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Regioselective alkylation of 1,2,4-triazole using ionic liquids under microwave conditions

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Abstract: 1-Substituted 1,2,4-triazole derivatives present in a large number of compounds and display a variety of bioactivities such as antibiotic, anti-inflammatory, anti-diabetic, antipsychotic, and anticancer. A regioselective protocol has been developed for the alkylation of 1,2,4-triazole using mild conditions. The 1-alkyl-1,2,4-triazole derivatives were synthesized under microwave conditions using potassium carbonate as a base and ionic liquid (hexylpyridinium bromide) as a solvent. The products were obtained in excellent yield, and the base-ionic liquid combination was recycled for a number of times.

Keywords: 1,2,4-triazole; green chemistry; ionic liquids; microwave; regioselective alkylation.

1 Introduction

1,2,4-Triazole is an important nucleus [1] present in a large number of compounds exhibiting a variety of bioactivities [2] including antibiotic, anti-inflammatory, anti-diabetic, antipsychotic, and anticancer activities. This nucleus is also a part of many herbicides, fungicides, and plant growth regulators [3]. The 1,2,4-triazole nucleus is stable to metabolism and act as an important pharmacophore by interacting at the active site of the receptor as hydrogen bond acceptor as well as donor. Owing to its polar nature, the triazole nucleus can increase the solubility of the ligands and may improve the pharmacokinetic and pharmacodynamic profile of the drugs [4].

Among the various 1,2,4-triazole derivatives, 1-substituted 1,2,4-triazole nucleus is of particular interest as it can be traced in many commercialized drugs [5] like rizatriptan, fluconazole, and terconazole. Two different methods are reported for the synthesis of anti-migraine drug rizatriptan, and the most obvious synthetic step for the introduction of 1,2,4-triazole is through alkylation reaction [6]. The triazole nucleus exists in two tautomeric forms, namely, 4*H*-1,2,4-triazoles and 1*H*-1,2,4-triazoles, and in general, the alkylation reaction results in the formation of an isomeric mixture of 1-substituted 1,2,4-triazole and 4-substituted 1,2,4-triazole. In addition to this, over-alkylation of the product may lead to salt formation [7]. The ratios of the isomers formed depend on the nature of the alkylating agents and reaction conditions. To obtain a single isomer, some regioselective protocols were also developed. For example, Astleford et al. [8] reported a regioselective alkylation of 1,2,4-triazoles from the corresponding 4-amino-1,2,4-triazoles. The products were obtained by subsequent deamination of the triazolium salt. Similarly, alkylation of 1,2,4-triazole was reported using NaOH as a base and DMF as a solvent. The products were obtained in a regioselective way; however, the isomer ratio of the crude mixtures of the synthesized compounds before the work up was only 90:10 [9]. In another report, the synthesis of 1-ethyl-1,2,4-triazole was performed under mild conditions using THF as a solvent and DBU as a base. The isomeric ratios of the product obtained vary from 94:6 to 86:14. The precipitation of DBU-HX from the reaction mixture and its separation by simple filtration was the advantage of this method [10]. Rezaei et al. [11] reported the regioselective formation of the N-1 isomer in higher yield using anhydrous potassium carbonate, sodium hydroxide, and tetra ethyl ammonium iodide. Mirzaei et al. [12] reported the regioselective alkylation of 1,2,4-triazoles wherein 1,2,4-triazole was dissolved in methanolic solution of sodium methoxide, and iodoalkane was added at -40°C. Thus, most of the methods reported for the regioselective alkylation of 1,2,4-triazole make use of strong bases like sodium hydride and sodium hydroxide and sub-zero temperatures (-40°C or -78°C). Therefore, we got interested in developing a milder protocol for the regioselective alkylation of 1,2,4-triazole. Different mild bases were explored using recyclable ionic liquids as solvent under microwave conditions. The reaction conditions were optimized with potassium carbonate as the base and 1-hexylpyridinum bromide as the solvent

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under microwave irradiations, which yielded 1-alkyl-1,2,4-triazoles regioselectively.

