



THIONYL CHLORIDE INDUCED CONVENIENT SYNTHESIS OF BENZAMIDES FROM 3-BROMO-5-NITROBENZOIC ACID AND AMINES UNDER SOLVENT FREE CONDITIONS

Shritesh D. Jagtap,^[a] Aniket P. Sarkate,^{[a]*} Arjun L. Khandare,^[b] Ishudeep K. Narula,^[a] Kshipra S. Karnik,^[a] Dattatraya N. Pansare,^[c] Rohini N. Shelke^[c]

Keywords: thionyl chloride; coupling reaction; benzamides; benzoic acid; solvent free.

A new method of thionyl chloride induced convenient synthesis of novel benzamides under solvent free conditions has been developed using benzoic acid and amines. The benzamides were synthesized through a coupling reaction of benzoic acid and different amines using thionyl chloride at room temperature. The abovementioned technique assists in the preparation of substituted benzamides which were obtained in good yields within 2–4 h using conventional heating. The developed method is flexible, economic, environment friendly; also is catalyst, ligand and solvent free and has major importance in industry and laboratory.

* Corresponding Authors

E-Mail: dbsaniket09@gmail.com

- [a] Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, 431004 (MS), India
- [b] Food Toxicology Division, Food and Drug Toxicology Research Centre, National Institute of Nutrition, Tarnaka, Hyderabad-500007, Telangana, India.
- [c] Department of Chemistry, Deogiri College, Station road, Aurangabad- 431005 (MS), India

INTRODUCTION

Preparation of bromo and nitro-substituted benzoic acids as precursors for preparation of pharmaceutically active benzamides is an important challenge of organic chemistry. The nitration of aromatic compounds may be achieved with many nitrating reagents but the conditions are incompatible with a range of compounds which are sensitive to oxidizing or strongly acidic conditions.^{1,2} Nitration of benzoic acid 62% nitric acid is successfully carried out under solvent-free condition in a biphasic mode in the presence of the Bronsted acidic ionic liquids; the only by-product is water and ionic liquids are capable of being reused without any separation.³ In this paper we give information about optimization of the initial reported method.

The classical bromination reactions involve the use of hazardous elemental bromine.⁴ That's why bromination reaction has been still attracting attention to develop the more practical method without the use of hazardous and highly toxic elemental bromine.⁵ Several acid-catalyzed N-bromosuccinimide (NBS) ring brominations have been reported and continue to be of interest, mainly in connection with the bromination of polyalkyl benzenes.^{5,6} In terms of ease of handling and availability, N-bromosuccinimide (NBS) is a superior brominating reagent.⁷ In this paper we give information about optimization the previously reported method to brominate 3-nitrobenzoic acid with NBS and sulfuric acid.

Benzamides are an important class of chemicals that have been widely used as chemical intermediates in organic synthesis, raw materials for engineering plastics, detergents, and lubricants.⁸ The conversion of carboxylic acids to amides is one of the most important transformations in organic synthesis. In general, the conversion of carboxylic acids to carboxamides requires an activation of the carboxyl group. The solvents in most organic reactions increase the reaction yield, stereoselectivity and chemoselectivity.⁹ The violent exothermic reactions are also controlled by the solvent which involves quick electron transfer from metal and that with a highly reactive species.¹⁰ On the other hand, the use of a solvent may decrease the reaction rate, produces waste solvent, enhances the production cost, and make a chemical operation risky when a flammable solvent is used.¹¹⁻¹² Solvent-free reactions are therefore becoming important from the viewpoint of green chemistry.¹³

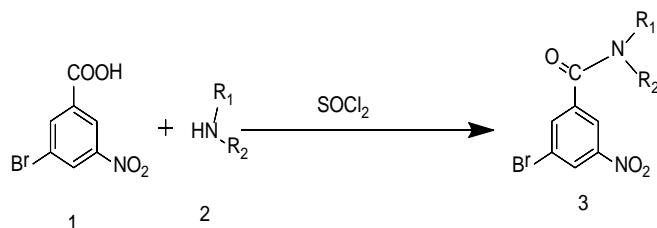
We have been engaged in the development of aromatic compounds as anti-cancer agents and have shown structure–activity relationships with several substituted benzoic acids (containing NO₂ and Br group) to which a heterocyclic aromatic amide group containing ring bound,¹⁴ therefore the amidation reactions of 3-bromo-5-nitro benzoic acid was performed in the presence of SOCl₂ as promoter in a solvent and catalyst free conditions.¹⁵

In continuation of our work,¹⁶⁻³³ we have developed the new protocol synthesis of benzamides from 3-bromo-5-nitrobenzoic acid and amines.

