

## Expedient phosgene-free synthesis of symmetrical diarylureas from carbamates

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Dedication to Prof Dr Stephen Hanessian

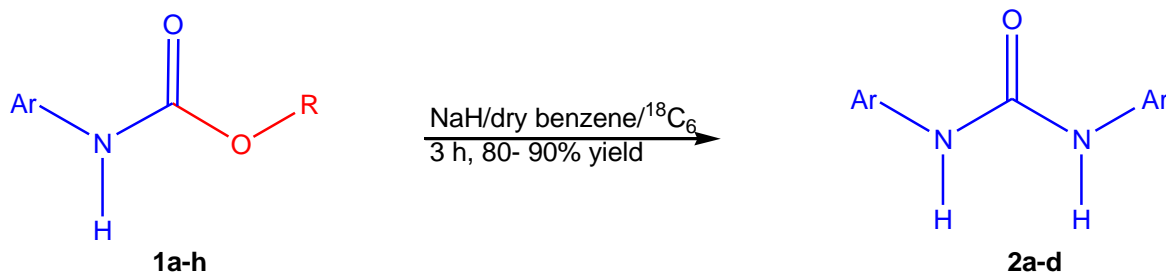
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### Abstract

A convenient method for synthesis of symmetrical diarylureas from carbamates is reported. The diarylureas were obtained in excellent yield when carbamates were boiled at reflux in dry benzene in the presence of sodium hydride as a catalyst and 18-Crown-6 ( $^{18}\text{C}_6$ ) as a co-catalyst. A plausible mechanism explains the formation of 1,3-diarylureas from carbamates in the presence of basic catalyst is reported. The chemical structure of the diarylureas was confirmed by spectroscopic techniques and compared with an authentic sample prepared using previously reported methods.



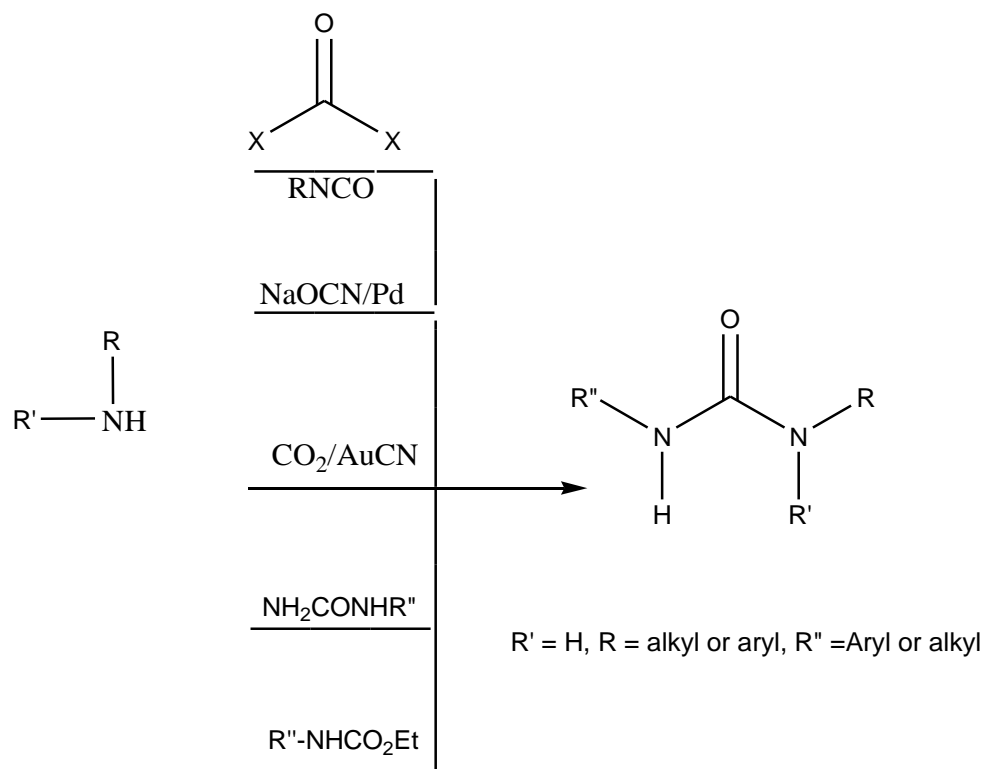
**Keywords:** Carbamates; phosgene free; symmetrical diaryl urea; 18-crown-6.