2 Materials and methods

2.1 General

The chemicals were purchased from Sigma-Aldrich (St. Louis, MO, US), Spectrochem (Mumbai, Maharashtra, India), and Loba Chemicals (Mumbai, Maharashtra, India) and were used without any further purification. Ionic liquids were synthesized in the laboratory, and the purity of the ionic liquids was checked by ^{1}H NMR before their use. All NMR experiments were recorded on a JEOL JNM ECS400 spectrometer at 400 MHz for proton NMR and 100 MHz for carbon NMR at ambient temperature (25°C). A CEM Discover© focused microwave (2450 MHz, 300 W) (Matthew, NC, USA) apparatus was used wherever mentioned.

2.2 General procedure

1,2,4-Triazole (4.3 mmol, 300 mg), potassium carbonate (6.5 mmol, 900 mg) was added in the ionic liquid (0.5 ml), and the reaction mixture was kept in an ice bath for 10 min. Thereafter, butyl bromide (4.3 mmol, 594.7 mg)/pentyl bromide (4.3 mmol, 655.5 mg)/hexyl bromide (4.3 mmol, 716.4 mg)/octyl bromide (4.3 mmol, 831.2 mg)/decyl bromide (4.3 mmol, 959.9 mg)/allyl bromide (4.3 mmol, 525 mg)/benzyl bromide (4.3 mmol, 742.3 mg) were added drop-wise to the reaction mixture, and the reaction mixture was irradiated to microwave for 10 min at 110°C. The reaction was monitored via TLC, and after completion of the reaction, the reaction mixture was extracted with diethylether (3×20 ml). The combined organic layer was washed with water, brine, and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to obtain a pure product in most of the cases.

2.3 Spectral data of different 1-alkyl-1,2,4-triazole [8, 11–15]

2.3.1 1-Butyl-1*H*-1,2,4-triazole [8, 12, 13] (1b): Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (3H, t, *J*=5.24 Hz, C4′H), 1.31 (2H, m, C3′H), 1.85 (2H, m, C2′H), 4.15 (2H, t, *J*=7.16 Hz, C1′H), 7.93 (1H, s, C3H), 8.05 (1H, s, C5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 13.6 (C4′), 19.7 (C3′), 31.8 (C2′), 49.6 (C1′), 142.9 (C5), 151.8 (C3).

2.3.2 1-Pentyl-1*H*-1,2,4-triazole [8, 11] (2b): Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, t, *J*=7.04 Hz, C5′H), 1.22 (6H, m, C4′H-C2′H), 1.83 (2H, t, *J*=7.4, C1′H), 7.87 (1H, s, C3H), 7.99 (1H, s, C5H); ^{13}C NMR (400 MHz, $CDCl_3$,) δ: 13.8 (C5′), 22.0 (C4′), 28.5 (C3′), 29.4 (C2′), 49.7 (C1′), 142.7 (C5), 151.7 (C3).

2.3.3 1-Hexyl-1*H*-1,2,4-triazole [15] (3b): Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, t, *J*=6.88 Hz, C6′H), 1.24 (6H, m, C5′H-C3′H), 1.83 (2H, m, C2′H), 4.12 (2H, t, *J*=7.16 Hz, C1′H), 7.90 (1H, s, C3H), 8.05 (1H, s, C5H); ^{13}C NMR (400 MHz, $CDCl_3$,) δ: 13.9 (C6′), 22.4 (C5′), 26.1 (C4′), 29.7 (C3′), 31.1 (C2′), 49.8 (C1′), 142.8 (C5), 151.6 (C3).

2.3.4 1-Octyl-1*H*-1,2,4-triazole [11, 14] (4b): Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80 (3H, t, *J*=6.64 Hz, C8′H), 1.20 (12H, m, C7′H-C2′H), 1.81 (2H, t, *J*=7.0 Hz, C1′H), 7.86 (1H, s, C3H), 7.99 (1H, s, C5H); ^{13}C NMR (400 MHz, $CDCl_3$,) δ: 14.0 (C8′), 22.5 (C7′), 26.4 (C6′), 28.9 (C5′), 29.0 (C4′), 29.7 (C3′), 31.6 (C2′), 49.7 (C1′), 142.7 (C5), 151.7 (C3).

