituted-1H-1,2,3-triazoles from directly prepared phenacyl azide and terminal alkyne using click cyclization





Scheme 3 Synthesis of symmetrical substituted triazoles using phenacyl azides and 1,3-diethynylbenzene

Hz), 6.29 (2H, s), 6.28 (2H, s). ^{13}C-NMR(125 MHz, DMSO-d_6): δ = 193, 146.97, 135.17, 135, 132.29, 130.55, 129.9, 129.1, 125.5, 124.26, 122.7, 56.91.

12c: IR (KBr): 1697(CO) cm^{-1}.^{1}H-NMR(500 MHz, DMSO-d_6): δ = 8.5 ppm (2H, s), 8.41 (1H, s), 8.11–8.10 (4H, d; j = 8.4 Hz), 7.90–7.89 (4H, d; j = 8.4 Hz), 7.79–7.76 (2H, t; j = 7.6 Hz), 7.60–7.57 (1H, t; j = 7.6 Hz), 7.15–7.146 (2H, d; j = 8.5 Hz), 6.19 ppm (s; 4H), 3.85 (s, 6H). ^{13}C-NMR(125 MHz, DMSO-d_6): δ = 194.9, 163.1, 141.9, 133.2, 131.66, 129.82, 128.4, 126, 123.96, 115.2, 56.58, 56.49.

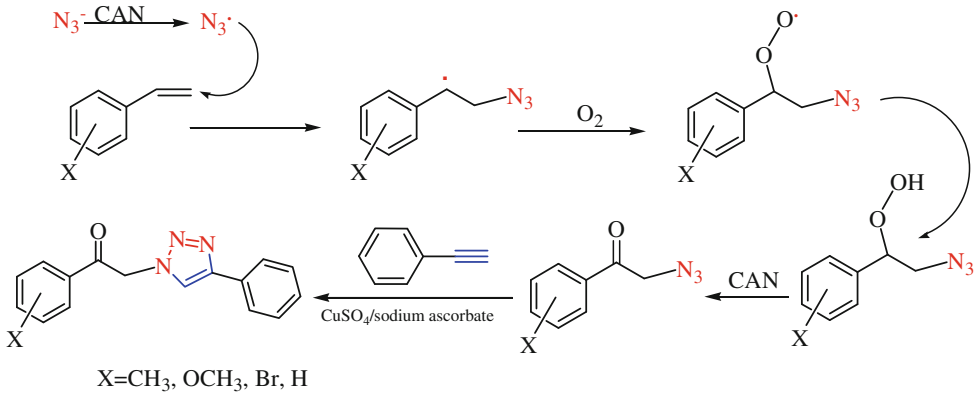
Results and discussion

The similar methods used previously to synthesize triazoles [21,22] exploited α-halo ketones and α-tosyloxy ketones, which themselves were prepared from their corresponding ketones. These methods applied the indirect preparation of α-azido ketones which was a long process and resulted in incomplete conversion. Moreover, a phase transfer catalyst was necessary in this step. α-Halo ketones suffer from tear-inducing properties, and ketones are more expensive than styrene precursors. Thus, a shorter route using cheaper precursors that do not have any tear-inducing properties would save time and money. The new method proposed herein utilizes a direct and shorter way to prepare α-azido ketones for synthesis of 1,4-disubstituted 1,2,3-triazoles with less expensive styrene precursors. In fact, in this method, CAN oxidant dissolved in methanol was added drop-wise to an ice-cold temperature stirring methanol solution of styrene and sodium azide, while the reaction mixture was continuously being purged with oxygen. The phenacyl azide was produced after 45 min in high yield (Scheme 1).

Various phenacyl azides prepared by this direct preparation method were treated to click cyclization with terminal alkynes in a mixture of H_2O/PEG as solvent. Using of H_2O/PEG mixture as a green solvent for cyclization is in line with click reaction characteristics [1–3]. The phase transfer catalytic properties of PEG work in a similar fashion to those of crown ethers and these properties significantly reduce cyclization times, as compared to other solvents [25–27]. It is worth noting that the solvent mixture can be reused up to three times without any loss of activity (Scheme 2).

The preparation of α-azido ketones was checked by thin layer chromatography and indentified by IR spectroscopy by signals at about 1680–1705cm^{-1}, for carbonyl groups, and 2100–2115cm^{-1}, for azide groups. Click condensations were confirmed by the appearance of a singlet in the region of 8–8.5 ppm in ^{1}H-NMR spectra, which corresponds to the hydrogen on 5-position of triazole ring. These results are consistent with the disappearance of the azide signal in the IR spectra. This characteristic singlet confirms the regioselective synthesis of 1,4-disubstituted triazole regioisomers (Schemes 2 and 3). The using of 1,3-diethynylbenzene in click cyclizations led to the synthesis of some interesting symmetrical triazoles (Table 1, entry 9c–12c and Scheme 3). A simple purification technique is one of the key characteristics of click reactions [1–3]. It should be noted that, although all the products were solid, it was fortunate that the products were insoluble in diethyl ether while the starting materials were soluble. Therefore, the products were easily purified by washing with diethyl ether and ethanol (for better purification solid products were dissolved in a minimum amount of ethyl acetate, then *n*-hexane was added drop-wise to precipitate pure products). All the products were obtained during short time interval in high yields. Styrenes with electron releasing and electron withdrawing groups gave good results. It seemed that the ring substituent had not a significant effect on reaction time and product yields (Table 1 and Scheme 2).

The proposed mechanism for this cyclization is shown in Scheme 4. In the presence of CAN, the azide anion is converted to an azide radical, which after attacking the



Scheme 4 Proposed mechanism for CAN/N_3 mediated 1,4-disubstituted-1H-1,2,3-triazole synthesis

β-position of styrene produces a benzyl radical. In the following step, azido peroxide is obtained in the presence of molecular oxygen. Finally, CAN converts the azido peroxide group to an azido ketone moiety, which in turn reacts with the terminal alkyne to produce 1,4-disubstituted triazole in the next step.

Conclusions

A new and facile approach to the synthesis of 1,4-disubstituted-1H-triazoles was reported. This method significantly reduced cyclization times, required a simple purification technique, utilized an environmentally benign green solvent mixture, and afforded products quickly in high yields.

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