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N-Sulfonylketenimines as Useful Synthons in a Novel Synthesis of Functionalized 2-Oxoindoline Derivatives

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The synthesis of a novel class of 2-oxoindolin-3-ylidene-(1-arylhydrazinyl)-2-aryl(alkyl)ethylidene derivatives *via* a copper-catalyzed tandem reaction of isatin, arylhydrazines, sulfonyl azides and terminal alkynes is described.

Keywords: 2-Oxoindolines, Ketenimines, Sulfonyl azide, Terminal alkyne, Isatin

INTRODUCTION

Isatin (indoline-2,3-dione), a natural product found in plants, has been isolated as a metabolic derivative of adrenaline [1,2]. Isatin derivatives show interesting aspects in organic reactions and mechanisms. High reactivity of isatins, their availability and their various biological activities have made them valuable building blocks in organic synthesis [3,4].

Ketenimines are nitrogen-containing heterocumulenes, which have attracted much attention due to their diverse chemistry and relative reactivity. Among the methods for the generation of ketenimines, the Cu-catalyzed azide-alkyne cycloaddition attracted much attention [5,6].

EXPERIMENTAL

General

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500.1 and 125.7 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with $CDCl_3$ as solvent. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

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General Procedure for the Synthesis of Products 6

Isatin **3** (1 mmol) and arylhydrazine **4** (1 mmol) were dissolved in MeCN (2 ml) and stirred for 30 min. Then, a mixture of the sulfonyl azide **2** (1.2 mmol), alkyne **1** (1 mmol), CuI (0.1 mmol) and Et_3N (1 mmol), in MeCN (3 ml) was slowly added and the mixture was stirred at room temperature under N_2 atmosphere. After completion of the reaction [about 6 h; TLC (AcOEt/hexane 1:4) monitoring], diluted with CH_2Cl_2 (2 ml) and aqueous NH_4Cl solution (3 ml), stirred for 30 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 ml) and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel (230-400 mesh; Merck), hexane/AcOEt 4:1] to give the product.

4-Methyl-*N*-(1-((*Z*)-2-(2-oxoindolin-3-ylidene)-1-phenylhydrazinyl)-2-phenylethylidene)benzene-sulfonamide (6a). Yield: 0.42 g 83%; Pale yellow powder; m.p. = 162-164 °C. IR (KBr): ν_{max} 3436, 1623, 1534, 1400, 1319, 1234, 1158, 1021 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 2.48 (3H, s, Me), 4.45 (2H, s, CH_2), 7.29-7.36 (4H, m, Ph), 7.39 (2H, d, ^{3}J = 7.4 Hz, Ar), 7.47-7.51 (7H, m, Ph), 7.60 (1H, t, ^{3}J = 7.5 Hz, Ar), 7.91 (2H, d, ^{3}J = 7.9 Hz, Ar),

7.98 (2H, d, ^3J = 7.9 Hz, Ar), 9.01 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 31.4 (Me), 42.2 (CH_2), 122.6 (C), 127.5 (CH), 128.7 (2CH), 129.0 (2CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 130.7 (CH), 131.6 ($2CH_2$), 131.9 ($2CH_2$), 132.3 (2CH), 132.6 (2CH), 134.4 (CH), 134.5 (C), 140.3 (C), 142.1 (C), 144.6 (C), 147.2 (C), 152.1 (C), 155.5 (C), 164.7 (C). MS (EI, 70 eV): *m/z* (%) = 508 (M^+, 2), 431 (10), 417 (16), 353 (19), 272 (23), 155 (100), 91 (70), 77 (54). Anal. calcd for $C_{29}H_{24}N_4O_3S$ (508.16): C, 68.49; H, 4.76; N, 11.02%. Found: C, 68.99; H, 4.39; N, 11.22%.