2.3.5 1-Decyl-1*H*-1,2,4-triazole [12, 15] (5b): Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, t, *J*=5.76 Hz, C10′H), 1.25 (14H, m, C9′H-C3′H), 1.86 (2H, m, C2′H), 4.14 (2H, t, *J*=6.92 Hz, C1′H), 7.92 (1H, s, C3H), 8.04 (1H, s, C5H); ^{13}C NMR (400 MHz, $CDCl_3$,) δ: 14.2 (C10′), 22.7 (C9′), 26.5 (C8′), 29.1 (C7′), 29.3 (C6′), 29.5 (C5′), 29.5 (C4′), 29.8 (C3′), 31.9 (C2′), 49.8 (C1′), 142.8 (C5), 151.9 (C3).

2.3.6 1-Allyl-1*H*-1,2,4-triazole [13] (6b): Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.75 (2H, d, *J*=1.28 Hz, C1′H), 5.22 (1H, dd, *J*=16.12 Hz, *J*=6.5 Hz transC3′H), 5.30 (1H, dd, *J*=9.16 Hz, *J*=6.5 Hz *cis* C3′H), 5.96 (1H, m, C2′H), 7.90 (1H, s, C3H), 8.05(1H, s, C5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 52.1 (C1′), 120.0 (C3′), 131.1 (C2′), 142.8 (C5), 151.9 (C3).

2.3.7 1-benzyl-1*H*-1,2,4-triazole [8, 13] (7b): Solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.29 (2H, s, CH_2), 7.23 (2H, m, C2′H, C6′H), 7.32 (3H, m, C3′H-C5′H), 7.94 (1H, s, C3H), 8.03 (1H, s, C5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 53.5 (**C**H_2), 127.9 (C1′), 128.6 (C2′, C6′), 129.0 (C3′, C5′), 134.5 (C4′), 143.0 (C5), 152.0 (C3).

3 Results and discussion

As evident from the above discussions, there are a number of methods reported for the alkylation of 1,2,4-triazoles by using different solvents such as acetonitrile, DMF, THF, etc. 1*H*-1,2,4-triazole exists in tautomeric equilibrium with the 4*H*-1,2,4-triazole. The interconversion of two tautomeric forms occurs rapidly, and it is difficult to separate them. However, there are a number of reports in the literature showing that alkylation of 1,2,4-triazole leads to regiomeric mixture of the products [8, 12]. Efforts have also been made to perform the alkylation reaction of 1,2,4-triazole in a regioselective manner. In continuation of our interest in ionic liquid-mediated organic synthesis [16, 17], we got interested in developing a green protocol for the alkylation of 1,2,4-triazole. Our objective was to develop a regioselective protocol for alkylation reaction and replace the volatile organic solvents with recyclable ionic liquids [18, 19]. Ionic liquids are a green alternative to the volatile organic solvents, which

can be reused and recycled in chemical transformations. The most common ionic liquids used in the organic reactions are imidazole and pyridinium-based cations with organic or inorganic anions. So two different series of ionic liquids, based on methyl imidazole and pyridinium cations, were synthesized and purified in the laboratory through standard procedures [20, 21]. Medium to long-chain alkyl halides (butyl to decyl) were used for the synthesis of ionic liquids via quaternization of methyl imidazole or pyridine. It was planned to perform the alkylation reaction of triazole under microwave conditions as microwave is known for increasing the reaction rates and substantially reducing the reaction time from hour to seconds [22]. More importantly, in some cases, microwave can impart desired stereoselectivity [23, 24] and regioselectivity to the products due to its unique heating mechanisms. In addition, ionic liquids are microwave compatible and efficiently absorb microwave energy and speed up the chemical transformations [25, 26]. Therefore, we decided to perform the alkylation reaction under microwave conditions as it may help in the regioselective alkylation of 1,2,4-triazole. Initially, 1,2,4-triazole, potassium carbonate, ionic liquid (1-butyl-3-methylimidazolium bromide), and hexylbromide were mixed and irradiated to microwave at 80°C for 10 min. The product was obtained in 52% yield along with the unreacted starting material. Thereafter, the reaction temperature was increased to 110°C, and the elevated reaction temperature improved the product yield to 62%. In order to further optimize the reaction conditions, the alkylation reaction was performed with different ionic liquids as described in Table 1. The product was obtained in all the ionic liquids, however, in varying amounts. Similarly different bases were investigated to optimize the reaction conditions (Table 1).