MATERIALS AND METHOD

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals were purchased from Sigma Aldrich and Avra labs. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. Melting points were recorded on SRS Optimelt. Melting points are uncorrected. The ¹H NMR

spectra were recorded on a 400 MHz Varian NMR spectrometer. The ¹³C were recorded on a 100 MHz Varian NMR spectrometer. Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.



Scheme 1. Synthesis of 3-bromo-5-nitrobenzamides

General procedure for the synthesis of 3-bromo-5-nitrobenzamides

Nitration of benzoic acid

Benzoic acid (10 g, 0.0406 mmol) and cc. sulfuric acid (25ml) were added to a reaction vessel and nitrating mixture (H₂SO₄+HNO₃) (H₂SO₄:HNO₃= 1:1.5, 16.5 ml) was added drop wise at 0-5°C temperature for 45 minutes and further the reaction was stirred for 1 h. Then the reaction mixture was quenched with the addition of cracked ice (precipitate formation was observed) and the product was obtained by vacuum filtration. Further the product was recrystallized with methanol. Melting point observed was 139-141°C.

Bromination of 3-nitrobenzoic acid

3-Nitrobenzoic acid (10 g, 0.0598 mmol), NBS (N-bromo succinamide, (11.66 g, 0.05979 mmol), and conc. H₂SO₄ (20ml) were added to a reaction vessel. The mixture was then heated to 80°C temperature for 2 h. Then the reaction was quenched with the addition of cracked ice (precipitate formation was observed) and the product was obtained by vacuum filtration. The reaction product was recrystallized from methanol. Melting point was found to be 159-161°C.

Coupling reaction

3-Bromo-5-nitro benzoic acid **1** (1 g, 0.0406 mmol), amines (primary or secondary) **2** (1eq.) and thionyl chloride (5 ml) were put into a reaction vessel. The mixture was then stirred at room temperature for 2-4 h. It was then extracted with ethyl acetate; the solvents were removed under vacuum and the obtained product was recrystallized from ethanol to yield the corresponding substituted benzamides. The ¹H and ¹³C NMR spectra are given in the Electronic Supplementary Information (ESI).

The following are the spectral analysis of the synthesized compounds:

Synthesis of 3-bromo-N-methyl-5-nitrobenzamide (3a)

¹H NMR (400 MHz, DMSO-d₆) & 8.67 (m, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 7.96 (s, 1H), 2.89 (d, 3H, J=5 Hz). ¹³C NMR 167.9, 148.3, 136.0, 134.7, 129.2, 124.5, 121.57, 26.67

Synthesis of 3-bromo-N-(2-hydroxyethyl)-5-nitrobenzamide (3b)

¹H NMR (400 MHz, DMSO-d₆) & 8.70(s, 1H), 8.42(s, 1H), 8.24 (s, 1H), 8.16(t, 1H), 4.50 (t, 1H), 3.55 (d, 1H) (d, 3H, J=5 Hz). ¹³C NMR 166.2, 148.7, 135.2, 134.4, 128.3, 124.5, 121.5, 60.12, 42.43

Synthesis of 3-bromo-N-butyl-5-nitrobenzamide (3c)

¹H NMR (400 MHz, DMSO-d₆) 8.69 (s, 1H), 8.49 (s, 1H), 8.27 (s, 1H), 8.05 (td, 1H), 3.30 (t, 2H), 1.54 (t, 2H), 1.34 (t, 1H), 0.91 (d, 3H, J=5 Hz). ¹³C NMR 166.2, 148.7, 135.3, 134.2, 127.9, 121.5, 39.6, 31.2, 20.4, 13.7

3-bromo-N,N-dimethyl-5-nitrobenzamide (3d)

