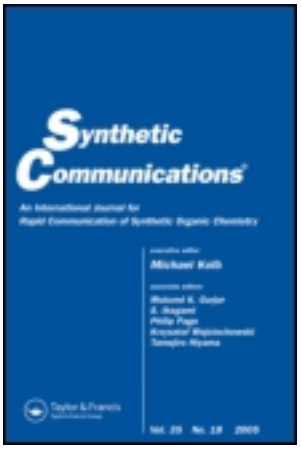

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 10 Jan 2012. Version of record first published: 21 Jun 2012

To cite this article: Kamleshwar Tiwari, Pankaj Kumar Verma, Shyam Babu Singh & Jagdamba Singh (2012): Synthesis of Imidazo[2,1-b]-1,3,4-thiadiazoles in DABCO as an Efficient and Recyclable Catalyst, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:20, 3021-3030

To link to this article: http://dx.doi.org/10.1080/00397911.2011.574329

Synthetic Communications®, 42: 3021–3030, 2012

ISSN: 0039-7911 print/1532-2432 online
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SYNTHESIS OF IMIDAZO[2,1-*b*]-1,3,4-THIADIAZOLES IN DABCO AS AN EFFICIENT AND RECYCLABLE CATALYST

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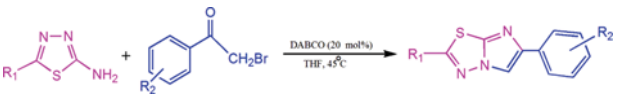
GRAPHICAL ABSTRACT



Abstract *An efficient and general method has been described for the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazole by the reaction of 2-aminothiadiazoles with phenacyl bromides in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO). The method is suitable for the synthesis of functionalized imidazothiadiazoles.*

Keywords 2-Aminothiadiazole; DABCO; imidazothiadiazole; phenacyl bromide

INTRODUCTION

Imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives have been of great interest among medicinal chemists for many years because of their anticancer,[1] antitubercular,[2] antibacterial,[3] antifungal,[4] anticonvulsant, analgesic,[5] and antisecretory[6] activities. Moreover, much interest has also been focused on the anti-inflammatory,[7] cardiotonic,[8] diuretic,[9] and herbicidal[10] activities displayed by compounds incorporating this heterocyclic system. Because the imidazo[2,1-b]-1,3,4-thiadiazole system is similar in part to levamisole (I), a well-known immunomodulator,[11] the possibility of reducing the harmful effects of the cytotoxic agents on the immune system is also very attractive. Biheterocycles containing benzofuran with pyridine, thiadiazoles, and chromone[12] rings have been found to exhibit antimicrobial, psychotropic, and anti-inflammatory activities. For example, efaroxan (2-imidazolinyl-2,3-dihydrobenzofuran) is a well-known antagonist of the α-2-adrenoreceptor.[13] Many recently reported benzofuran derivatives are good anti-inflammatory agents.[14,15] Similarly

Received February 1, 2011.

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tetramisole (II), a broad-spectrum antithelmintic,[16] also contains imidazo[2,1-*b*]-1,3,4-thiadiazole (Fig. 1).

This has generated much interest in the synthesis of these compounds. The most common method of synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazole is the reaction of 5-*R*-2-amino-1,3,4-thiadiazoles with α-haloketones. However, these reactions are performed in organic solvents at reflux temperatures giving only moderate yields; therefore, this synthetic methodology does not provide the possibility of synthesizing a wide range of derivatives of imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives.

Besides these methods, there are many other methods[17] that provide good yields. These methods suffer from tedious workup, long reaction time, use of metal catalyst, and narrow scope of substrates. Moreover, some of the methods have some drawbacks such as unsatisfactory yields and expensive and detrimental metal reagents.

