Unusual Cleavage of N-N Bond of 1-Arylamino-1,2,3-triazole Derivatives: A Simple and Alternate Approach to 4,5-Disubstituted-1*H*-1,2,3-triazoles

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In this communication, the authors described the synthesis of 1-arylamino-1,2,3-triazole derivatives *via* diazo transfer reaction on active methylene hydrazones. Further, we have observed the reduction of 1-arylamino-1,2,3-triazole using Pd/C, H₂ to result in unusual N-N bond cleavage to give 4,5-disubstituted-1*H*-1,2,3-triazole.

Keywords: N-N bond cleavage, Reduction, 1,2,3-Triazole, 1-Amino-1,2,3-triazole, Diazo transfer reaction.

INTRODUCTION

Nitrogen containing heterocycles and their derivatives have emerged as promising candidates in the field of medicinal chemistry, due to their ability to form hydrogen bonding with the target proteins as well as π -stacking interactions [1-5]. Among them indole [6], pyrrole [7], imidazole [8] and triazole [9] derivatives had received more attention due to the availability of several synthetic routes to access them with diversity in substituents. Particularly 1,2,3-triazole derivatives with their high dipole moment (about 5D) had been reported to possess antifungal [10], antibacterial [11], anticancer [12], antituberculosis [13] properties.

The simplest and most versatile method to access 1,2,3-triazole derivatives is the 3+2 cycloaddition between organic azide and alkyne in the presence of CuSO₄ and ascorbic acid. This reaction is popularly known as Huisgen 1,3-dipolar cycloaddition [14-17], one of the most studied click reactions. Since the invention of this method, several modifications have been made to obtain derivatives of 1,2,3-triazoles and have been studied for their biological activities [18-20].

The major limitation of this approach includes the poor regio selectivity with internal alkyne which reduces the substrate scope to obtain 4,5-disubstituted-1*H*-1,2,3-triazole. Another limitation includes the inability to introduce heteroatom on 1-position of 1,2,3-triazole as the corresponding azide is not available.

In continuation of our research work on the synthesis of heterocycles from diazo compounds, we got interest in the synthesis of 1-amino-1,2,3-triazole derivative, which could be expected to have more interaction with protein targets due to the possibility to form extra hydrogen bonding *via* 1-NH₂ group. The most common approach to obtain unsubstituted 1-amino-1,2,3-triazole is MnO₂ promoted oxidation of glyoxal dihydrazone [21]. Unfortunately, it lacks selectivity when we go for 4,5-disubstituted 1-amino-1,2,3-triazole from the corresponding dione. Cunha *et al.* [22] reported synthesis of 1-arylamino-1,2,3-triazole from diazo carbonyl compounds. Recently, we reported the synthesis of N-Boc protected 1-amino-1,2,3-triazole [23] *via* diazo transfer reaction on β -keto ester derived hydrazones. In this communication, we report the synthesis of 1-arylamino 1,2,3-triazole derivatives and cleavage of N-N bond of them to obtain 4,5-disubstituted 1,2,3-triazole under mild reduction condition using H₂, Pd/C as catalyst.

EXPERIMENTAL

All the solvents were distilled under nitrogen atmosphere from the following drying agents. Ethanol was distilled by fractional distillation method. Acetonitrile was distilled from P₂O₅ and immediately used. All the substrates and chromatographic solvents were purchased from commercial suppliers and used without further purification.

All the reactions were carried out in oven dried glassware under nitrogen atmosphere with freshly distilled dry solvents

under anhydrous conditions unless otherwise indicated. Column chromatography was performed with silica gel (200–400 mesh) or neutral aluminium oxide. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using base solution of potassium permanganate or anisaldehyde or vanillin. Melting points were recorded in GUNA Melting point apparatus and are uncorrected. NMR spectra were recorded at room temperature on 300 or 500 MHz FT NMR Spectrometer (Bruker). Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz.