¹H NMR (400 MHz, DMSO-d₆) 8.59 (s, 1H), 8.44 (s, 1H), 8.13 (s, 1H), 3.01 (s, 6H). ¹³C NMR 170.2, 148.1, 136.5, 134.5, 120.9, 36.47

(3-Bromo-5-nitrophenyl)(piperazin-1-yl)methanone (3e)

¹H NMR (400 MHz, DMSO-d₆) 8.60 (s, 1H), 8.44(s, 1H), 8.14 (s, 1H), 3.56 (t, 3H), 3.48 (d, 2H), 2.81 (t, 3H), 2.16 (d, 1H). ¹³C NMR 169.0, 148.2, 135.9, 135.1, 127.6, 123.4, 121.3, 47.3, 45.9

3-Bromo-N-(4-methoxybenzyl)-5-nitrobenzamide (3f)

¹H NMR (400 MHz, DMSO-d₆) 8.70 (d, 1H), 8.48 (s, 1H), 8.19 (s, 1H), 7.25(d, 2H), 6.86 (d, 3H), 4.44 (s, 1H), 3.79 (s, 6H). ¹³C NMR 166.2, 158.9, 149.2, 135.7, 135.1, 133.2, 129.1, 128.4, 124.9, 121.7, 113.8, 55.3, 44.4

(3-Bromo-5-nitrophenyl)(2-methylpiperazin-1-yl)methanone (3g)

¹H NMR (400 MHz, DMSO-d₆) 8.63 (s, 3H), 8.46 (s, 3H), 8.17 (s, 3H), 4.46 (t, 1H), 3.69 (d, 3H), 3.66 (d, 3H), 3.06 (t, 2H), 2.99(d, 4H), 2.93(d, 2H), 2.10(t, 2H), 1.25(t, 8H). ¹³C NMR 168.9, 148.5, 136.9, 135.0, 127.9, 123.3, 121.4, 51.4, 45.5, 44.4, 16.12

N-Benzyl-3-bromo-5-nitrobenzamide (3h)

¹H NMR (400 MHz, DMSO-d₆) 8.69(t, 5H), 8.67(s), 8.65 (s, 2H), 8.45(s, 1H), 7.34(d, 3H), 7.24 (t, 1H), 4.54 (d, 3H) ¹³C NMR 166.1, 149.1, 138.6, 135.7, 134.4, 128.3, 128.1, 124.9, 121.7, 43.2

3-Bromo-5-nitro-N-(o-tolyl)benzamide (3i)

¹H NMR (400 MHz, DMSO-d₆) 9.68(s, 1H), 8.73(s, 1H), 8.45 (s, 1H), 8.20(s, 1H), 7.18 (t, 2H), 2.31(s, 3H). ¹³C NMR 165.3, 149.1, 138.9, 135.6, 134.9, 133.2, 129.1, 128.5, 127.2, 125.5, 124.2, 121.6, 119.0, 17.7

3-Bromo-N-(furan-2-ylmethyl)-5-nitrobenzamide (3j)

¹H NMR (400 MHz, DMSO-d₆) 8.70(s, 1H), 8.58(t, 2H), 8.45 (s, 1H), 8.20(s, 1H), 7.34(d, 1H), 6.28 (d, 3H), 4.50 (d, 4H). ¹³C NMR 166.4, 151.8, 149.1, 142.4, 135.6, 134.9, 128.1, 134.8, 122.1, 110.4, 107.8, 37.3,

RESULTS AND DISCUSSION

The substituted benzamides are synthesized as per the established route of synthesis. The thionyl chloride was used as promoter in the synthesis (Scheme 1). We have optimized the condition for the preparation of our substituted products. Some solvents and solvent free conditions were also tested. We have presented the optimization conditions in Table 1.