## Introduction

Urea (carbamide) and its derivatives are interesting organic compounds, which have a unique chemical structure and numerous applications in a variety of fields. For example, in the field of biochemicals and pharmaceuticals, urea is applied directly as an active component or intermediate for treatment of many health disorder and some chronic diseases. Sorafenib (Nexavar®) and Regorafenib (Stivarga®) are both derivatives of diarylureas. Both compounds were approved by the Food and Drug Administration (FDA) in the United States in 2005 and 2013 respectively, for treating copious tumor cells and hepatocellular carcinoma.<sup>1-3</sup> Imatinib (Gleevec®) is another example of the same scaffold, which has proved to be a breakthrough in treatment of chronic leukemia.<sup>4</sup> Other derivatives of the diarylurea such as, Tivozanib, Linifanib and Lenvatinib are on clinical trials as effective agents toward treating of different types of tumors.<sup>5-7</sup> In another pharmaceutical application, diarylurea derivatives were exhibited an excellent anti-inflammatory effect *via* selective inhibition of COX2 over COX1 isoenzyme.<sup>8,9</sup> Additionally, diarylurea derivatives act as intermediates in the synthesis of different biologically active compounds. These compounds have a diverse range of activities including antibacterial, antithrombotic, antimalarial and broad-spectrum anticancer agents.<sup>10-13</sup> Also, diarylureas were used as catalyst or cocatalyst in some chemical transformations. For example, diarylureas were applied as catalyst for specific epoxidation of alkenes and as cocatalyst for asymmetric aziridination reactions.<sup>14, 15</sup>

Considerable attention was paid toward the accessibility of the diarylurea derivatives from either natural sources or chemical transformations with low hazardous reaction conditions. The 1, 3-disubstituted ureas were isolated in low quantities from various natural sources. For example, four different *N,N'*-disubstituted urea derivatives were isolated from the roots of evergreen shrub of *Pentadiplandra brazzeana*.<sup>16</sup> Since the first synthesis of urea, from cyanic acid, by Friedrich Wöhler in 1828, which is considered as a major mile stone in the history of organic chemistry, many methods and approaches for synthesis of urea and its derivatives were reported in literature.

Traditionally, the reaction of highly toxic and corrosive phosgene and related analogues with aromatic amines was the commonly used method for synthesis of this scaffold.<sup>17-23</sup> Therefore, recently prodigious efforts were devoted to develop efficient phosgene-free methods for preparing the 1,3-disubstituted urea derivatives. The major approaches for these methods are presented in scheme 1. Generally, all of these methods start by the reaction of amines with isocyanates or analogues,<sup>24,25</sup> or the catalytic carbonylation of amines by either carbon monoxide or carbon dioxide.<sup>26,27,28</sup> (Scheme 1). Additionally, the traditional reactions of amines with either urea or its *N*-monosubstituted derivatives were used as efficient approaches for synthesis of the 1,3-disubstituted ureas.<sup>29-31</sup>



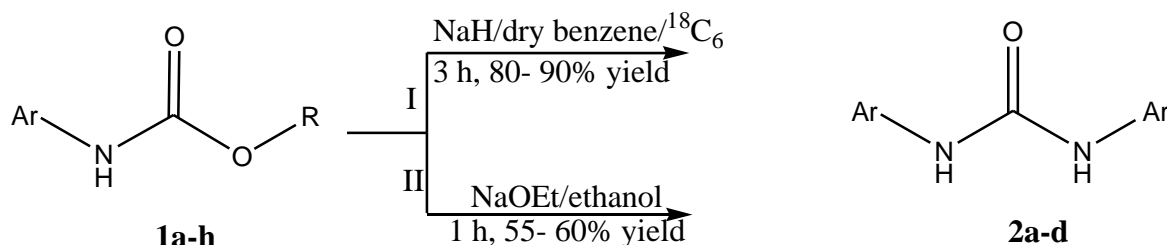
**Scheme 1.** General scheme for the reported phosgene-free approaches for synthesis of 1,3-disubstituted ureas.