General procedure for 1-arylamino 1,2,3-triazole: A two neck round bottom flask was charged with β -keto ester (5 mmol), 2,4-dinitro phenyl hydrazine (5.5 mmol), ethanol (15 mL), few drops of conc. HCl and heated at 50 °C for 1 h. After confirming the formation of hydrazone by TLC, ice cooled water or ice cubes are added in to the reaction mixture. The product will form as yellow precipitate, that precipitate has been filtered by normal filter paper. In second step hydrazone (3 mmol), DBU (3.3 mmol) and a solution imidazole sulfonyl azide (3.3 mmol) in CH_3CN (10 mL) was added and the reaction mixture was cooled to -20 to 25 °C. After 2 h, the reaction was quenched with water, diluted with CH_2Cl_2 washed with water, brine, dried over anhydrous Na_2SO_4 . The organic layer was concentrated under reduced pressure to get the crude product, which was purified by column chromatography (silica gel) using petroleum ether/ethyl acetate (85:15) to get pure compound.

General procedure for reductive cleavage of N-N bond from 1-arylamino 1,2,3-triazole: A two neck round bottom flask was charged with 1-arylamino-1,2,3-triazole (1 mmol), methanol (5 mL) this mixture was kept under hydrogen gas atmosphere. In this atmosphere we have to add Pd/C (100 mg) powder carefully. This reaction mixture allowed to run under room temperature for overnight, after completion of the reaction we have to filter using celite powder. The organic layer was concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel) using petroleum ether/ethyl acetate (65:35) to get pure compound (**Scheme-I**).

Scheme-I: Synthesis of 1-arylamino-1,2,3-triazole

Spectroscopic data for 1-arylamino-1,2,3-triazole

Ethyl 1-((2,4-dinitrophenyl)amino)-5-methyl-1H-1,2,3-triazole-4-carboxylate (a): Light brown solid, yield 92 %, m.p. 104 °C, IR (v, cm^{-1}): 3359, 3260, 1725, 1613, 1532, 1344, 1307, 1158, 1095, 906, 817. ^1H NMR (300 MHz, CDCl_3): δ 10.89 (brs, 1H), 9.19 (s, 1H), 8.35 (dd, 1H, $J = 6.9, 2.4$ Hz), 6.31 (d, 1H, $J = 9.3$ Hz), 4.49 (q, 2H, $J = 6.9, 7.2$ Hz), 2.60 (s, 3H), 1.41 (m, 3H, $J = 7.2, 5.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 160.48, 145.11, 140.30, 140.26, 135.44, 132.16, 130.52, 122.83, 114.70, 61.23, 13.89, 8.37. HRMS (ESI): m/z [M +

H] $^+$ calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_6\text{O}_6$ Calculated = 336.2603, found = 336.2601.

Methyl 1-((2,4-dinitrophenyl)amino)-5-methyl-1H-1,2,3-triazole-4-carboxylate (b): Yellow powder, yield 90 %, m.p. 160 °C, IR (v, cm^{-1}): 3300, 2952, 1729, 1615, 1508, 1343, 1103, 524. ^1H NMR (300 MHz, CDCl_3): δ 10.68 (s, 1H), 9.23 (s, 1H), 8.36 (dd, 1H, $J = 6.9, 2.4$ Hz), 6.30 (d, 1H, $J = 9.3$ Hz), 4.02 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 161.13, 145.31, 141.11, 140.43, 135.85, 132.74, 130.86, 123.26, 114.89, 52.46, 8.63. HRMS (ESI): m/z [M + H] $^+$ calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_6\text{O}_6$: Calculated = 322.2337, found = 322.2333.

Allyl 1-((2,4-dinitrophenyl)amino)-5-methyl-1H-1,2,3-triazole-4-carboxylate (c): Light brown powder, yield 85 %, m.p. 142 °C, IR (v, cm^{-1}): 3311, 3098, 1726, 1612, 1345, 1097, 925, 826, 734. ^1H NMR (500 MHz, CDCl_3): δ 10.92 (s, 1H), 9.17 (s, 1H), 8.33 (dd, 1H, $J = 1.5, 2.5$ Hz), 6.31 (d, 1H, $J = 4$ Hz), 6.02 (q, 1H, $J = 1.5, 4.5$ Hz), 5.41 (d, 1H, $J = 1$ Hz), 5.33 (d, 1H, $J = 1$ Hz), 4.87 (d, 2H, $J = 1$ Hz), 2.6 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 160.54, 145.48, 141.03, 140.76, 135.82, 132.80, 131.57, 130.96, 123.31, 119.53, 115.10, 66.19, 8.83. HRMS (ESI): m/z [M + H] $^+$ calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_6\text{O}_6$. Calculated = 342.2710, found = 342.2711.