Recently, use of nonmetallic reagents is an area of growing interest because of environmental regulations. Among the various organic bases, 1,4-diazabicyclo [2,2,2]octane (DABCO) has been employed as a organic-hindered base to bring about various organic transformations such as deprotection of peptides,[18] and as a catalyst for the Baylis–Hillman reaction,[19] isoxazole preparation,[20] o-alkylations of phenols,[21] and deprotection of benzylic trimethylsilyl ethers,[22] substituted imidazoles,[23] xanthates,[24] and ethyldiazoacetates.[25] To the best of our knowledge, there is no report on the synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives using organic bases. Herein we report a simple, efficient, and general method for the preparation of substituted imidazo[2,1-*b*]-1,3,4-thiadiazole (C) derivatives by the reaction of 2-aminothiadiazole (A) with phenacyl bromides (B) in the presence of DABCO (Scheme 1).

We have initiated our study with the reaction of phenacyl bromide with 2-aminothiadiazole in the presence of different organic bases such as quinuclidine, DABCO, urotropine, and Troger's base in tetrahydrofuran (THF) (Table 1).

It was observed that the reaction proceeded efficiently using DABCO and resulted in good yield of the desired product in a short reaction time (55 min). However, with other bases the reaction was comparatively slow and gave less yield of the product even after stretching the reaction time. In addition to this, we have screened acyclic tertiary amines such as triethylamine (TEA) and N_1,N_1,N_2-triethyl-N_2-methylethane-1,2-diamine and found that the reaction was very sluggish with poor yield (10–20%) even with extended reaction time (4–5 h). We have attempted different ratios of DABCO (10, 15, 20, 25, 30, and 40 mol%) and observed that 20 mol% was suitable for the optimum conversion. The increase in the molar ratio of DABCO also did not improve the yield.

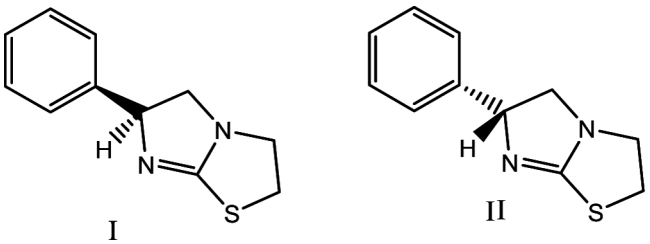
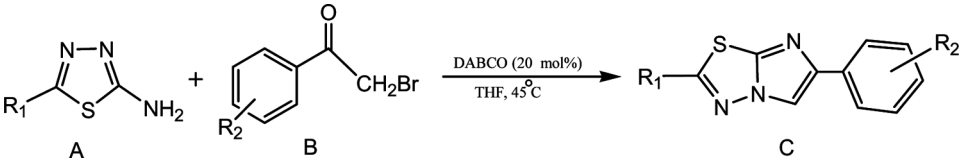


Figure 1. Levamisole and tetramisole.



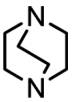
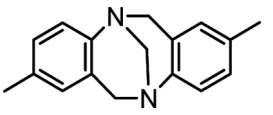
Scheme 1. Synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazole.

To further optimize the reaction conditions, the reaction was studied in different solvents such as benzene, toluene, dichloromethane, and acetonitrile. The reaction proceeded in all the solvents with different degrees of conversion (Table 2). However, THF was the solvent of choice in terms of reaction time and yield.

The formation of product may be explained by the reaction of phenacyl bromide (**2**) with DABCO (**1**), which forms the quaternary salt (**3**).[26] Later it reacts with 2-aminothiadiazole, and subsequent cyclization and dehydration results in expected product (**8**) (Scheme 2).

The scope of this DABCO-catalyzed imidazo[2,1-*b*]-1,3,4-thiadiazole formation was explored under optimal condition, and the results are summarized in Table 3. We have studied the electronic effects of the substituent on the rate of the reaction and the mode of formation of imidazo[2,1-*b*]-1,3,4-thiadiazole. It was observed that electron-rich substituent on the 2-aminothiadiazole slightly influence the reaction because electron-releasing groups slightly increase electron density over NH_2 group of 2-aminothiadiazoles. We have also examined phenacyl bromides having different substituent such as Cl, Br, OMe, and Me. The electron-rich functionalities influence the reaction and furnish the corresponding imidazo[2,1-*b*]-1,3,4-thiadiazoles in good yield, whereas the electron-withdrawing substituent on phenacyl bromide gave

Table 1. Screened bases for the reaction of phenacyl bromide with 2-aminothiadiazole

Entry	Base	Conversion (%)	Yield[a] (%)
1		65	60
2		100	95
3		50	47
4		55	52

[a]Isolated yields.