Furthermore, carbamates have been used for the synthesis of different symmetrical or asymmetrical 1,3-disubstituted ureas, by aminolysis reaction with primary or secondary amines in the presence of different catalysts. For example, series of substituted ureas were prepared from different carbamates when treated with amines in the presence of ethylmagnesium bromide (EtMgBr),<sup>32</sup> bis(trimethylaluminum)-1,4-diazabicyclo [2.2.2]octane adduct (DABAL-Me3),<sup>33</sup> or 2-chloropyridine/Tf<sub>2</sub>O,<sup>34</sup> aluminium trimethyl((AlMe<sub>3</sub>)/toluene mixture.<sup>35</sup> All these approaches involve reaction of carbamates with a primary or a secondary amine to produce the required 1,3-disubstituted ureas. Recently, triethylamine and dimethylformamide (DMF) were used with some limitations for synthesis of particular 1,3-disubstituted phenyl ureas.<sup>36</sup> Other miscellaneous synthesis methods for 1,3-diaryl ureas can also be found in literature.<sup>37-39</sup> For example, diarylureas were unexpectedly synthesized from the reaction of nicotinic acids and ethylchloroformate with a moderate yield (60-65%).<sup>40</sup> Moreover, diaryl ureas were obtained *via* C-N cross coupling reaction of the *N*-aryl urea with the aryl halides in presence of Pd.<sup>41</sup>

## Results and Discussion

In this work, we report an expedient phosgene-free method for synthesis of symmetrical diaryl ureas from carbamates. In a typical procedure, when a solution of carbamate (**1**)<sup>42</sup> in dry benzene, under argon atmosphere, was heated to boiling reflux in the presences of sodium hydride and catalytic amount of crown ether (<sup>18</sup>C<sub>6</sub>) as a co-catalyst, after the reaction work-up, the diaryl ureas (**2**) were obtained in an excellent yield (85-90%) (Scheme 2, Table 1). It is worthy to mention that, when the reaction was conducted in absence of crown ether (<sup>18</sup>C<sub>6</sub>), no diaryl urea was detected or isolated from the reaction even after long period of boiling

reflux. In order to assess other basic conditions, sodium ethoxide was used as a catalyst and ethanol as a solvent. When the sodium ethoxide was used in a 1:1 molar ratio (ethoxide/carbamate) the diaryl urea was not isolated after the final work-up of the reaction. However, the product was formed only when the sodium ethoxide was used in a molar ratio of 4:1 (ethoxide/carbamate). The reactions were completed after 1 hour heating under reflux and the products were isolated in good yields, ranging from 55 to 60 %. (Rout II scheme 2).

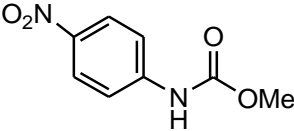
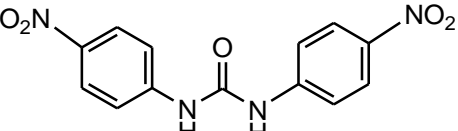
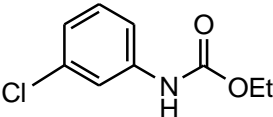
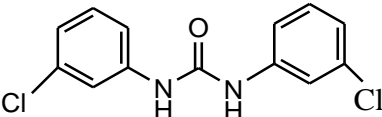
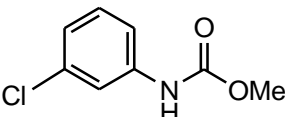
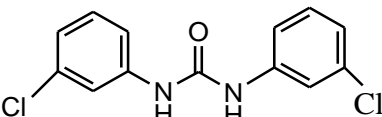


**Scheme 2.** Synthesis of diaryl urea (**2**) from carbamate (**1**) by two routes, I) NaH/dry benzene/ <sup>18</sup>C<sub>6</sub> and II) NaOEt/ethanol.