***N*-(1-((Z)-2-(2-Oxoindolin-3-ylidene)-1-phenylhydrazinyl)-2-phenylethylidene)benzenesulfonamide (6b).** Yield: 0.43 g 87%; Pale yellow powder; m.p.: 143-145 °C. IR (KBr): ν_{max} 3430, 1633, 1504, 1405, 1329, 1222, 1156, 1018 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 4.48 (2H, s, CH_2), 7.01 (2H, d, ^3J = 7.7 Hz, Ar), 7.21 (1H, t, ^3J = 7.4 Hz, Ar), 7.29-7.35 (4H, m, Ph), 7.38 (1H, d, ^3J = 7.4 Hz, Ar), 7.40-7.44 (3H, m, Ph), 7.48-7.52 (4H, m, Ph), 7.64 (1H, t, ^3J = 7.5 Hz, Ar), 7.93 (2H, t, ^3J = 7.9 Hz, Ar), 8.22 (1H, d, ^3J = 7.9 Hz, Ar), 9.51 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 44.8 (CH_2), 122.2 (C), 124.6 (CH), 128.0 (2CH), 128.1 (2CH), 129.0 (CH), 129.3 (CH), 129.6 (CH), 130.0 ($2CH_2$), 130.9 ($2CH_2$), 131.3 (CH), 132.4 (2CH), 132.8 (2CH), 134.5 (CH), 136.8 (CH), 140.1 (C), 141.6 (C), 145.6 (C), 148.2 (C), 153.5 (C), 157.2 (C), 161.5 (C). MS (EI, 70 eV): *m/z* (%) = 494 (M^+, 3), 417 (6), 353 (10), 145 (24), 141 (100), 91 (48), 77 (50). Anal. Calcd. for $C_{28}H_{22}N_4O_3S$ (494.14): C, 68.00; H, 4.48; N, 11.33%. Found: C, 68.32; H, 4.15; N, 11.38%.

***N*-(1-((Z)-2-(2-Oxoindolin-3-ylidene)-1-phenylhydrazinyl)-2-phenylethylidene)methanesulfonamide (6c).** Yield: 0.34 g 79%; Pale yellow powder; m.p.: 122-125 °C. IR (KBr): ν_{max} 3389, 1692, 1541, 1426, 1339, 1265, 1162, 1025 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 3.65 (3H, s, Me), 4.45 (2H, s, CH_2), 7.20-7.36 (6H, m, Ph), 7.47-7.50 (5H, m, Ph), 7.61 (1H, t, ^3J = 7.5 Hz, Ar), 7.97 (2H, d, ^3J = 7.9 Hz, Ar), 9.15 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 31.5 (Me), 43.0 (CH_2), 122.5 (C), 128.8 (2CH), 129.2 (CH), 129.3 (2CH), 129.4 (2CH), 132.5 (2CH), 133.2 (CH), 133.3 (CH), 134.1 (2CH), 134.4 (CH), 136.1 (C), 137.6 (C), 145.2 (C), 152.7 (C), 156.8 (C), 164.7 (C). MS (EI, 70 eV): *m/z* (%) = 432 (M^+, 4), 355 (8), 353 (11), 287 (34), 245 (32), 91 (45), 78 (100), 77 (70). Anal. Calcd. For $C_{23}H_{20}N_4O_3S$ (432.49): C, 63.87; H, 4.66; N, 12.95%. Found: C, 63.12; H, 4.80; N, 12.31%.