tert-Butyl 1-((2,4-dinitrophenyl)amino)-5-methyl-1H-1,2,3-triazole-4-carboxylate (d): Light brown powder, yield 76 %, m.p. 186 °C, IR (v, cm^{-1}): 3274, 2986, 1717, 1610, 1524, 1332, 1155, 828. ^1H NMR (500 MHz, CDCl_3): δ 9.20 (s, 1H), 8.28 (dd, 1H, $J = 6.5, 2.5$ Hz), 6.29 (d, 1H, $J = 9$ Hz), 4.10 (s, 1H), 2.57 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 160.11, 145.63, 141.17, 139.80, 137.33, 132.86, 130.96, 129.97, 123.39, 119.25, 115.14, 83.39, 28.45, 8.92. HRMS (ESI): m/z [M + H] $^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_6\text{O}_6$ Calculated = 364.3134, found = 364.3136.

Benzyl 1-((2,4-dinitrophenyl)amino)-5-methyl-1H-1,2,3-triazole-4-carboxylate (e): Light yellow crystals, yield 83 %, m.p. 158 °C, IR (v, cm^{-1}): 3092, 1723, 1605, 1510, 1344, 1100, 833, 742. ^1H NMR (500 MHz, CDCl_3): δ 10.76 (s, 1H), 9.17 (s, 1H), 8.31 (d, 1H, $J = 9.5$ Hz), 7.47 (d, 1H, $J = 7.5$ Hz), 7.38 (m, 5H, $J = 7, 4.5$ Hz), 5.42 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 160.73, 145.48, 141.22, 140.73, 135.98, 135.36, 132.87, 130.98, 128.87, 128.80, 127.48, 123.39, 115.10, 67.37, 8.88. HRMS (ESI): m/z [M + H] $^+$ calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_6$. Calculated = 398.3297, found = 398.3302.

Ethyl 1-((2,4-dinitrophenyl)amino)-5-phenyl-1H-1,2,3-triazole-4-carboxylate (f): Orange colour powder, yield 88 %, m.p. 130 °C, IR (v, cm^{-1}): 3484, 2116, 1693, 1614, 1506, 1334, 1138, 1088, 754. ^1H NMR (500 MHz, CDCl_3): δ 11.51 (s, 1H), 9.13 (s, 1H), 8.64 (dd, 1H, $J = 7, 2.5$ Hz), 8.11 (d, 2H, $J = 5$ Hz), 7.91 (t, 1H, $J = 4$ Hz), 7.76 (t, 2H, $J = 2, 3.5$ Hz), 7.52 (s, 1H), 4.43 (q, 2H, $J = 7, 7.5$ Hz), 1.37 (t, 3H, $J = 7, 7$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ 163.03, 144.56, 139.12, 138.84, 134.34, 131.20, 130.57, 130.41, 130.06, 129.01, 128.09, 123.45, 117.21, 62.82, 14.58. HRMS (ESI): m/z [M + H] $^+$ calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_6$. Calculated = 398.3297, found = 398.3294.

1-(1-((2,4-Dinitrophenyl)amino)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone (g): Dark brown solid, yield 93 %, m.p. 116 °C, IR (v, cm^{-1}): 3446, 3126, 1610, 1533, 1346, 1124, 904, 843, 735. ^1H NMR (500 MHz, CDCl_3): δ 8.77 (s, 1H),

8.54 (dd, 1H, $J = 6, 2.5$ Hz), 7.27 (d, 1H, $J = 9$ Hz), 6.10 (s, 1H), 2.28 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 152.44, 146.36, 145.76, 141.08, 138.04, 129.50, 127.49, 121.07, 108.99, 13.55, 11.69. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_6\text{O}_5$. Calculated = 306.2343, found = 306.2342.

1-((2,4-Dinitrophenyl)amino)-6,6-dimethyl-6,7-dihydro-1H-benzo[d][1,2,3]triazol-4(5H)-one (h): Orange powder, yield 72 %, m.p. 130 °C, IR (v, cm^{-1}): 3237, 2963, 2124, 1605, 1513, 1338, 1265, 1136. ^1H NMR (300 MHz, CDCl_3): δ 10.44 (s, 1H), 9.14 (s, 1H), 8.38 (dd, 1H, $J = 2.7, 0.3$ Hz), 7.46 (d, 1H, $J = 9.6$ Hz), 2.62 (s, 2H), 2.52 (s, 2H), 1.14 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 190.35, 147.66, 145.22, 141.42, 138.49, 132.26, 130.16, 123.23, 116.65, 51.11, 45.29, 31.03, 27.97. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_6\text{O}_5$. Calculated = 346.2982, found = 346.2979.