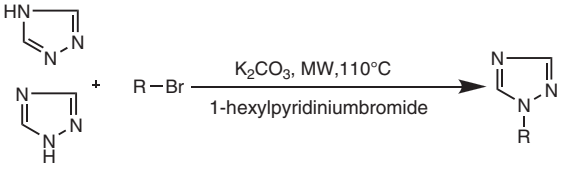
It was observed that, in general, the reactions were clean with pyridinium-based ionic liquids compared to the imidazolium-based ionic liquids and 1-hexylpyridinum bromide with potassium carbonate as base provided the best yield (88%) of the product (Table 2).

We came across some literature reports [13] suggesting that the alkylation reaction of 1,2,4-triazole generally lead to the formation of two isomers, and as one of the isomers is water soluble, so it might disappear during aqueous work up. Hence, we performed a non-aqueous work up of the reaction mixture, and proton NMR of the product suggested that only one of the isomers was formed, which further confirmed the regioselectivity of the developed method. Once the reaction conditions were optimized, the reaction was performed with different alkylhalides, and the products were obtained in excellent yields as reported in Table 2. The reactions were also performed with allyl

Table 1: Use of different ionic liquids and base for the alkylation reaction.

Sr. no	Ionic liquids	Base	% Yield
1.	1-butyl-3-methylimidazolium bromide	K_2CO_3	62
2.	1-hexyl-3-methylimidazolium bromide	K_2CO_3	65
3.	1-decyl-3-methylimidazolium bromide	K_2CO_3	64
4.	1-butylpyridinium bromide	K_2CO_3	69
5.	1-hexylpyridinium bromide	K_2CO_3	88
6.	1-decylpyridinium bromide	K_2CO_3	84
7.	1-hexylpyridinium bromide	Na_2CO_3	68
8.	1-hexylpyridinium bromide	$NaHCO_3$	64
9.	1-hexylpyridinium bromide	NaOH	59

Table 2: Alkylation of 1,2,4-triazole using different alkyl halides.



Sr. no	Alkyl halide (a)	Time in min.	Product (b) R	% Yield[a]	Ref.
1.	C_4H_9Br	10	$-C_4H_9$	88	[8, 12, 22]
2.	$C_5H_{11}Br$	10	$-C_5H_{11}$	85	[8, 11]
3.	$C_6H_{13}Br$	10	$-C_6H_{13}$	87	[15]
4.	$C_8H_{17}Br$	10	$-C_8H_{17}$	88	[11, 14]
5.	$C_{10}H_{21}Br$	10	$-C_{10}H_{21}$	86	[12, 15]
6.	$CH_2{=}CHCH_2Br$	12	$-CH_2CH{=}CH_2$	82	[22]
7.	$C_6H_5CH_2Br$	15	$-CH_2C_6H_5$	84	[8, 22]

[a]Isolated yields.

bromide (entry 6, Table 2) and benzyl bromide (entry 7, Table 2), and the corresponding products were obtained in good yields.

Further, for comparison, a reaction was performed under conventional conditions by mixing 1,2,4-triazole, potassium carbonate, and hexylbromide in ionic liquid (1-hexylpyridiniumbromide) and heating the reaction mixture at 110°C for 24 h. The product was obtained but in a lower yield (56%) along with the formation of unidentified side products. This clearly illustrated that microwave irradiation not only speeds up the reaction but also provided the product with improved yield.

In order to check the reusability of the ionic liquid and base, after completion of the first reaction cycle, the product was extracted with diethylether, and the remaining ionic liquid and base was reused for five cycles without any appreciable loss in the activity, thus, making the developed protocol green and environmentally sustainable. The volatile organic solvents were successfully replaced with the ionic liquid, and the products could be obtained within 15 min of reaction time under microwave conditions.

4 Conclusion

In conclusion, we have developed a regioselective protocol for the synthesis of alkyl derivatives of 1,2,4-triazole using ionic liquids under microwave conditions. The volatile organic solvents were replaced with recyclable ionic liquids, and the alkylated products were obtained within 15 min of reaction time. The base-ionic liquid mixture was reused successfully for five cycles.