4-Methyl-*N*-(1-((Z)-1-(4-nitrophenyl)-2-(2-oxoindolin-3-ylidene)hydrazinyl)-2-phenylethylidene)benzenesulfonamide (6d). Yield: 0.43 g 78%; Pale yellow powder; m.p. = 188-190 °C. IR (KBr): ν_{max} 3339, 1625, 1530, 1489, 1329, 1276, 1188, 1001 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 2.40 (3H, s, Me), 4.42 (2H, s, CH_2), 6.92 (2H, d, ^3J = 7.5 Hz, Ar), 7.28-7.34 (5H, m, Ph), 7.49-7.55 (6H, m, Ph), 7.83 (2H, d, ^3J = 7.5 Hz, Ar), 8.01 (1H, d, ^3J = 7.9 Hz, Ar), 8.22 (1H, d, ^3J = 7.9 Hz, Ar), 9.42 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 31.0 (Me), 42.9 (CH_2), 122.4 (C), 127.9 (CH), 128.1 (2CH), 129.1 (2CH), 129.2 (CH), 129.4 (C), 129.8 (CH), 130.0 (CH), 131.9 ($2CH_2$), 132.2 ($2CH_2$), 133.3 (2CH), 133.9 (2CH), 134.9 (CH), 136.5 (C), 141.3 (C), 144.1 (C), 146.6 (C), 149.2 (C), 155.4 (C), 160.1 (C), 162.8 (C). MS (EI, 70 eV): *m/z* (%) = 553 (M^+, 2), 462 (10), 431 (30), 398 (16), 155 (100), 145 (32), 91 (70), 77 (40). Anal. Calcd. for $C_{29}H_{23}N_5O_5S$ (553.59): C, 62.92; H, 4.19; N, 12.65%. Found: C, 63.09; H, 4.70; N, 12.82%.

***N*-(1-((Z)-1-(4-Nitrophenyl)-2-(2-oxoindolin-3-ylidene)hydrazinyl)-2-phenylethylidene)benzenesulfonamide (6e).** Yield: 0.41 g 76%; Pale yellow powder; m.p. = 179-181 °C. IR (KBr): ν_{max} 3421, 1673, 1592, 1464, 1339, 1275, 1158, 1018 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 4.47 (2H, s, CH_2), 6.99 (2H, d, ^3J = 7.7 Hz, Ar), 7.33 (2H, d, ^3J = 7.4 Hz, Ar), 7.49-7.58 (8H, m, Ph), 7.63 (1H, t, ^3J = 7.4 Hz, Ar), 7.95-8.03 (4H, m, Ph), 8.22 (1H, d, ^3J = 7.9 Hz, Ar), 9.62 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 44.6 (CH_2), 122.4 (C), 124.8 (CH), 128.2 (2CH), 128.7 (2CH), 129.0 (CH), 129.5 (CH), 129.6 (CH), 130.2 ($2CH_2$), 131.4 ($2CH_2$), 131.9 (CH), 132.9 (2CH), 133.5 (2CH), 134.2 (CH), 138.7 (C), 140.6 (C), 144.9 (C), 145.3 (C), 148.2 (C), 157.1 (C), 159.1 (C), 162.4 (C). MS (EI, 70 eV): *m/z* (%) = 539 (M^+, 2), 448 (6), 398 (10), 145 (18), 141 (100), 122 (48), 91 (64), 77 (52). Anal. Calcd. for $C_{28}H_{21}N_5O_5S$ (539.13): C, 62.33; H, 3.92; N, 12.98%. Found: C, 62.13; H, 4.05; N, 12.87%.

***N*-(1-((Z)-1-(4-Nitrophenyl)-2-(2-oxoindolin-3-ylidene)hydrazinyl)-2-phenylethylidene)methanesulfonamide (6f).** Yield: 0.35 g 73%; Pale yellow powder; m.p. = 150-153 °C. IR (KBr): ν_{max} 3408, 1672, 1544, 1439, 1333, 1256, 1160, 1020 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 3.11 (3H, s, Me), 4.50 (2H, s, CH_2), 6.91 (2H, d, ^3J =

7.9 Hz, Ar), 7.22-7.26 (3H, m, Ph), 7.31 (2H, d, ^3J = 7.9 Hz, Ar), 7.38 (2H, t, ^3J = 7.9 Hz, Ar), 7.41 (2H, d, ^3J = 7.5 Hz, Ar), 7.80 (1H, d, ^3J = 7.9 Hz, Ar), 8.02 (1H, d, ^3J = 7.9 Hz, Ar), 9.07 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 31.3 (Me), 43.9 (CH_2), 123.4 (C), 128.5 (2CH), 129.0 (CH), 129.2 (2CH), 129.3 (2CH), 132.9 (2CH), 133.8 (CH), 134.3 (CH), 134.9 (2CH), 135.8 (C), 136.1 (C), 138.8 (C), 145.2 (C), 152.9 (C), 156.0 (C), 164.4 (C). MS (EI, 70 eV): *m/z* (%) = 477 (M^+, 4), 398 (9), 386 (11), 355 (21), 145 (34), 91 (41), 78 (100), 77 (70). Anal. Calcd. for $C_{23}H_{19}N_5O_5S$ (477.11): C, 57.85; H, 4.01; N, 14.67%. Found: C, 57.12; H, 4.45; N, 14.17%.