Table 2. Imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives formation in different solvent conditions

Entry	Solvent	Yield[a] (%)
1	Benzene	65
2	Toluene	67
3	THF	95
4	CH_3CN	75
5	CH_2Cl_2	56

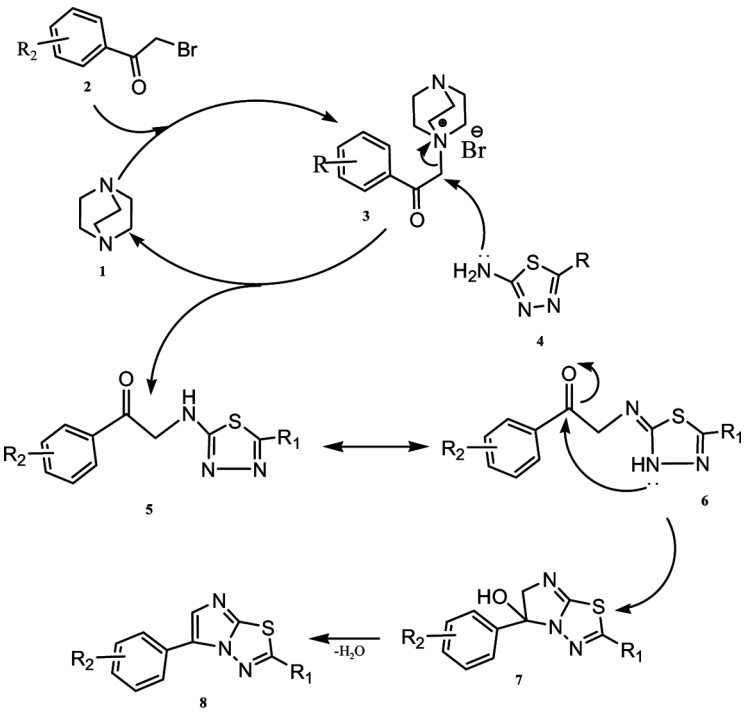
[a]All the reactions were carried out at 45 °C.

comparatively poor yield of imidazo[2,1-*b*]-1,3,4-thiadiazole under identical conditions. It is worth mentioning that the present method provides access for the synthesis of new functionalized imidazo[2,1-*b*]-1,3,4-thiadiazoles. These imidazo[2,1-*b*]-1,3,4-thiadiazoles may provide scope for further extension to build up pharmaceutically important molecules.

EXPERIMENTAL

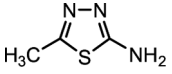
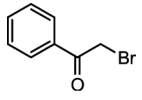
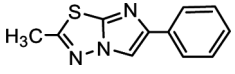
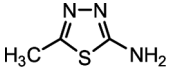
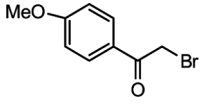
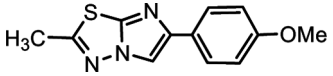
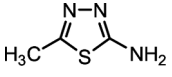
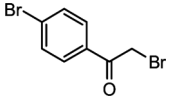
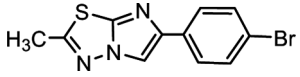
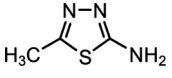
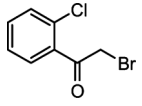
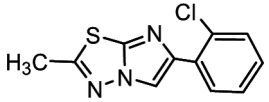
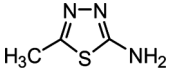
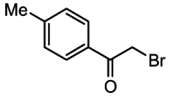
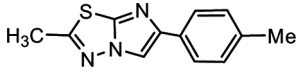
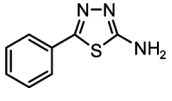
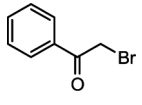
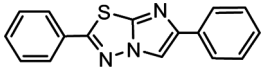
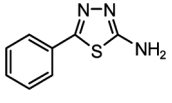
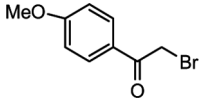
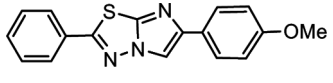
General Procedure for the Synthesis of Target Molecule