**Table 1.** Synthesis of diaryl ureas (**2**) from carbamates (**1**)

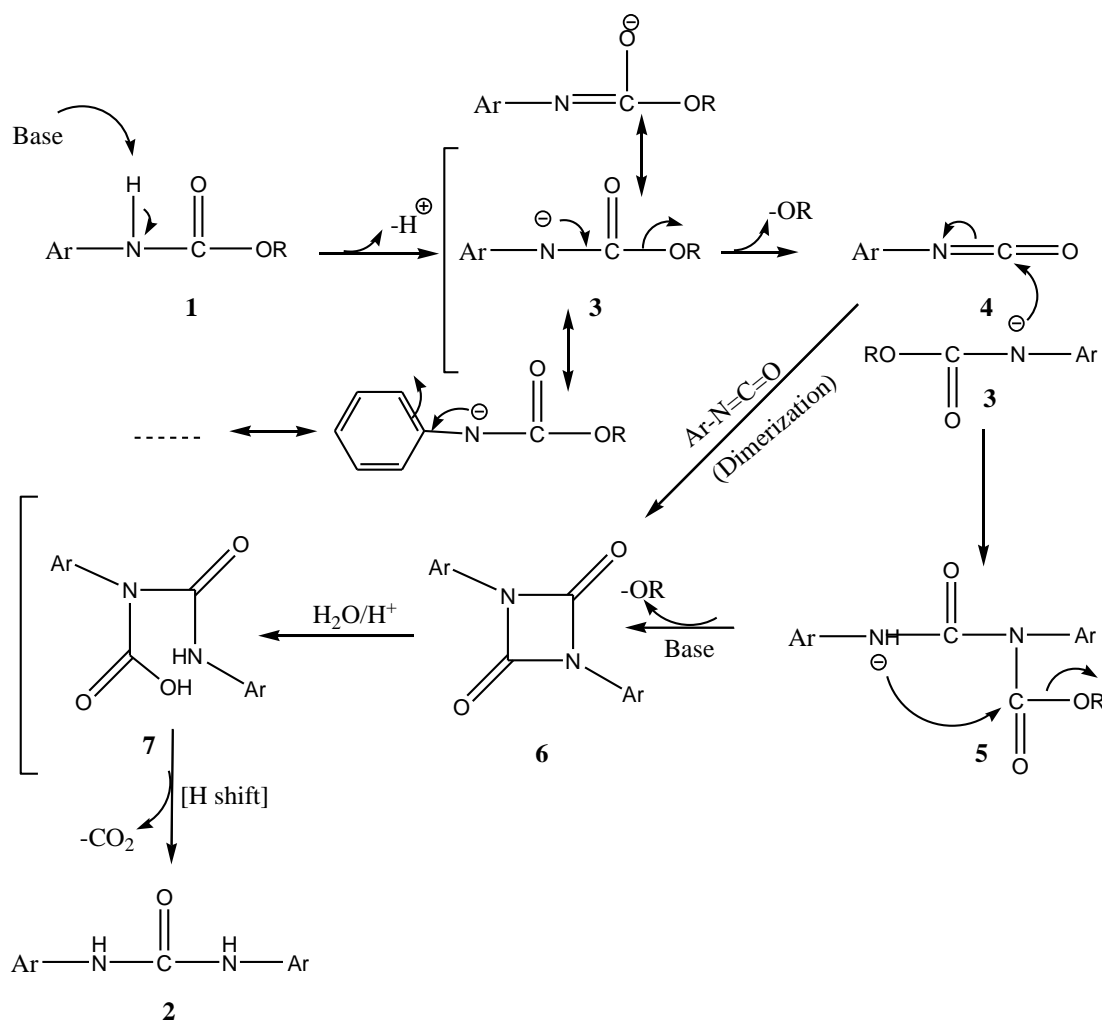
Entry	Substrate structure (1a-h)	Product structure (2a-d)	Yield (%) Route I (Route II)	m.p. °C (Lit.)
1			88 (55)	176-178 (174) <sup>43</sup>
2			86	
5			83 (50)	223-225 (225-227) <sup>43</sup>
6			81	
7			80 (55)	>300 (310) <sup>43</sup>