4-Methyl-*N*-(1-((Z)-2-(2-oxoindolin-3-ylidene)-1-phenylhydrazinyl)hexylidene)benzenesulfonamide (6g). Yield: 0.34 g 69%; Pale yellow oil; IR (KBr): ν_{max} 3332, 1685, 1577, 1489, 1320, 1273, 1138, 1032 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 0.92 (3H, t, ^3J = 6.8 Hz, Me), 1.32-1.37 (2H, m, CH_2), 1.41-1.47 (2H, m, CH_2), 2.07-2.10 (2H, m, CH_2), 2.40 (3H, s, Me), 2.92 (2H, t, ^3J = 6.8 Hz, CH_2), 7.16 (2H, d, ^3J = 7.5 Hz, Ar), 7.23 (1H, t, ^3J = 7.5 Hz, Ar), 7.31 (2H, t, ^3J = 7.5 Hz, Ar), 7.37 (2H, d, ^3J = 7.5 Hz, Ar), 7.42-7.46 (2H, m, Ph), 7.57 (2H, d, ^3J = 7.5 Hz, Ar), 8.07 (1H, d, ^3J = 7.9 Hz, Ar), 8.26 (1H, d, ^3J = 7.9 Hz, Ar), 9.01 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.4 (Me), 17.1 (CH_2), 21.4 (CH_2), 21.5 (CH_2), 30.0 (Me), 38.2 (CH_2), 126.4 (CH), 127.1 (2CH), 127.9 (2CH), 128.0 (CH), 128.4 (C), 129.0 (CH), 130.2 (CH), 131.4 (2CH), 133.9 (2CH), 134.9 (CH), 141.2 (C), 143.0 (C), 145.5 (C), 147.3 (C), 155.4 (C), 159.6 (C), 161.5 (C). MS (EI, 70 eV): *m/z* (%) = 488 (M^+, 1), 417 (7), 343 (20), 155 (100), 145 (22), 91 (70), 77 (41), 71 (55). Anal. calcd for $C_{27}H_{28}N_4O_3S$ (488.19): C, 66.37; H, 5.78; N, 11.47%. Found: C, 66.19; H, 5.90; N, 11.16%.

***N*-(1-((Z)-2-(2-Oxoindolin-3-ylidene)-1-phenylhydrazinyl)hexylidene)methanesulfonamide (6h).** Yield: 0.27 g 65%; Pale yellow oil; IR (KBr): ν_{max} 3338, 1683, 1587, 1480, 1321, 1289, 1136, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 0.94 (3H, t, ^3J = 6.8 Hz, Me), 1.33-1.36 (2H, m, CH_2), 1.40-1.46 (2H, m, CH_2), 2.04-2.07 (2H, m, CH_2), 2.90 (2H, t, ^3J = 6.8 Hz, CH_2), 3.61 (3H, s, Me), 7.17 (2H, d, ^3J = 7.5 Hz, Ar), 7.25 (1H, t, ^3J = 7.5 Hz, Ar), 7.34 (2H, t, ^3J = 7.5 Hz, Ar), 7.55 (1H, t, ^3J = 7.5 Hz, Ar), 7.64 (1H, t, ^3J = 7.5 Hz, Ar), 8.03 (1H, d, ^3J = 7.9 Hz, Ar), 8.27 (1H, d, ^3J = 7.9 Hz, Ar), 9.18 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 13.2 (Me), 17.7 (CH_2), 22.7 (CH_2), 23.0 (CH_2), 30.8 (Me), 38.5 (CH_2), 126.9 (CH), 127.9 (2CH), 128.0 (2CH), 129.2 (CH), 130.5 (CH), 131.9 (CH), 132.0 (C), 134.8 (CH), 145.7 (C), 147.3 (C), 155.2 (C), 159.5 (C), 164.7 (C). MS (EI, 70 eV): *m/z* (%) = 412 (M^+, 3), 341 (9), 333 (17), 267 (25), 145 (44), 78 (100), 71 (49). Anal. Calcd. for $C_{21}H_{24}N_4O_3S$ (412.16): C, 61.14; H, 5.86; N, 13.58 %. Found: C, 61.32; H, 5.97; N, 13.03%.