Table 1. Effect of solvents in the preparation of **3a**

Entry	Solvents	Time, h	Yield, ^a %
1	Toluene	20	58
2	DMF	18	31
3	Methanol	12	32
4	Dichloromethane	9	85
5	Solvent free	2	94

^aIsolated yield

As can be seen from the above data, the reaction goes well in the absence of any solvent and the reaction time as well as the percentage yield of the synthesized compounds better than in the presence of solvents. Using toluene as the solvent the time required for completion was 20 h with only 58% yield (Table 1, Entry 1). Using N,N-dimethylformamide (DMF) the yield drastically decreased to 31% with 18 h of reaction time (Table 1, Entry 2). Methanol was also tried but the obtained yield was again very low (Table 1, Entry 3). Dichloromethane (DCM) was used which to our surprise gave 85% yield in 9 h but the product obtained was somewhat sticky which required further purification (Table 1, Entry 4). Lastly the reaction was carried out in the solvent free condition which not only increased the yield to 94% but also decreased the reaction time to 2 h (Table 1, Entry 5). Hence further derivatization was carried out in a solvent free condition to obtain the required products. The possible reaction mechanism is explained in Figure 1.

The first step is that 3-bromo-5-nitro benzoic acid reacts with the thionyl chloride species to form a 3-bromo-5-nitrobenzoyl chloride complex which acts as an intermediate for the coupling reaction. Due to high electronegativity of benzoyl chloride group, coordination is orientated by the partial charges on NH⁺ and on the electronegative 3-bromo-5-nitrobenzoyl chloride group which assists the substitution by the amines to get desired product.

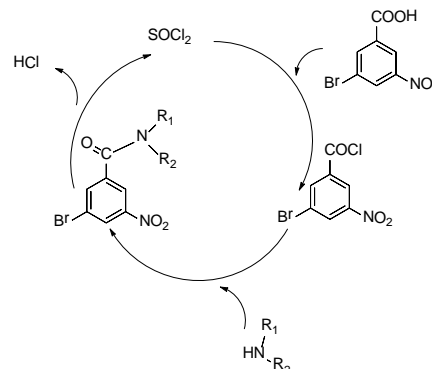




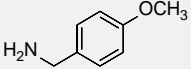
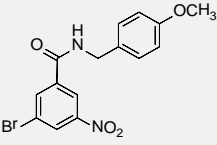

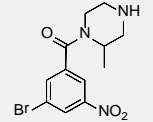
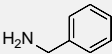
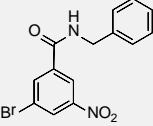

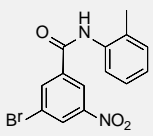
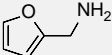
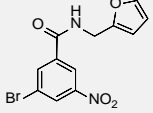
Figure 2. The plausible reaction mechanism

CONCLUSION

We have prepared novel benzamides using thionyl chloride to perform the coupling reaction of 3-bromo-5-nitrobenzoic acid and amines. Our method has minimum environmental impact, is flexible and economic. The reaction is done without using any transition metal catalyst, ligand, base, toxic or hazardous reagent, additives, promoters and organic solvent (i.e. solvent free). We believe that this substituted benzamide compound protocol has major importance in industry, laboratory as well as a drug intermediate due to all its advantages.

Table 2. Synthetic details of the prepared 3-bromo-5-nitrobenzamides

Entry	Amines	Prepared compound	Time, h	%Yield	Melting or boiling point, °C
3a	<chem>CCN</chem>		2	94	143
3b	<chem>NCCO</chem>		2	90	136.8
3c	<chem>CCCN</chem>		2	91.5	141
3d	<chem>CN(C)C</chem>		3	85	298 (BP)

3e			3	80	142.9
3f			4	91	210 (BP)
3g			3	85	260 (BP)
3h			4	90	240 (BP)
3i			2	90	250 (BP)
3j			3	80	400 (BP)

ACKNOWLEDGMENTS

The authors are thankful to The Head, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada university, Aurangabad 431004 (MS) providing the laboratory facilities.