A mixture of phenacyl bromide (1 equiv) and DABCO (20 mol%) was stirred at 45 °C for 5 min. Then 2-aminothiadiazole (1 equiv) was added slowly, and the resultant



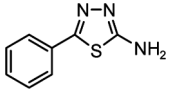
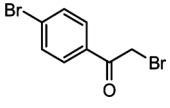
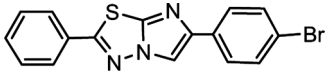
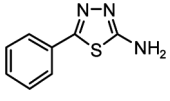
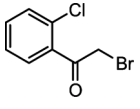
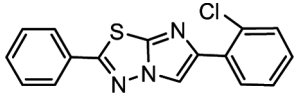
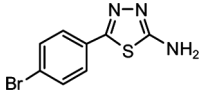
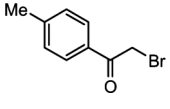
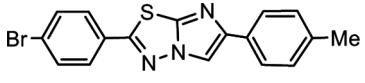
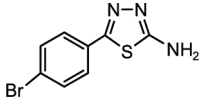
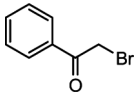
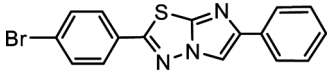
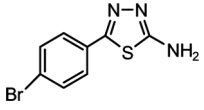
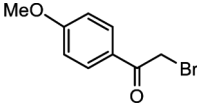
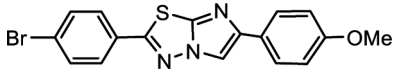
Scheme 2. Mechanism for the formation of imidazo[2,1-*b*]-1,3,4-thiadiazole.

Table 3. Synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazole in the presence of DABCO[a]

Entry	2-Aminothiadiazole	Phenacyl bromide	Product	Time (min)	Yield[b] (%)
1				55	95
2				55	97
3				60	90
4				60	90
5				55	96
6				55	94
7				55	95

(*Continued*)

Table 3. Continued

Entry	2-Aminothiadiazole	Phenacyl bromide	Product	Time (min)	Yield[b] (%)
8				55	89
9				55	88
10				60	94
11				60	93
12				60	95

[a]Reaction conditions: phenacyl bromide (1 equiv), 2-aminothiadiazole (1 equiv), DABCO (20 mol%), in THF at 45 °C.
[b]Isolated product.

mixture was stirred at the same temperature for 50 min. After completion of the reaction, as indicated by thin-layer chromatography (TLC), the mixture was poured into water. It was extracted with ethylacetate (3×15 ml), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was passed through a small pad of silica gel to give the pure product (ethyl acetate–hexane 1:4). All the compounds were characterized by infrared (IR), ^{1}H NMR, mass spectral data, and elemental analysis.

Compound C_1

Mp 135–137 °C (lit. mp 135–137 °C).[27] IR (υ_{max}, cm^{-1}, KBr) 2924, 1676, 1587, 1534, 1468, 1344; ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 1.27 (s, 3H, CH_3), 8.01 (s, 1H, C_5-H imidazole), 7.37–7.95 (m, 5H, Ar-H); HRMS (M^+) 215.052.

Compound C_2

Mp 200–202 °C (lit. mp 200–202 °C).[28] IR (υ_{max}, cm^{-1}, KBr) 2922, 1695, 1573, 1499, 1375; ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 1.27 (s, 3H, CH_3), 7.99 (s, 1H, C_5-H imidazole), 7.03–7.42 (m, 4H, Ar-H), 3.62 (s, 3H, -OCH_3); HRMS (M^+) 245.064.

Compound C_3

Mp 210–212 °C (lit. mp 210–212 °C).[28] IR (υ_{max}, cm^{-1}, KBr) 2922, 1603, 1539, 1476, 1345; ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 1.23 (s, 3H, CH_3), 8.01 (s, 1H, C_5-H imidazole), 7.38–7.54 (m, 4H, Ar-H); HRMS (M^+) 292.963.