Table 1. Continued

Entry	Substrate structure (1a-h)	Product structure (2a-d)	Yield (%) Route I (Route II)	m.p. °C (Lit.)
8	 (1f)	 (2c)	89	
9	 (1g)	 (2d)	82 (52)	247-249 (245-248) <sup>44</sup>
10	 (1h)	 (2d)	90	

A plausible mechanism that explains the formation of the products is depicted in scheme 3. The reaction starts by basic abstraction of hydrogen from the amidic nitrogen in the carbamate molecules **1** to produce a carbamate anion **3**. The formation of this anion is favored because it is stabilized by resonance and delocalization of the negative charge due to the carbonyl group and the aromatic ring. Then, the carbamate anion undergoes a further stabilization *via* an intramolecular rearrangement, under the reaction conditions, to produce the isocyanate **4** after removal of alkoxy group (OR) as a good leaving group.<sup>45,46</sup> Subsequently, the carbamate anion (**3**) acts as a nucleophile and attack the isocyanate **4** (addition-elimination reaction, similar to the reaction of amine with isocyanate) to form the four-membered ring diamide intermediate **6** (1,3-diazetidone-2,4-diones often simply called uretidine diones or uretediones) *via* addition intermediate **5**.<sup>44</sup> Alternatively, the four-membered ring intermediate **6** could be formed *via* dimerization of isocyanate **4** under the reaction conditions.<sup>47</sup> Then, reaction proceeds analogously to the previously reported mechanism for conversion of isocyanate to 1,3-disubstituted urea in basic medium.<sup>44</sup> Therefore, ring opening by hydrolysis of the cyclic diamide **6** would produce carbamic acid intermediate **7**. The elimination of carbon dioxide with hydrogen shift in the later intermediate would produce the desired 1,3-symmetrical disubstituted urea **2**.

The chemical structure of the products were confirmed by spectroscopic techniques and by comparison with authentic samples prepared using previously reported methods.<sup>44</sup>



**Scheme 3.** A plausible mechanism for formation of symmetrical 1,3-diaryl ureas from carbamates.

## Conclusions

In conclusion, a series of diarylurea derivatives were successfully synthesized with high yields, >80%, by refluxing carbamates in benzene for three hours in the presence of sodium hydride as a catalyst and  $^{18}\text{C}_6$  as a co-catalyst catalyst. The diarylureas were not formed in the absence of  $^{18}\text{C}_6$ , even after a long time of heating under reflux, indicating the key role of it in the synthesis process. Alternatively, the same products were prepared, in lower yield (<60%) when four fold of sodium ethoxide was used as a catalyst in boiling ethanol. A plausible mechanism has been suggested to explain the formation of 1,3-diarylureas from carbamates in the presence of basic catalyst. The structure of the synthesized compounds was confirmed by spectroscopic techniques. Also, the measured melting points of the prepared compounds were consistent with the values reported in literature, indicating that the synthesis produced a pure product.

## Experimental Section

**General.** The nuclear magnetic resonance ( $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR) spectra were measured on Bruker spectrometers. The infrared spectra were recorded with Perkin-Elmer 983 spectrophotometer. The electron impact ionization mass spectra (EIMS) were accomplished on a Varian AMD 604 instrument. All the reactions were monitored by TLC. Benzene was dried over metallic sodium before using. Other solvents were used directly without further purification. Carbamates (**1a-h**) were prepared using reported method.<sup>42</sup>

**Route 1.** A mixture of carbamate (**1**) (5 mmol), sodium hydride (10 mmol) in dry benzene (15 mL) and one crystal of 18-Crown-6, was heated under reflux boiling in Argon atmosphere for 3 hours (the reaction was monitored by TLC). The reaction mixture was left to cool then, poured onto 50 ml of cooled diluted HCl with continuous stirring. The reaction mixture was extracted with ethyl acetate and dried over anhydrous  $\text{MgSO}_4$ . The crude diaryl ureas were obtained after concentrated and evaporation under vacuum and recrystallized from an appropriate solvent.