Supporting information: Full experimental details, ^{1}H and ^{13}C NMR spectral data of synthesized compounds, and ionic liquids can be found with the online version of this article.

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Conflict of interest statement: The authors confirm that they have no conflicts of interest regarding the content of this article.

References

[1] Potts K. *Chem. Rev.* 1961, 61, 87–127.
[2] Wahi A, Singh A. *Asian J. Biochem. Pharma. Res.* 2011, 2, 193–205.
[3] Oh K, Yamada K, Asami T, Yoshizawa Y. *Bioorgan. Med. Chem. Lett.* 2012, 22, 1625–1628.
[4] Wang S, Li Q-S, Su M-G. *J. Chem. Eng. Data* 2007, 52, 856–858.
[5] Street LJ, Baker R, Davey WB, Guiblin AR, Jelley RA, Reeve AJ, Routledge H, Sternfeld F, Watt AP. *J. Med. Chem.* 1995, 38, 1799–1810.
[6] Chen C-Y, Lieberman DR, Larsen RD, Reamer RA, Verhoeven TR, Reider PJ, Cottrell IF, Houghton PG. *Tetrahedron Lett.* 1994, 35, 6981–6984.
[7] Daily LA, Miller KM. *J. Org. Chem.* 2013, 78, 4196–4201.
[8] Astleford BA, Goe GL, Keay JG, Scriven EFV. *J. Org. Chem.* 1989, 54, 731–732.
[9] Katritzky AR, Kuzmierkiewicz W, Greenhill JV. *Recl. Trav. Chim. Pay B.* 1991, 110, 369–373.
[10] Norcross RD, von Matt P, Kolb HC, Belluš D. *Tetrahedron* 1997, 53, 10289–10312.
[11] Rezaei Z, Khabnadideh S, Pakshir K, Hossaini Z, Amiri F, Assadpour E. *Eur. J. Med. Chem.* 2009, 44, 3064–3067.
[12] Mirzaei YR, Twamley B, Shreeve JNM. *J. Org. Chem.* 2002, 67, 9340–9345.
[13] Bulger PG, Cottrell IF, Cowden CJ, Davies AJ, Dolling U-H. *Tetrahedron Lett.* 2000, 41, 1297–1301.
[14] Katritzky AR, Darabantu M, Aslan DC, Oniciu DC. *J. Org. Chem.* 1998, 63, 4323–4331.
[15] Adamer V, Laus G, Griesser UJ, Schottenberger H. *Z. Naturforsch* 2013, 68, 1154–1162.
[16] Sharma A, Kumar R, Sharma N, Kumar V, Sinha AK. *Adv. Synth. Catal.* 2008, 350, 2910–2920.
[17] Kumar R, Sharma A, Sharma N, Kumar V, Sinha AK. *Eur. J. Org. Chem.* 2008, 2008, 5577–5582.
[18] Welton T. *Chem. Rev.* 1999, 99, 2071–2084.
[19] Dupont J, de Souza RF, Suarez PA. *Chem. Rev.* 2002, 102, 3667–3692.
[20] Huddleston J, Rogers R. *Chem. Commun.* 1998, 1765–1766.
[21] Min G-H, Yim T, Lee HY, Huh DH, Lee E, Mun J, Oh SM, Kim YG. *Bull. Korean Chem. Soc.* 2006, 27, 847–852.
[22] Fustero S, del Pozo C, Mulet C, Lazaro R, Sánchez-Roselló M. *Chem. Eur. J.* 2011, 17, 14267–14272.
[23] Rahmati A, Alizadeh Kouzehrash M. *Chin. J. Chem.* 2011, 29, 2373–2378.
[24] Zahran MA, Salama HF, Abdin YG, Gamal-Eldeen AM. *J. Chem. Sci.* 2010, 122, 587–595.
[25] Varma RS, Namboodiri VV. *Chem. Commun.* 2001, 643–644.
[26] Deetlefs M, Seddon KR. *Green Chem.* 2003, 5, 181–186.

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