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Synthesis of 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide via three-component reaction of trichloroacetyl isocyanate, (*N*-isocyanimino)triphenylphosphorane, and benzoic acid derivatives

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Abstract: The three-component reaction of benzoic acid derivatives, (*N*-isocyanimino)triphenylphosphorane, and trichloroacetyl isocyanate in a 1:1:1 ratio in CH_3CN occurred at room temperature, and the 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide derivatives produced were formed in high yields. The reaction proceeded smoothly and cleanly under mild reaction conditions and no side reactions were observed. The structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and elemental analysis.

Key words: Multicomponent reactions, 1,3,4-oxadiazoles, trichloroacetyl isocyanate, (*N*-isocyanimino)triphenylphosphorane, aza-Wittig

1. Introduction

Multicomponent reaction processes, in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the components, naturally comply with many of these stringent requirements for ideal organic syntheses.[1] Multicomponent reactions can be applied for the synthesis of various heterocycles.[2–5] 1,3,4-Oxadiazoles are heterocyclic compounds with two nitrogen atoms and one oxygen atom in a five membered ring. 1,3,4-Oxadiazoles are important heterocycles, because they have broad biological activities such as antiviral,[6] antibacterial,[7] antitumor,[8] antituberculosis,[9] anti-inflammatory,[10] anticonvulsant,[11] and anti-Alzheimer activities.[12] There have been many efforts towards the synthesis and investigation of biological activities of 1,3,4-oxadiazole derivatives in the last two decades. Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles such as reaction of acylhydrazines with isothiocyanates, reaction of carboxylic acids with acid hydrazides, reaction of hydrazide with carbon disulfide in basic medium, cyclodehydration reaction of diacylhydrazines, reaction of hydrazides with orthoesters, cyclization oxidative reaction of *N*-acylhydrazones, and reaction of *N*-acylbenzotriazoles with acyl hydrazides.[13–20] Recently, a one-pot method for the synthesis of 1,3,4-oxadiazole derivatives from (*N*-isocyanoimino)triphenylphosphorane has been reported.[21–25] No procedure has been reported for the synthesis of 1,3,4-oxadiazoles by multicomponent reaction of (*N*-isocyanimino)triphenylphosphorane in the presence of trichloroacetyl isocyanate, and thus, in connection with our interest in the synthesis of heterocycles,[26–28] we report a three-component reaction of benzoic acid derivatives (**1**), (*N*-isocyanimino)triphenylphosphorane

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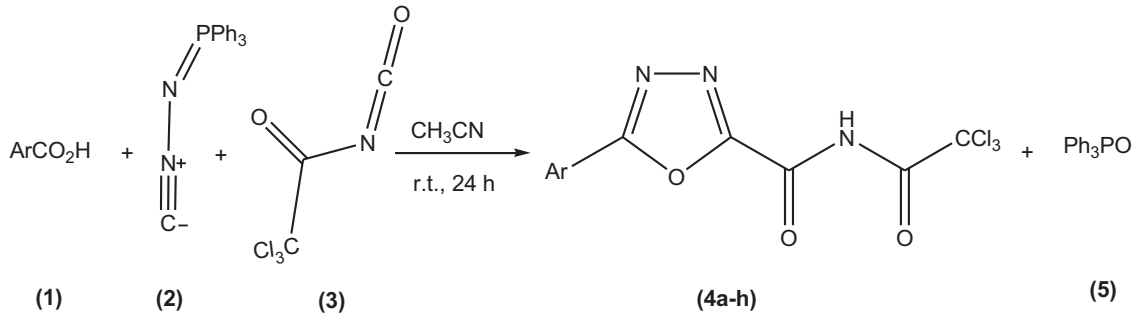
(**2**), and trichloroacetyl isocyanate (**3**) leading to 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide derivatives (**4**).

2. Results and discussion

The benzoic acid derivatives (**1**), (*N*-isocyanimino)triphenylphosphorane (**2**), and trichloroacetyl isocyanate (**3**) reacted in a 1:1:1 ratio in CH_3CN at room temperature via a three-component reaction to give 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide derivatives (**4a**–**h**) (Scheme 1; Table). The structures of the products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analyses. For example, the ^{1}H NMR spectrum of **4a** exhibited distinct signals arising from 4 aromatic CH as two doublets (δ_H = 7.67 and 7.95), and a NH as a singlet (δ_H = 8.50). The ^{13}C NMR spectrum of **4a** showed 9 distinct resonances arising from the CCl_3 (δ_C = 91.78), C=C (δ_C = 122.31, 128.51, 131.60, and 132.52), C=N (δ_C = 152.70 and 152.84), and C=O (δ_C = 163.87 and 164.16). The IR spectrum of **4a** showed a NH stretching vibration at 3393 cm^{-1}. The mass spectrum of **4a** showed a molecular ion peak at m/z 411.