**Route 2.** A mixture of carbamate (**1**) (5 mmol) and sodium ethoxide (20 mmol) in ethanol (15 mL) was heated under reflux boiling in argon atmosphere for one hour. The reaction mixture was left to cool then, poured onto 50 ml of cooled diluted HCl with continuous stirring. The reaction mixture was extracted with ethyl acetate and dried over anhydrous  $\text{MgSO}_4$ . The crude diaryl ureas were obtained after concentrated and evaporation under vacuum and recrystallized from an appropriate solvent.

**1,3-Bispyridinylurea (2a).** It was obtained as white solid from ethanol, mp 176-178 °C (174 °C).<sup>43</sup> IR ( $\text{cm}^{-1}$ ) 3282.2 (NH), 1630.3 (C=O amide), 15579.2, 1542.  $^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ )  $\delta$  11.20 (brs, H, NH),  $\delta$  8.37 (d,  $J$  6.7 Hz, 1H),  $\delta$  7.69 (m, 2H),  $\delta$  6.99 (d,  $J$  8.0 Hz, 1H).  $^{13}\text{C}$  NMR:  $\delta$  153.6, 152.6, 147.3, 138.3, 118.2, 113.2. MS, EI,  $m/z$  (%): 214 (14), 121 (26), 94 (100), 78 (21), 67 (34).

**1,3-Bis(2-nitrophenyl)urea (2b).** Recrystallization from ethanol yielded dark yellow crystals with mp 223-225°C (lit. 225–227 °C).<sup>43</sup> IR ( $\text{cm}^{-1}$ ) 3320.1 (NH), 1650.1 (C=O).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , ppm)  $\delta$ : 8.21, (s, 2H); 7.50, (m, 2H); 7.12, (s, 1H); 6.87, (s, 1H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , ppm):  $\delta$  146.1, 135.6, 130.2, 125.1, 119.1, 115.4.

**1,3-Bis(4-nitrophenyl)urea (2c).** Recrystallization from ethanol yielded pale yellow crystals with mp >300 °C (lit. 310 °C).<sup>44</sup> IR ( $\text{cm}^{-1}$ ) 3310.4 (NH), 1655.7 (C=O).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , ppm)  $\delta$ : 9.13 (s, 2H), 7.84 (s, 2H), 7.43 (s, 4H), 7.12 (s, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , ppm):  $\delta$  152.3, 140.9, 133.1, 130.3, 121.6, 117.7, 116.8.

**1,3-Bis(3-chlorophenyl)urea (2d).** Recrystallization from ethanol yielded colorless crystals with mp =247-249°C (lit. 245-248 °C).<sup>44</sup> IR ( $\text{cm}^{-1}$ ) 3285.9 (NH), 1632.3 (C=O amide).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , ppm)  $\delta$ : 8.85 (s, 2H), 7.52 (s, 2H), 7.12 (s, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , ppm):  $\delta$  148.9, 138.7, 132.5, 129.9, 120.1, 118.2.

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## Supplementary Material

Copies of  $^1\text{H}$ -NMR,  $^{13}\text{C}$ -NMR, MS, IR spectra are available in the Supplementary Material file associated with this article.