1-((2,4-Dinitrophenyl)amino)-6-phenyl-6,7-dihydro-pyrano[3,4-d][1,2,3]triazol-4(1H)-one (i): Reddish brown solid, yield 73 %, m.p. 138 °C, IR (v, cm^{-1}): 3294, 2924, 1699, 1605, 1503, 1329, 1261, 1064, 913. ^1H NMR (500 MHz, CDCl_3): δ 10.53 (s, 1H), 9.01 (s, 1H), 8.30 (dd, 1H, $J = 2.6, 2.5$ Hz), 7.72 (d, 1H, $J = 9.5$ Hz), 7.34 (m, 5H, $J = 11, 11.5$ Hz), 6.53 (t, 1H, $J = 9.5$ Hz), 1.34 (d, 2H, $J = 7.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ 158.89, 145.37, 142.86, 141.08, 136.78, 135.38, 133.92, 132.97, 131.01, 129.87, 128.22, 126.34, 123.61, 116.93, 116.80, 80.67, 29.85. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{12}\text{N}_6\text{O}_6$. Calculated = 396.3138, found = 396.3135.

Spectroscopic data for reduced 1-arylamino-1,2,3-triazole

Methyl 5-methyl-1H-1,2,3-triazole-4-carboxylate (j): Light brown powder, yield 75 %, m.p. 199 °C, IR (v, cm^{-1}): 3014, 2774, 1725, 1594, 1426, 1313, 1125, 1027, 785. ^1H NMR (300 MHz, DMSO): δ 15.42 (brs, 1H), 3.82 (s, 3H), 2.50 (dd, 3H, $J = 1.8, 13.5$ Hz). ^{13}C NMR (75 MHz, DMSO): δ 161.67, 141.27, 134.48, 51.45, 9.48. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_5\text{H}_7\text{N}_3\text{O}_2$. Calculated = 141.1280, found = 141.1282.

Ethyl 5-methyl-1H-1,2,3-triazole-4-carboxylate (k): White solid, yield 79 %, m.p. 178 °C, IR (v, cm^{-1}): 3103, 3005, 2811, 1716, 1592, 1444, 1311, 1242, 1125, 1018. ^1H NMR (300 MHz, DMSO): δ 15.41 (brs, 1H), 4.30 (q, 2H, $J = 7.2, 6.9$ Hz), 2.51 (m, 3H, $J = 1.8, 1.8$ Hz), 1.33 (t, 3H, $J = 6.9, 7.2$ Hz). ^{13}C NMR (75 MHz, DMSO): δ 161.19, 141.25, 134.70, 60.14, 14.04, 9.53. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_6\text{H}_9\text{N}_3\text{O}_2$. Calculated = 155.1546, found = 155.1543.

Allyl 5-methyl-1H-1,2,3-triazole-4-carboxylate (l): Light brown crystals, yield 77 %, m.p. 120 °C, IR (v, cm^{-1}): 3100, 2927, 1720, 1594, 1466, 1316, 1299, 1119, 960. ^1H NMR (500 MHz, DMSO): δ 15.34 (brs, 1H), 4.28 (d, 2H, $J = 7$ Hz), 1.69 (m, 1H, $J = 7.5, 6.5$ Hz), 1.31 (dd, 4.5, 2.5 Hz), 0.962 (s, 3H). ^{13}C NMR (125 MHz, DMSO): δ 161.37, 142.40, 135.15, 132.31, 118.59, 65.67, 10.33. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_7\text{H}_9\text{N}_3\text{O}_2$. Calculated = 167.1653, found = 167.1654.

1-(1-((2,4-Diaminophenyl)amino)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone (m): Brown solid, yield 78 %, m.p. 119 °C, IR (v, cm^{-1}): 3448, 3329, 3201, 2920, 1627, 1517, 1329, 1205, 729. ^1H NMR (500 MHz, DMSO): δ 6.69 (s, 1H), 6.06 (d, 1H), 5.99 (s, 1H), 5.94 (dd, 1H, $J = 0.5, 0.5$ Hz), 5.12 (s, 2H), 4.47 (s, 2H), 2.19 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, DMSO): δ 149.66, 147.34, 145.36, 140.60, 128.33,

115.23, 105.39, 103.72, 100.54, 14.24, 11.63. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_6\text{O}$. Calculated = 246.2685, found = 246.2686.