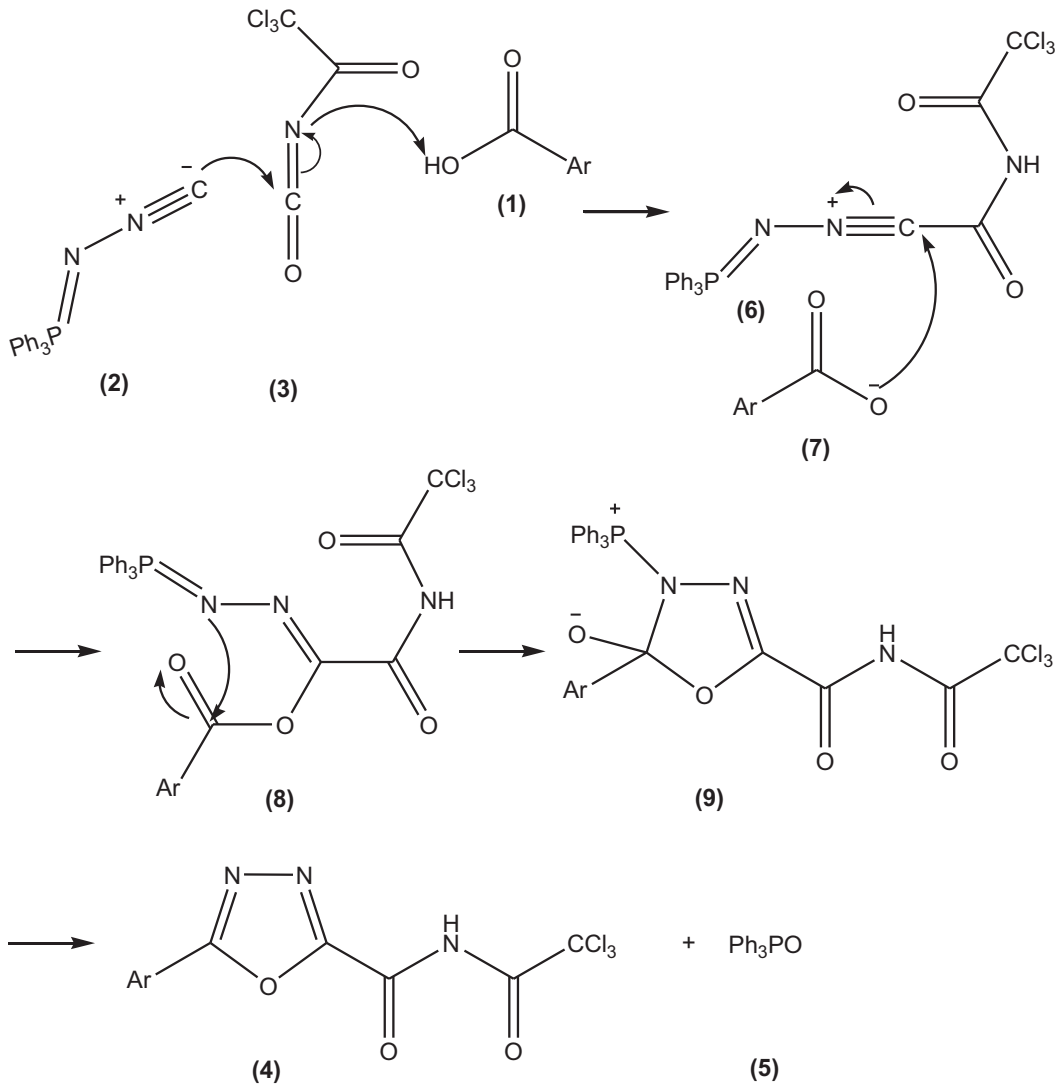


Scheme 1. Three-component reaction of (*N*-isocyanimino)triphenylphosphorane, trichloroacetyl isocyanate, and benzoic acid derivatives (see Table).

Table. Synthesis of 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide derivatives.