## References

1. Robert, K.; Ann, F.; Haleh, S.; Shenghui, T.; Gene, W.; Josephine, J.; Chengyi, L.; Brian, B.; Nallaperumal, C.; David, M.; Rajeshwari, S.; Patricia, G.; Robert, J.; Richard, P. *Clin. Cancer Res.* **2006**, *12*, 7271.  
<https://doi.org/10.1158/1078-0432.CCR-06-1249>.
2. Gillian, K.; Armando, S. *Drugs* **2009**, *69*, 223.  
<https://doi.org/10.1126/science.1106753>.
3. Catherine, T. F. *Gastroenterology & Hepatology* **2017**, *13*, 122.  
PMID: [28450818](https://pubmed.ncbi.nlm.nih.gov/28450818/).
4. Pray, L. *Nature Education* **2008**, *1*, 37.
5. Han, H.; Tim, E. *Expert Review of Anticancer Therapy* **2013**, *13*, 649.  
<https://doi.org/10.1586/era.13.40>
6. Marlow, M.; Al-Ameedee, M.; Smith, T.; Wheeler, S.; Stocks, M.J. *Chem. Commun.* **2015**, *51*, 6384.  
<https://doi.org/10.1039/c5cc00454c>.
7. Loretta, F.; Medical, W. *American Health & Drug Benefits* **2015**, *8*, 177.
8. Afshin, Z.; Samaneh, K.; Atefeh, H.; Bahram, D.; Orkideh, G. D.; Mehdi, H.; *Bioorg. Med. Chem. Lett.* **2008**; *18*; 1336.  
<https://doi.org/10.1016/j.bmcl.2008.01.021>
9. Ashish P. K.; Girish D. H.; Rajesh H. T.; Atish H.; Vandana M. K.; *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6611.  
<https://doi.org/10.1016/j.bmcl.2012.08.118>.
10. Pratiksha, S.; Jagdish, K.; Arun, K. M.; Hashim, S.R. *Med. Chem.* **2015**, *5*, 479.  
<https://doi.org/10.4172/2161-0444.1000305>
11. Mohammed, I. E.; Chang, H. *Chem. Pharm. Bull.* **2014**, *62*, 25.  
<https://doi.org/10.1248/cpb.c13-00249>
12. Chenshu, L.; Ke, T.; Yan, L.; Peng, L.; Ziyun, L.; Dali, Y.; Xiaoguang, C.; Haihong, H. *Eur. J. Med. Chem.* **2014**, *77*, 351.  
<https://doi.org/10.1016/j.ejmech.2014.03.020>
13. Garuti, L.; Roberti, M.; Bottegoni, G.; Ferraro, M. *Current Medicinal Chemistry* **2016**, *23*, 1528.  
<https://doi.org/10.2174/0929867323666160411142532>
14. Adam, S.; Hafiz, A.; Elghamry, I.; *Reac Kinet Mech Cat* **2018**, *124*, 779.  
<https://doi.org/10.1007/s11144-018-1399-8>.
15. Shang-H.; Rong-Jie, C.; *Tetrahedron* **2016**, *72*, 2607.  
<https://doi.org/10.1016/j.tet.2014.12.063>
16. Apollinaire, T.; David, N.; Dieudonné, N.; Johnson, F.; Olov, S. *J. Nat. Prod.* **1999**, *62*, 1435  
<https://doi.org/10.1021/np990111f>.
17. Nowick, J. S.; Powel, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364.  
<https://doi.org/10.1021/jo00052a069>