RESULTS AND DISCUSSION

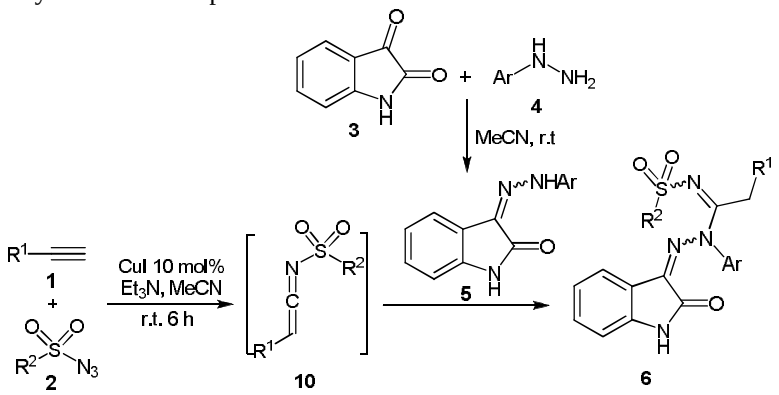
The formation of ketenimine intermediates from terminal alkynes and sulfonyl azides, in the presence of copper catalysts has encouraged us to trap these intermediates using nucleophilic addition reactions [7-9]. Herein, we report an efficient procedures for the synthesis of 2-oxoindolin-3-ylidene-(1-arylhydrazinyl)-2-aryl(alkyl)ethylidene derivatives **6** containing a sulfonamide group *via* the Cu-catalyzed four-component tandem reaction of terminal alkyne **1**, sulfonyl azides **2**, isatin (**3**) and arylhydrazines (**4**), in moderate to good yields (Table 1).

Initially, phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), isatin (**3**) and phenylhydrazine (**4a**), were selected as the model substrates. Several catalysts such as CuI, CuCl, CuBr and copper powder were tested with CuI giving the best results. Among several solvents screened, MeCN was the best. When the reaction was performed in MeCN in the presence of 1 equiv. of triethylamine at room temperature for six hours, it was found that the desired product **6a** was obtained in 83% yield (Table 1). Thus, the optimized reaction conditions used were 10 mol% of CuI, 1 mmol of alkyne, 1.2 mmol of sulfonyl azide, 1 mmol of phenylhydrazine and 1 mmol of isatin in MeCN at room temperature.

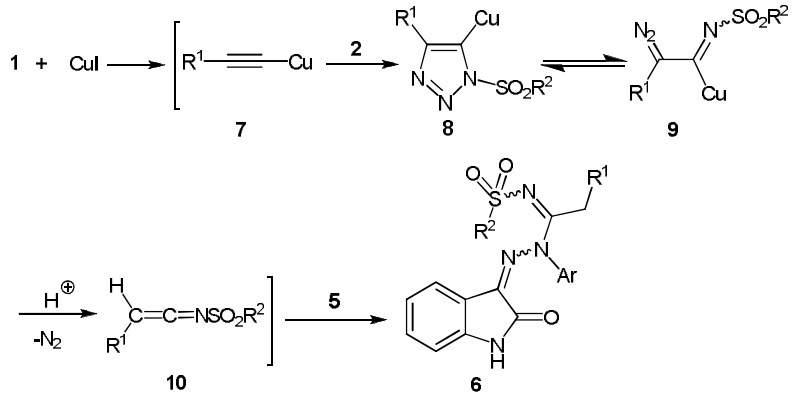
Phenylacetylene readily participates in the coupling to furnish products **6a-f** in good yields (Table 1). Aliphatic acetylenes served as low yielding substrates compared to phenylacetylene. Aromatic and aliphatic sulfonyl azides reacted efficiently.