Compounds	Ar	Yield [%]	Compounds	Ar	Yield [%]
4a	4-BrC_6H_4	88	**4e**	4-MeC_6H_4	85
4b	4-ClC_6H_4	86	**4f**	3-MeC_6H_4	90
4c	4-FC_6H_4	83	**4g**	4-*t*-BuC_6H_4	83
4d	C_6H_5	81	**4h**	4-$BrCH_2C_6H_4$	80

A mechanistic rationalization for this reaction is depicted in Scheme 2. Nucleophilic addition of (*N*-isocyanimino)triphenylphosphorane (**2**) to trichloroacetyl isocyanate (**3**), which is facilitated by its protonation with the carboxylic acid **1** leads to the nitrilium intermediate **6**. This intermediate may be attacked by the conjugate base of the carboxylic acid **7** to form the adduct **8**. The adduct **8** may undergo an intramolecular aza-Wittig reaction of the iminophosphorane moiety with the ester carbonyl to afford the 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide derivatives (**4**) by removal of triphenylphosphine oxide (**5**) from intermediate **9**.



Scheme 2. A proposed mechanism for the formulation of 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide derivatives.

3. Conclusions

The reported method offers a mild, simple, and efficient route for the preparation of 5-aryl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide derivatives via a three-component reaction of benzoic acid derivatives, (*N*-isocyanimino)triphenylphosphorane, and trichloroacetyl isocyanate in high yields and under fairly mild reaction conditions.

4. Experimental

The starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were recorded on a Jasco FT-IR 6300 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-250 Avance spectrometer at 250.0 and 62.9 MHz,

respectively. The elemental analyses were realized using a Heraeus CHN-O-rapid analyzer. Mass spectra were recorded on an Agilent Technology (HP) 5973 mass spectrometer operating at an ionization potential of 70 eV.

5. General procedure for the preparation of 4

To a magnetically stirred solution of (*N*-isocyanimino)triphenylphosphorane (**2**) (1 mmol) and trichloroacetyl isocyanate (**3**) (1 mmol) in CH_3CN (7 mL) was added dropwise at room temperature a solution of benzoic acid derivatives (**1**) (1 mmol) in CH_3CN (5 mL) over 15 min. The mixture was stirred for 24 h. The solvent was removed under reduced pressure, and the viscous residue was purified by preparative thin layer chromatography using silica gel powder and petroleum ether:ethyl acetate as solvent (10:3). The solvent was removed under reduced pressure and the pure products were obtained.

The characterization data of the compounds are given below:

5-(4-Bromophenyl)-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4a)

White plate crystals; Yield: 88%. mp 102.6–104.8 °C; *Anal.* calcd. for $C_{11}H_5BrCl_3N_3O_3$ (413.44): C, 31.96; H, 1.22; N, 10.16%; Found: C, 32.03; H, 1.17; N, 10.11%; IR: υ_{max} 3393 (NH), 1699 (C=O), 1605 (C=N), 1382, 1109, 830, 757, 649, 617, 440 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 8.50 (s, 1H, NH), 7.95 (d, $^3J_{HH}$ = 8.4 Hz, 2H, arom CH), 7.67 (d, $^3J_{HH}$ = 8.4 Hz, 2H, arom CH) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 163.87 and 164.16 (2C=O), 152.70 and 152.84 (2C=N), 128.51 and 132.52 (4CH, arom), 122.31 and 131.60 (2C, arom), 91.78 (CCl_3) ppm; MS (EI): m/z411 (M^+, 0.35), 404 (6.48), 375 (5.48), 171 (100), 169 (82.6), 90 (22.3).

5-(4-Chlorophenyl)-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4b)

White plate crystals; Yield: 86%. mp 110.5–112.3 °C; *Anal.* calcd. for $C_{11}H_5Cl_4N_3O_3$ (368.99): C, 35.81; H, 1.37; N, 11.39%. Found: C, 35.86; H, 1.42; N, 11.35%. IR: υ_{max} 3374 (NH), 1694 (C=O), 1607 (C=N), 1385, 1107, 832, 760, 649, 618, 439 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 8.49 (s, 1H, NH), 8.02 (d, $^3J_{HH}$ = 8.0 Hz, 2H, arom CH), 7.51(d, $^3J_{HH}$ = 8.0 Hz, 2H, arom CH) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 163.85 and 164.03 (2C=O), 151.07 and 152.75 (2C=N), 128.39 and 129.56 (4CH, arom), 121.88 and 138.40 (2C, arom), 91.77 (CCl_3) ppm.