RESULTS AND DISCUSSION

In continuation of our work on synthesis of 1-amino-1,2,3-triazole, we looked for a simple and readily available reagent to form hydrazone with β -keto ester. Even though, *tert*-butyl carbazate yielded the desired product, in reasonable yield. We were not able to isolate the hydrazone intermediate as the hydrazone was sensitive to water to give back the β -keto ester. Our search for low-cost and readily available hydrazine led us to choose 2,4-dinitro phenyl hydrazine over phenyl hydrazine which underwent cyclization to give 5-methyl-2-phenyl-1H-pyrazol-3(2H)-one [24]. The interesting observation to note about 2,4-dinitro phenyl hydrazine is that it could not be employed by Cunha *et al.* [22] to get the corresponding 1,2,3-triazole as the nucleophilicity is relatively less to attack the carbonyl group of α -diazo β -keto ester.

Initially, we prepared hydrazones by treating 2,4-dinitrophenyl hydrazine with β -keto ester in the presence of HCl (catalytic amount) in EtOH at 60 °C. The hydrazone was crystallized in MeOH and was employed as such for further reaction. We were of less interest on the ratio of E and Z geometrical isomers of hydrazone, since the stereochemistry is destroyed during the diazo transfer reaction.

2,4-Dinitrophenyl hydrazine was chosen over phenyl hydrazine as the later resulted in cyclization to give 5-methyl-2-phenyl-1H-pyrazol-3(2H)-one. The $-\text{NO}_2$ groups on aryl ring decreases the nucleophilicity of hydrazine nitrogen as a result no cyclization was observed in the case of 2,4-dinitrophenyl hydrazine. Thus obtained hydrazone was subjected to diazo transfer reaction using imidazole sulfonyl azide as the source of diazo in the presence of DBU. The water solubility of resulting imidazole sulfonamide simplified the purification process by column chromatography.

In order to study the scope of this method, we prepared several hydrazones from various β -keto esters as well as 1, 3-diones and subjected them to diazo transfer reaction (Table-1). Indeed, we obtained the corresponding cyclized 1-arylamino-1,2,3-triazole in good yields. Our attempts to isolate the diazo intermediate were not fruitful. The spontaneous cyclization may be attributed to the bulkiness of aromatic ring.

After achieving the synthesis of 1-arylamino-1,2,3-triazoles *via* smooth cyclization, the difficult job was to further modify the triazole to get scaffolds with potential applications. We envisaged that the reduction of nitro group would result in amine which could serve as better scaffold for several applications [25-27]. Surprisingly, when we attempted the reduction of NO_2 group with H_2 , Pd/C in MeOH, we observed N-N bond cleavage of N-arylamino triazole to give 1H-1,2,3-triazole derivatives instead of diamine (Scheme-II).

Reductive cleavage of N-N bond is rarely used in organic synthesis as the methods available require harsh conditions or non-readily available catalyst. Raney Ni and Adam's catalyst ($\text{PtO}_2 \cdot \text{H}_2\text{O}$) have been reported to cleave N-N bond [28-34]. Encouraged by this unusual reductive cleavage of N-N bond, we screened a few 1-arylamino-1,2,3-triazoles to obtain the corresponding 1H-1,2,3-triazole in good yield.

TABLE-1
 SYNTHESIS OF 1-ARYLAMINO-1,2,3-TRIAZOLE^a

Entry	R ₁	R ₂	Substrate	Product
a	OEt	Me		
b	OMe	Me		
c	O-Allyl	Me		
d	Ot-Bu	Me		
e	OBn	Me		
f	OEt	Ph		
g	Me	Me		
h	—	—		
i	—	—		

^aReaction condition: i) β -keto ester (5 mmol), 2,4-DNPH (5.5 mmol), EtOH (15 mL), 50 °C, 1 h; ii) hydrazone (3 mmol), imidazole sulfonyl azide (3.3 mmol), DBU (3.3 mmol), CH₃CN (10 mL) 2 h.