REFERENCES

- ¹Zolfigol, M., Ghaemi, E., Madrakian, E, **2001**, 6, 614-620. <https://dx.doi.org/10.3390/60700614>
- ²Bak, R., Smallridge, A., *Tetrahedron Lett.*, **2001**, 42, 6767-6769. [https://doi.org/10.1016/S0040-4039\(01\)01378-8](https://doi.org/10.1016/S0040-4039(01)01378-8)
- ³Qiao, K., Chiaki, Y., *Chem Lett.*, **2004** 33, 808-809. <https://doi.org/10.1246/cl.2004.808>
- ⁴Moriuchi, T., Yamaguchi, M., Kikushima, K., Hirao, T., *Tetrahedron Lett.*, **2007**, 48, 2667-2670. <https://doi.org/10.1016/j.tetlet.2007.02.074>
- ⁵Moriuchi, T., Yamaguchi, M., Kikushima, K., Hirao, T., *Tetrahedron Lett.*, **2005**, 51, 340-342. <https://doi.org/10.1016/j.tetlet.2009.11.016>
- ⁶Hoffmann, K., Carlsen, P., *Syn. Comm.*, **1999**, 29, 1607-1610. <https://doi.org/10.1080/00397919908086142>
- ⁷Carreño, M., Ruano, G., Miguel, G., Toledo, A., Urbano, A., *J. Org. Chem.*, **1995**, 60, 5328-5331. <https://doi.org/10.1021/jo00121a064>
- ⁸Tanemura, K., Suzuki, T., Nishidi, Y., Satsumabayashi, K., Horaguchi, T., *Chem Comm.*, **2004**, 470-471. <https://doi.org/10.1039/B315340A>
- ⁹Fujwara, H., Ogasawara, Y., Kotani, M., Yamaguchi, K., Mizuno, N., *Chem. Asian J.*, **2008**, 3, 1715-1721. <https://doi.org/10.1002/asia.200800067>
- ¹⁰Ema, T., Nanjo, Y., Shiratori, S., Terao, Y., Kimura, R., *Org. Lett.*, **2016**, 18, 5764-5767. <https://doi.org/10.1021/acs.orglett.6b03115>
- ¹¹Ema, T., Miyazaki, Y., Koyama, S., Yano, Y., Sakai, T., *Chem Comm.*, **2012**, 48, 4489-4491. <https://doi.org/10.1039/C2CC30591G>
- ¹²Ema, T., Miyazaki, Y., Shimonishi, J., Maeda, C., Hasegawa, J., *J. Am. Chem. Soc.*, **2014**, 136, 15270-15279. <https://doi.org/10.1021/ja507665a>
- ¹³Maeda, C., Taniguchi, T., Ogawa, K., Ema, T., *Angew. Chem. Int.*, **2015**, 54, 134-138. <https://doi.org/10.1002/anie.201409729>
- ¹⁴Maeda, C., Shimonishi, J., Miyazaki, R., Hasegawa, J., Ema, T., *Chem. Eur. J.*, **2016**, 22, 6556-6563. <https://doi.org/10.1002/chem.201600164>
- ¹⁵Susanta, S., Becker, F., Banik, K., *Tetrahedron Lett.*, **2000**, 41, 8017-8020. [https://doi.org/10.1016/S0040-4039\(00\)01397-6](https://doi.org/10.1016/S0040-4039(00)01397-6)
- ¹⁶Desmukh, S.V., Pawar, C.D., Pansare, D. N., Chavan, S.L., Pawar, R.P., Ubale, M.B. *Eur. Chem. Bull.* **2019**, 8(4), 115-122. DOI: <http://dx.doi.org/10.17628/ecb.2019.8.115-122>
- ¹⁷Walle, M. R., Pansare, D. N., Kamble, S. S., Pawar, R. P., Ingale, R.D., *Eur. Chem. Bull.* **2019**, 8(3), 101-104. DOI: <http://dx.doi.org/10.17628/ecb.2019.8.101-104>
- ¹⁸Gaikwad, D. D., Pawar, C. D., Pansare, D.N., Chavan, S. L., Pawar, U. D., Shelke, R. N., Chavan, S. L., Pawar, R. P., Zine, A. M., *Eur. Chem. Bull.* **2019**, 8(3), 78-84. <http://dx.doi.org/10.17628/ecb.2019.8.78-84>