5-(4-Fluorophenyl)-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4c)

White needle crystals; Yield: 83%. mp 136.7–138.8 °C; *Anal.* calcd. for $C_{11}H_5Cl_3FN_3O_3$ (352.53): C, 37.48; H, 1.43; N, 11.92%. Found: C, 37.42; H, 1.47; N, 11.85%. IR: υ_{max} 3374 (NH), 1698 (C=O), 1606 (C=N), 1384, 1109, 832, 754, 649, 614, 439 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.50 (s, 1H, NH), 7.13–7.25 and 8.04–8.16 (2m, 4H, arom CH) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 164.35 and 166.98 (2C=O), 166.18 (d, $^1J_{CF}$ = 255.1 Hz, C, arom), 152.66 and 152.79 (2C=N), 129.44 (d, $^3J_{CF}$ = 8.8 Hz, 2CH, arom), 119.76 (d, $^4J_{CF}$ = 3.6 Hz, C, arom), 116.51 (d, $^2J_{CF}$ = 22.0 Hz, 2CH, arom), 91.78 (CCl_3) ppm.

5-Phenyl-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4d)

White plate crystals; Yield: 81%. mp 105.2–107.4 °C; *Anal.* calcd. for $C_{11}H_6Cl_3N_3O_3$ (334.54): C, 39.49; H, 1.81; N, 12.56%. Found: C, 39.42; H, 1.83; N, 12.62%. IR: υ_{max} 3374 (NH), 1695 (C=O), 1615 (C=N),

1384, 1109, 832, 750, 649, 616, 439 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.52 (s, 1H, NH), 7.38–8.18 (m, 5H, arom CH) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 164.26 and 165.50 (2C=O), 151.54 and 153.72 (2C=N), 129.36, 128.49, 130.16, and 133.73 (aromatic carbons), 91.72 (CCl_3) ppm.

5-(4-Methylphenyl)-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4e)

White needle crystals; Yield: 85%. mp 106.9–108.8 °C; *Anal.* calcd. for $C_{12}H_8Cl_3N_3O_3$ (348.57): C, 41.35; H, 2.31; N, 12.06%. Found: C, 41.28; H, 2.33; N, 12.12%. IR: υ_{max} 3381 (NH), 1699 (C=O), 1611 (C=N), 1383, 1105, 830, 731, 648, 612, 442 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.50 (s, 1H, NH), 7.99 (d, $^3J_{HH}$ = 8.2 Hz, 2H, arom CH), 7.35 (d, $^3J_{HH}$ = 8.2 Hz, 2H, arom CH), 2.46 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 163.93 and 164.97 (2C=O), 152.52 and 154.80 (2C=N), 127.09 and 129.87 (4CH, arom), 120.65 and 142.70 (2C, arom), 91.88 (CCl_3), 21.69 (CH_3) ppm.

5-(3-Methylphenyl)-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4f)

White plate crystals; Yield: 90%. mp 136.4–138.3 °C; *Anal.* calcd. for $C_{12}H_8Cl_3N_3O_3$ (348.57): C, 41.35; H, 2.31; N, 12.06%. Found: C, 41.40; H, 2.28; N, 12.09%. IR: υ_{max} 3374 (NH), 1699 (C=O), 1619 (C=N), 1383, 1109, 831, 751, 649, 615, 476 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.51 (s, 1H, NH), 7.38–7.46 and 7.89–7.94 (2m, 4H, arom CH), 2.47 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 163.91 and 164.84 (2C=O), 152.25 and 154.56 (2C=N), 124.28, 127.67, 129.07, and 132.91 (4CH, arom), 123.29 and 139.10 (2C, arom), 91.84 (CCl_3), 21.36 (CH_3) ppm.

5-[4-(tert-Butyl)phenyl]-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4g)

White needle crystals; Yield: 83%. mp 135.6–137.5 °C; *Anal.* calcd. for $C_{15}H_{14}Cl_3N_3O_3$ (390.65): C, 46.12; H, 3.61; N, 10.76%. Found: C, 46.18; H, 3.63; N, 10.72%. IR: υ_{max} 3423 (NH), 1695 (C=O), 1618 (C=N), 1378, 1102, 826, 752, 650, 472 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.48 (s, 1H, NH), 8.04 (d, $^3J_{HH}$ = 8.4 Hz, 2H, arom CH), 7.57 (d, $^3J_{HH}$ = 8.4 Hz, 2H, arom CH), 1.39 (s, 9H, *t*-Bu) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 162.62 and 166.50 (2C=O), 152.45 and 155.69 (2C=N), 134.23 and 143.75 (2C, arom), 126.15 and 126.97 (4CH, arom), 91.86 (CCl_3), 35.14 ($C(CH_3)_3$), 31.12 ($C(CH_3)_3$) ppm.