Structures of products **6a-h** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectrum of **6a** exhibited three singlets for methyl (2.48 ppm), methylene (4.45 ppm) and NH (9.01 ppm) protons, along with characteristic multiplets for the aromatic protons.

Table1. Synthesis of Compounds **6a-h**



Entry	**1-6**	R^1	R^2	Ar	Yield of **6** (%)
1	**a**	Ph	Tol	Ph	83
2	**b**	Ph	Ph	Ph	87
3	**c**	Ph	Me	Ph	79
4	**d**	Ph	Tol	4-O_2N-C_6H_4	78
5	**e**	Ph	Ph	4-O_2N-C_6H_4	76
6	**f**	Ph	Me	4-O_2N-C_6H_4	73
7	**g**	*n*-Bu	Tol	Ph	69
8	**h**	*n*-Bu	Me	Ph	65



Scheme 1. A plausible mechanism for the formation of products **6**

The ^{13}C NMR spectrum of **6a** exhibits 23 signals in agreement with the proposed structure. The mass spectrum of **6a** displayed the molecular ion peak at *m*/*z* = 508. The NMR spectra of compounds **6b-h** are similar to those of **6a**, except for the substituents, which showed characteristic signals in the appropriate regions of the spectra.

A plausible mechanism for the formation of products **6** is given in Scheme 1. The yellow copper acetylide **7**, formed from **1** and CuI, is converted to ketenimine **10** by well-documented transformations [10-12]. Intermediate **10** undergoes nucleophilic addition reaction with **5**, generated *in situ* from **3** and **4**, to give product **6**.

In conclusion, we have developed a multicomponent protocol for the synthesis of a novel class of 2-oxoindolin-3-ylidene-(1-arylhydrazinyl)-2-aryl(alkyl)ethylidene derivatives *via* a Cu-catalyzed tandem reaction of isatin,

arylhydrazines, sulfonyl azides and terminal alkynes.

REFERENCES

[1] I. Chiyanzu, E. Hansell, J. Gut, P.J. Rosenthal, J.H. Mckerrowb, K. Chibale, Bioorg. Med. Chem. Lett. 13 (2003) 3527.

[2] M.R. Almeida, G.G. Leitao, B.V. Silva, J.P. Barbosa, A. Pinto, J. Braz. Chem. Soc. 21 (2012) 764.

[3] T. Jiang, K.L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Tuntlad, K. Zhang, D. Karanewsky, Y. He, Bioorg. Med. Chem. Lett. 16 (2006) 2109.

[4] T. Aboul-Fadl, F.A.S. Bin-Jubair, Int. J. Res. Pharm. Sci. 1 (2010) 113.

[5] P. Lu, Y.G. Wang, Synlett 2 (2010) 166.

[6] S.H. Kim, S.H. Park, J.H. Choi, S. Chang, Chem. Asian. J. 6 (2011) 2618.

[7] I. Yavari, A. Sheikhi, M. Nematpour, Z. Taheri, Synth. Commun. 2014, Accepted.

[8] I. Yavari, M. Nematpour, E. Sodagar, Synlett 24 (2013) 161.

[9] I. Yavari, M. Nematpour, S. Yavari, F. Sadeghizadeh, Tetrahedron Lett. 53 (2012) 1889.

[10] Fokin, V.; Sharpless, K. B.; Chang, S. Angew. Chem. Int. Ed. 2007, 46, 1730.

[11] E.J. Yoo, S. Chang, Curr. Org. Chem. 13 (2009) 1766.

[12] M. Meldal, C. Tornoe, Chem. Rev. 108 (2008) 2952.