Scheme-II: N-N bond cleavage

Interestingly, 1-arylamino-1,2,3-triazole with acyl group at 4-position was employed for this reduction only –NO₂ group got reduced while N-N bond was intact. Thus we were able to get N-N bond cleavage as well as NO₂ reduction depending on the substituents.

Even though one may expect the role of ketone for the change in the course of the reaction, the electronic effect on the reaction pathway is not well understood. As we were curious to study the driving force behind the N-N bond cleavage, we prepared 1-arylamino-1,2,3-triazole from α -diazo carbonyl compound and phenyl hydrazine following the method reported by Cunha *et al.* [22] and subjected to reduction with H₂, Pd/C. Interestingly, there was no N-N bond cleavage which led us to conclude that the two NO₂ groups on aryl ring pulled the electron density and weakened the N-N bond (Fig. 1).

Fig. 1. Failure of N-N bond cleavage

Conclusion

In conclusion we have synthesized several N-arylamino-1,2,3-triazole derivatives *via* diazo transfer reaction. We have also described the cleavage of N-N bond of N-arylamino-1,2,3-triazole in the presence of H₂, Pd/C. This is an unusual observation and could be utilized in organic synthesis in the future. This protocol could also serve as an alternate method to Huisgen cyclization to get 4,5-disubstituted 1,2,3-triazole with regioselectivity.