5-[4-(Bromomethyl)phenyl]-*N*-(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide (4h)

White needle crystals; Yield: 80%. mp 138.6–140.9 °C (dec); *Anal.* calcd. for $C_{12}H_7BrCl_3N_3O_3$ (427.47): C, 33.72; H, 1.65; N, 9.83%. Found: C, 33.68; H, 1.67; N, 9.77%. IR: υ_{max} 3437 (NH), 1685 (C=O), 1618 (C=N), 1097, 850, 711, 641, 604 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.51 (s, 1H, NH), 8.10 (d, $^3J_{HH}$ = 8.4 Hz, 2H, arom CH), 7.58 (d, $^3J_{HH}$ = 8.4 Hz, 2H, arom CH), 4.56 (s, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 163.62 and 166.80 (2C=O), 152.71 and 154.62 (2C=N), 127.58 and 129.83 (4CH, arom), 123.40 and 141.82 (2C, arom), 92.10 (CCl_3), 32.16 (CH_2Br) ppm.

References

1. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
2. Eckert, H. *Molecules* **2012**, *17*, 1074–1102.

3. Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323–8359.
4. Nenajdenko, V. G. *Isocyanide Chemistry*; Wiley-VCH: Weinheim, Germany, 2012.
5. Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
6. Li, Z.; Zhan, P.; Liu, X. *Mini-Rev. Med. Chem.* **2011**, *11*, 1130–1142.
7. Joshi, D.; Parikh, K. S. *Med. Chem. Res.* **2014**, *23*, 1855–1864.
8. Bondock, S.; Adel, S.; Etman, H. A.; Badria, F. A. *Eur. J. Med. Chem.* **2012**, *48*, 192–199.
9. Patel, R. V.; Kumari, P.; Chikhalia, K. H. *Med. Chem.* **2013**, *9*, 596–607.
10. Sahoo, B. M.; Dinda, S. C.; Ravi Kumar, B. V.V.; Panda, J.; Brahmkshatriya, P. S. *Lett. Drug Des. Discovery* **2014**, *11*, 82–89.
11. Gupta, A.; Kashaw, S. K.; Jain, N.; Rajak, H.; Soni, A.; Stables, J. P. *Med. Chem. Res.* **2011**, *20*, 1638–1642.
12. Saitoh, M.; Kunitomo, J.; Kimura, E.; Hayase, Y.; Kobayashi, H.; Uchiyama, N.; Kawamoto, T.; Tanaka, T.; Mol, C. D.; Dougan, D. R.; et al. *Bioorg. Med. Chem.* **2009**, *17*, 2017–2029.
13. Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett.* **2004**, *45*, 3257–3260.
14. Yang, S.-J.; Lee, S.-H.; Kwak, H.-J.; Gong, Y.-D. *J. Org. Chem.* **2013**, *78*, 438–444.
15. Brown, B. J.; Clemens, I. R.; Neesom, J. K. *Synlett* **2000**, 131–133.
16. Park, Y.-D.; Kim, J.-J.; Chung, H.-A.; Kweon, D.-H.; Cho, S.-D.; Lee, S.-G.; Yoon, Y.-J. *Synthesis* **2003**, 560–564.
17. Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275–3278.
18. Patel, K. N.; Jadhav, N. C.; Jagadhane, P. B.; Telvekar, V. N. *Synlett* **2012**, *23*, 1970–1972.
19. Oliveira, C. S.; Lira, B. F.; Barbosa-Filho, J. M.; Lorenzo, J. G. F; Athayde-Filho, P. F. *Molecules* **2012**, *17*, 10192–10231.
20. Katritzky, A. R.; Mohapatra, P. P.; Huang, L. *Arkivoc* **2008**, *ix*, 62–68.
21. Adib, M.; Sheikhi, E.; Karimzadeh, M.; Bijanzadeh, H. R.; Amanlou, M. *Helv. Chim. Acta* **2012**, *95*, 788–794.
22. Ramazani, A.; Ahmadi, Y.; Rouhani, M.; Shajari, N.; Souldozi, A. *Heteroat. Chem.* **2010**, *21*, 368–372.
23. Ramazani, A.; Rouhani, M.; Rezaei, A.; Shajari, N.; Souldozi, A. *Helv. Chim. Acta* **2011**, *94*, 282–288.
24. Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Synthesis* **2010**, 4082–4086.
25. Adib, M.; Riazati Kesheh, M.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2009**, 1575–1578.
26. Shajari, N.; Kazemizadeh, A. R.; Ramazani, A. *J. Serb. Chem. Soc.* **2012**, *77*, 1175–1180.
27. Ramazani, A.; Shajari, N.; Mahyari, A.; Ahmadi, Y. *Mol. Divers.* **2011**, *15*, 521–527.
28. Kazemizadeh, A. R.; Hajaliakbari, N.; Hajian, R.; Shajari, N.; Ramazani, A. *Helv. Chim. Acta* **2012**, *94*, 594–597.