18. Pavel, M. ; Ramnarayan, S. R.; *J. Org. Chem.* **1994**, 59, 1937.  
<https://doi.org/10.1021/jo00086a061>
19. Robert, A. B.; Santhakumar, V.; Chiaki, Y.; Scott, D. T. *Tetrahedron Lett.* **1998**, 39, 6267.
20. Patil-Sen, Y.; Dennison, S.R.; Snape, T.J. *Bioorg. Med. Chem.* **2016**, 24, 4241.  
<https://doi.org/10.1016/j.bmc.2016.07.017>.
21. Blain, M.; Yau, H.; Jean-Gerard, L.; Auvergne, R.; Benazet, D.; Schreiner, P. R.; Caillol, S.; Andrioletti, B.; *ChemSusChem* **2016**, 9, 2269.  
<https://doi.org/10.1002/cssc.201600778>.
22. Sanabria, C. M.; do Casal, M. T.; de Souza, R. B. A.; de Aguiar, L. C. S.; de Mattos, M. C. S.; *Synthesis* **2017**, 49, 164.  
<https://doi.org/10.1055/s-0036-1588370>.
23. Lin, B.; Waymouth, R. M.; *J. Am. Chem. Soc.* **2017**, 139, 1645.  
<https://doi.org/10.1021/jacs.6b11864>
24. Shahnaz, P.; Syed, M. A.; Rashid, A. K.; Khalid, K.; Nighat, A.; Tahira, B. S.; *Synthetic Commun.* **2005**, 35, 1663.  
<https://doi.org/10.1081/SCC-200061656>.
25. Sedighe, S.-R.; Ghadamali, K.; Amirhossein, S.; Ali, J.-N.; Mahboubbeh, R.; Mahmoud, M.; Farshid, H.; *Research in Pharmaceutical Sciences* **2018**, 13, 82.  
<https://doi.org/10.4103/1735-5362.220971>
26. Xiaopeng, Z.; Zhengwei, L.; Yan, W.; Shuxiang, D.; Xueli, N.; Guisheng, Z. *ARKIVOC* **2016** (v) 197.  
<https://doi.org/10.3998/ark.5550190.p009.683>.
27. Fengshou, T.; Yahong, C.; Xiaofang, W.; Peng, L.; Shiwei, L. *Journal of Chemistry* **2015**.  
<https://doi.org/10.1155/2015/210806>.
28. Maotong, X.; Andrew, R. J.; Douglas, W. S.; *Angew. Chem. Int. Ed.* **2017**, 56, 14277.  
<https://doi.org/10.1002/anie.201708921>.
29. Kotecki, B. J.; Fernando, D. P.; Haight, A. R.; Lukin, K. A. *Org. Lett.* **2009**, 11, 947.  
<https://doi.org/10.1021/ol802931m>
30. Gavade, S. N.; Balaskar, R. S.; Mane, M. S.; Pabrekar, P. N.; Shingare, M. S.; Mane, D. V. *Chin. Chem. Lett.* **2011**, 22, 675.  
<https://doi.org/10.1016/j.cclet.2010.12.018>
31. Gavade, S.; Balaskar, R.; Mane, M.; Pabrekar, P. N.; Mane, D. *Synth. Commun.* **2012**, 42, 1704.  
<https://doi.org/10.1080/00397911.2010.543747>.
32. Basha, A. *Tetrahedron Lett.* **1988**, 29, 2526.
33. Kang, S.; Kim, H. K. *Tetrahedron* **2018**, 74, 4036  
<https://doi.org/10.1016/j.tet.2018.06.011>.
34. Yan, X.; Sun, H.; Xiang, H.; Yu, D.-G.; Luo, D.; Zhou, X. *Chem Commun* **2018**, 54, 8606.  
<https://doi.org/10.1039/c8cc03954b>.
35. Moon, S.-Y.; Kim, U.B.; Sung, D.; Kim, W. S.; *J. Org. Chem.* **2015**, 80, 1856.  
<https://doi.org/10.1021/jo502828r>.
36. Yamasaki, R.; Honjo, Y.; Ito, A.; Fukuda, K.; Okamoto, I.; *Chem. Pharm. Bull.* **2018**, 66, 880.  
<https://doi.org/10.1248/cpb.c18-00394>.
37. Shahnaz, P.; Sana, M.; Khalid, M. K.; *J. Chem. Soc. Pak.* **2010**, 32, 229.
38. Qi, L.; Nathan, W. L.; Yitzhak, T. *Tetrahedron Lett.* **2001**, 42, 1445.

39. Dianxi, Z.; Qifeng, X.; Ruiyuan, C.; Dongmei, Z.; Wu, Z. *Molecules* **2016**, *21*, 677.  
<https://doi.org/10.3390/molecules21050677>.
40. Fotini, K.; Athanasios, P.; Spyros, P.; Evy, M. Z. *Polyhedron* **1996**, *15*, 1034.
41. Breitler, S.; Oldenhuis, N. J.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 3262.  
<https://doi.org/10.1021/ol201210t>
42. Elghamry, I. *Synthetic Commun.* **2009**, *39*, 3010.  
<https://doi.org/10.1080/00397910802564741>
43. Osawa, A.; Araki, H.; Igeta, H. *Chem. Pharm. Bull.* **1980**, *28*, 3570.
44. Preveen, S.; Abdul Hai, S. M.; Khan, R. A. *Synthetic Commun.* **2005**, *35*, 1663.  
<https://doi.org/10.1081/SCC-200061656>.
45. Woodcok, D. J. *Chem. Commun.* **1968**, 267.
46. Hegarty, A. F.; Forst, L. A. J. *Chem Soc. Perkin Trans. 2* **1973**, 1719.
47. Parodi, F. *Comprehensive Polymer Science and Supplements* **1989**, *5*, 387.