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CONFLICT OF INTEREST

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

REFERENCES

- W. Tuo, N. Leleu-Chavain, J. Spencer, S. Sansook, R. Millet and P. Chavatte, *J. Med. Chem.*, **60**, 4 (2017); <https://doi.org/10.1021/acs.jmedchem.6b00538>.
- L.M. De Coen, T.S.A. Heugebaert, D. García and C.V. Stevens, *Chem. Rev.*, **116**, 80 (2016); <https://doi.org/10.1021/acs.chemrev.5b00483>.
- F. Meyer, *Chem. Commun.*, **52**, 3077 (2016); <https://doi.org/10.1039/C5CC09414C>.
- E.A. Burakova, I.V. Saranina, N.V. Tikunova, Z.K. Nazarkina, P.P. Laktionov, L.A. Karpinskaya, V.B. Anikin, V.V. Zarubaev and V.N. Silnikov, *Bioorg. Med. Chem.*, **24**, 6012 (2016); <https://doi.org/10.1016/j.bmc.2016.09.064>.
- P. Martins, J. Jesus, S. Santos, L.R. Raposo, C. Roma-Rodrigues, P.V. Baptista and A.R. Fernandes, *Molecules*, **20**, 16852 (2015); <https://doi.org/10.3390/molecules200916852>.
- D.F. Taber and P.K. Tirunahari, *Tetrahedron*, **67**, 7195 (2011); <https://doi.org/10.1016/j.tet.2011.06.040>.
- X. Li, M. Chen, X. Xie, N. Sun, S. Li and Y. Liu, *Org. Lett.*, **17**, 2984 (2015); <https://doi.org/10.1021/acs.orglett.5b01281>.
- J. Li and L. Neuville, *Org. Lett.*, **15**, 6124 (2013); <https://doi.org/10.1021/ol4029622>.
- J. Thomas, J. John, N. Parekh and W. Dehaen, *Angew. Chem. Int. Ed.*, **126**, 10319 (2014); <https://doi.org/10.1002/ange.201403453>.
- V.S. Pore, M.A. Jagtap, S.G. Agalave, A.K. Pandey, M.I. Siddiqi, V. Kumar and P.K. Shukla, *MedChemComm*, **3**, 484 (2012); <https://doi.org/10.1039/c2md00205a>.
- O.A. Phillips, E.E. Udo, M.E. Abdel-Hamid and R. Varghese, *Eur. J. Med. Chem.*, **44**, 3217 (2009); <https://doi.org/10.1016/j.ejmech.2009.03.024>.
- W.T. Li, W.H. Wu, C.H. Tang, R. Tai and S.T. Chen, *ACS Comb. Sci.*, **13**, 72 (2011); <https://doi.org/10.1021/co1000234>.
- M.S. Costa, N. Boechat, É.A. Rangel, F.C. da Silva, A.M.T. de Souza, C.R. Rodrigues, H.C. Castro, I.N. Junior, M.C.S. Lourenço, S.M.S.V. Wardell and V.F. Ferreira, *Bioorg. Med. Chem.*, **14**, 8644 (2006); <https://doi.org/10.1016/j.bmc.2006.08.019>.
- R. Huisgen, *Angew. Chem.*, **75**, 604 (1963); <https://doi.org/10.1002/ange.19630751304>.
- P.W. Szafranski, P. Kasza and M.T. Cegla, *Tetrahedron Lett.*, **56**, 6244 (2015); <https://doi.org/10.1016/j.tetlet.2015.09.110>.
- V.D. Bock, H. Hiemstra and J.H. Van Maarseveen, *Eur. J. Org. Chem.*, **2006**, 51 (2006); <https://doi.org/10.1002/ejoc.200500483>.
- S.G. Hansen and H.H. Jensen, *Synlett*, 3275 (2009); <https://doi.org/10.1055/s-0029-1218366>.
- P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, **113**, 4905 (2013); <https://doi.org/10.1021/cr200409f>.
- I.E. Valverde, A. Bauman, C.A. Kluba, S. Vomstein, M.A. Walter and T.L. Mindt, *Angew. Chem. Int. Ed.*, **52**, 8957 (2013); <https://doi.org/10.1002/anie.201303108>.
- S.G. Agalave, S.R. Maujan and V.S. Pore, *Chem. Asian J.*, **6**, 2696 (2011); <https://doi.org/10.1002/asia.201100432>.
- G. Kaplan, G. Drake, K. Tollison, L. Hall and T. Hawkins, *J. Heterocycl. Chem.*, **42**, 19 (2005); <https://doi.org/10.1002/jhet.5570420104>.
- A.K. Jordão, P.P. Afonso, V.F. Ferreira, M.C.B.V. de Souza, M.C.B. Almeida, C.O. Beltrame, D.P. Paiva, S.M.S.V. Wardell, J.L. Wardell, E.R.T. Tiekink, C.R. Damaso and A.C. Cunha, *Eur. J. Med. Chem.*, **44**, 3777 (2009); <https://doi.org/10.1016/j.ejmech.2009.04.046>.
- R. Nagarajan, J. Jayashankaran and L. Emmanuvel, *Tetrahedron Lett.*, **57**, 2612 (2016); <https://doi.org/10.1016/j.tetlet.2016.04.112>.
- K. Sarker, R. Patel, C. Dadida, and D. J. Sen, *World. J. Pharm. Res.*, **4**, 2191 (2015).
- T. Schabel, C. Belger and B. Plietker, *Org. Lett.*, **15**, 2858 (2013); <https://doi.org/10.1021/ol401185t>.
- C.W. Cheung and X. Hu, *Nat. Commun.*, **7**, 12494 (2016); <https://doi.org/10.1038/ncomms12494>.
- F. Li, B. Frett and H. Li, *Synlett*, **25**, 1403 (2014); <https://doi.org/10.1055/s-0033-1339025>.
- R. Adams, F.L. Cohen and O.W. Rees, *J. Am. Chem. Soc.*, **49**, 1093 (1927); <https://doi.org/10.1021/ja01403a035>.
- T.L. Gilchrist, D. Hughes and R. Wasson, *Tetrahedron Lett.*, **28**, 1573 (1987); [https://doi.org/10.1016/S0040-4039\(01\)81045-5](https://doi.org/10.1016/S0040-4039(01)81045-5).
- P.A. Jacobi, M.J. Martinelli and S. Polanc, *J. Am. Chem. Soc.*, **106**, 5594 (1984); <https://doi.org/10.1021/ja00331a032>.
- P. Magnus, N. Garizi, K.A. Seibert and A. Ornholdt, *Org. Lett.*, **11**, 5646 (2009); <https://doi.org/10.1021/ol902313v>.
- Q. Tang, C. Zhang and M. Luo, *J. Am. Chem. Soc.*, **130**, 5840 (2008); <https://doi.org/10.1021/ja711153b>.
- Y. Tang, H. Yang, X. Ju, H. Huang, C. Lu and G. Cheng, *J. Mater. Chem.*, **2**, 4127 (2014); <https://doi.org/10.1039/c3ta14485b>.
- I. Pogorelic, M. Filipan-Litvic, S. Merkaš, G. Ljubic, I. Cepanec and M. Litvic, *J. Mol. Catal. Chem.*, **274**, 202 (2007); <https://doi.org/10.1016/j.molcata.2007.05.020>.