- ¹⁹Pravin N. Chavan, Dattatraya N. Pansare, Rohini N. Shelke. *J. Chin. Chem. Soc.* **2019**, in press
<https://doi.org/10.1002/jccs.201800411>
- ²⁰Shelke, R.N., Pansare, D. N., Pawar R. P., Shinde, D. B., Thopate, S. R., *Eur. Chem. Bull.* **2019**, 8(2), 63-70. DOI: [10.17628/ecb.2019.8.63-70](https://doi.org/10.17628/ecb.2019.8.63-70)
- ²¹Pansare, D. N., Shelke, R. N., Khade, M. C., Jadhav, V. N., Pawar, C. D., Jadhav, R. A., Bembalkar, S. R., *Eur. Chem. Bull.* **2019**, 8(1), 7-14. DOI: [10.17628/ecb.2019.8.7-14](https://doi.org/10.17628/ecb.2019.8.7-14)
- ²²Pansare, D. N., Shelke, R. N., Khade, M. C., Jadhav, V. N., Pawar, C. D., Deshmukh, S.U., Dhas, A. K., Chavan, P. N., Sarkate, A. P., Pawar, R. P., Shinde, D. B., Thopate, S. R., *Eur. Chem. Bull.* **2019**, 8(1), 1-6. DOI: [10.17628/ecb.2019.8.1-6](https://doi.org/10.17628/ecb.2019.8.1-6)
- ²³Shelke, R. N., Pansare, D. N., Khade, M. C., Jadhav, V. N., Pawar, C. D., Deshmukh, S.U., Sarkate, A. P., Gore N. S., Pawar, R. P., Shinde, D. B., Thopate, S. R., *Eur. Chem. Bull.* **2019**, 8(2), 63. DOI: [10.17628/ecb.2019.8.63-70](https://doi.org/10.17628/ecb.2019.8.63-70)
- ²⁴Pansare, D. N., Shelke, R. N., Pawar, C. D., *Lett. Org. Chem.*, **2017**, 14(7), 517.
<https://doi.org/10.2174/1570178614666170524142722>
- ²⁵Pansare, D. N., Shelke, R. N., Shinde, D. B., *J. Het. Chem.*, **2017**, 54(6), 3077. <https://doi.org/10.1002/jhet.2919>
- ²⁶Pansare, D. N., Shinde, D. B., *J. Saudi. Chem. Soc.*, **2017**, 21, 434. <https://doi.org/10.1016/j.jscs.2015.10.005>
- ²⁷Tiwari, S. V., Siddiqui, S., Seijas, J. A., Vazquez-Tato, M. P., Sarkate, A. P., Lokwani, D. K., Nikalje, A. P. G., *Molecules*, **2017**, 22 (6), 995.
<https://doi.org/10.3390/molecules22060995>
- ²⁸Tiwari, S. V., Seijas, J. A., Vazquez-Tato, M. P., Sarkate, A. P., Lokwani, D. K., Nikalje, A. P. G., *Molecules* **2016**, 21 (8), 894. <https://doi.org/10.3390/molecules21080894>
- ²⁹Pawar, C. D., Sarkate, A. P., Karnik, K. S., Bahekar, S. S., Pansare, D. N., Shelke R. N., Jawale, C. S., Shinde, D. B., *Bioorg. Med. Chem. Lett.*, **2016**, 26 (15), 3525.
<https://doi.org/10.1016/j.bmcl.2016.06.030>
- ³⁰Dofe, V. S., Sarkate, A. P., Lokwani, D. K., Kathwate, S. H., Gill, C. H., *Res. Chem. Int.*, **2017**, 43 (1), 15.
<https://doi.org/10.1007/s11164-016-2602-z>
- ³¹Sarkate, A. P., Bahekar, S. S., Wadhai, V. M., Ghandge, G. N., Wakte, P. S., Shinde, D. B., *Synlett* **2013**, 24, 1513. DOI: 10.1055/s-0033-1338869
- ³²Doherty, W., Adler, N., Knox, A., Nolan, D., McGouran, J., Nikalje, A. P. G., Lokwani, D., Sarkate, A., Evans, P., *Eur. J. Org. Chem.*, **2017**, 1, 175.
<https://doi.org/10.1002/ejoc.201601221>
- ³³Lokwani, D., Azad, R., Sarkate, A., Reddanna, P., Shinde, D., *Bioorg. Med. Chem.*, **2015**, 23 (15), 4533.
<https://doi.org/10.1016/j.bmc.2015.06.008>

This paper was presented at the “International Symposium on Exploring New Horizons in Chemical Sciences”, January 10–12, 2019, Aurangabad, India (ENHCS–2019).

Received: 20.03.2019
Accepted: 03.05.2019.