Compound C_4

Mp 169–172 °C. IR (υ_{max}, cm^{-1}, KBr) 2924, 1597, 1504, 1474, 1342; ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 1.27 (s, 3H, CH_3), 7.94 (s, 1H, C_5-H imidazole), 7.30–7.62 (m, 4H, Ar-H); HRMS (M^+) 249.013.

Compound C_5

Mp 158–160 °C (lit. mp 158–160 °C).[28] IR (υ_{max}, cm^{-1}, KBr) 2922, 1697, 1571, 1498, 1318; ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 1.27 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 7.03–7.38 (m, 4H, Ar-H), 8.02 (s, 1H, C_5-H imidazole); HRMS (M^+) 229.068.

Compound C_6

Mp 206–208 °C (lit. mp 206–208 °C).[27] IR (υ_{max}, cm^{-1}, KBr) 2924, 1679, 1595, 1501, 1486, 1323; ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 7.14–7.58 (m, 10H, Ar-H), 8.01 (s, 1H, C_5-H imidazole); HRMS (M^+) 277.069.

Compound C_7

Mp 178–180 °C, IR (υ_{max}, cm^{-1}, KBr) 2924, 1638, 1573, 1506, 1391, 1317; ^1H NMR (δ, 300 MHz, $CDCl_3$) 6.94–7.42 (m, 9H, Ar-H), 8.02 (s, 1H, C_5-H imidazole), 3.63 (s, 3H, -OCH_3); HRMS (M^+) 307.078.

Compound C_8

Mp 220–222 °C. IR (υ_{max}, cm^{-1}, KBr) 2922, 1603, 1537, 1472, 1346; ^1H NMR (δ, 300 MHz, $CDCl_3$) 7.34–7.67 (m, 9H, Ar-H), 8.01 (s, 1H, C_5-H imidazole); HRMS (M^+) 354.978.

Compound C_9

Mp 154–156 °C. IR (υ_{max}, cm^{-1}, KBr) 2922, 1614, 1560, 1479, 1337; ^1H NMR (δ, 300 MHz, $CDCl_3$) 7.27–7.67 (m, 9H, Ar-H), 8.01 (s, 1H, C_5-H imidazole); HRMS (M^+) 311.029.

Compound C_{10}

Mp 274–276 °C. IR (υ_{max}, cm^{-1}, KBr) 2922, 1598, 1510, 1482, 1327; ^1H NMR (δ, 300 MHz, $CDCl_3$) 1.27 (s, 3H, CH_3), 7.25–7.57 (m, 9H, Ar-H), 7.99(s, 1H, C_5-H imidazole); HRMS (M^+) 368.992.

Compound C_{11}

Mp 144–146 °C. IR (υ_{max}, cm^{-1}, KBr) 2924, 1673, 1592, 1537, 1492, 1346; ^1H NMR (δ, 300 MHz, $CDCl_3$) 7.28–7.62 (m, 9H, Ar-H), 8.10(s, 1H, C_5-H imidazole); HRMS (M^+) 354.977.

Compound C_{12}

Mp 260–262 °C. IR (υ_{max}, cm^{-1}, KBr) 2924, 1676, 1587, 1534, 1468, 1344; ^1H NMR (δ, 300 MHz, $CDCl_3$) 7.01–7.69 (m, 9H, Ar-H), 8.02(s, 1H, C_5-H imidazole); HRMS (M^+) 384.987.

CONCLUSION

In conclusion, we have demonstrated an efficient and mild method for the synthesis of functionalized Imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives using DABCO as a catalyst. This method is applicable for a variety of phenacyl bromides and 2-aminothiadiazole. Moreover, this protocol provides access for the synthesis of functionalized Imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives.

ACKNOWLEDGEMENTS

We sincerely thank SAIF, Punjab University, Chandigarh, for providing micro analyses and spectra. K. T., P. K. V., and S. B. S. are grateful to the University Grants Commission, New Delhi, for the award of junior research Fellowships.

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