http://www.e-journals.in
DOI:10.7598/cst2014.727

Chemical Science Transactions
2014, **3(3),** 1140-1146

**RESEARCH ARTICLE**

# Development of New Methodology for the Synthesis of Substituted Aromatic Amides

Y. L. N. MURTHY*, DASI SAMSONU and BHAGAVATHULA S DIWAKAR

Department of Organic Chemistry, School of Chemistry, Andhra University,
Visakhapatnam-530003, India
*murthyyln@gmail.com*

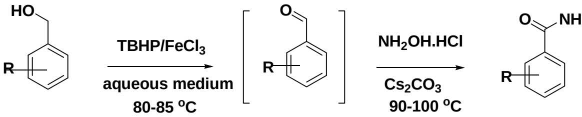
Received 18 September 2013 / Accepted 6 October 2013

**Abstract:** Aromatic substituted amide derivatives were synthesized directly by the single step oxidation of substituted benzyl alcohols by tert- butyl hydroperoxide (TBHP) using cesium carbonate as catalyst in presence of aqueous media. All the compounds were obtained in good yields.

**Keywords:** Oxidation, Tert- butyl hydroperoxide (TBHP), Aromatic amides, Benzyl alcohol

## Introduction

The amide bond plays a key role in organic and biological chemistry. The amide linkage is an important functional group due to its extensive presence in natural products, pharmaceutical compounds and synthetic polymers. The most common traditional method for the synthesis of the amides is treatment of activated carboxylic acid derivatives with amines[1]. Numerous alternative strategies such as the Staudinger reaction[2], the Schmidt reaction[3] and the Beckmann rearrangement[4] have been developed. Compared to the general synthetic methods based on the reaction between activated forms of carboxylic acids and amines, the synthesis of amides directly from alcohols and amines would be a desirable chemical transformation[5,6]. It would afford a highly economical synthetic route due to the availability and stability of the starting materials. However, in most of these methods, stoichiometric amounts of various reagents are required and equimolar amounts of by-products are produced as waste. Only a limited number of systems have been developed so far to achieve this transformation, which are promoted by homogeneous or heterogeneous catalysts[7]. Ru- or Rh-based transition metal complexes[8-12], Ag- or Au-based supported catalysts[13,14] and Cu salt[15] have been used to directly convert alcohols and amines into amides. These synthetic protocols sharea common underlying mechanism that involves three main consecutive steps: (1) activation- the oxidation of alcohols toform aldehydes; (2) bond construction-the coupling of aldehydes with amines to produce hemiaminals as reactive intermediates; (3) dehydrogenation-subsequent oxidation of hemiaminals to amides through $H_2$ liberation or H transfer toa hydrogen acceptor. Since alcohols are less reactive and an increase in their oxidation level is required for this type of transformation, the synthetic strategies would involve oxidative activation of the alcohols. Another key feature of such strategies is that both oxidation steps, (1) and (3), are necessarily catalyzed by the same catalyst, making catalyst development extremely challenging. Traditional alcohol oxidation employs the strongest stoichiometric oxidizing agents, such as PCC, PDC, $MnO_4$, $MnO_2$, $Na_2 Cr_2 O_7$, TEMPO, $CrO_3$ and so on[16-22]. These oxidation operations are quite useful in lab, but these oxidants are expensive, hazardous or toxic. Mean while toxic solvents are usually used to dissolve oxidizing agents and a large amount of inorganic wastes are produced after workup. Hence, in terms of economical and environment concern, catalytic oxidation processes with inexpensive and environmental-friendly oxidants are extremely valuable. Here in we report that different benzyl alcohols can be selectively oxidized to their corresponding amides with high yields by tert- butyl hydroperoxide (TBHP) using cesium corbonate ($Cs_2CO_3$) as a catalyst in the presence of aqueous medium (Scheme 1).



**Scheme 1.** Synthesis of aromatic amides from different benzyl alcohols

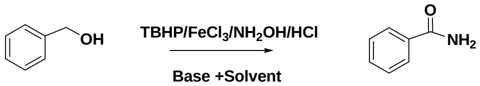
## Experimental

A mixture of benzyl alcohol (0.5 mL), tertiary butyl hydrogen peroxide (0.1 mL) ferric chloride (10 mg) and 3 mL of water was stirred at 80-85 °C for 5 h upto the formation of aldehyde (check TLC). After formation of aldehyde, at the same temperature add hydroxyl ammonium hydrochloride (60 mg) and cesium carbonate (170 mg) then stirrered at 90-100 °C temperature for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into cold water and the products were extracted with dichloromethane. The organic layer was dried over magnesium sulphate and products were collected under reduced pressure. The crude product thus obtained was recrystallized from ethanol or methanol and purity of the compound was checked by HPLC (>99%). All the compounds were well characterized by IR, NMR and Mass spectroscopic technique

## Results and Discussion

In order to establish best reaction conditions, initially different solvent systems with different bases were studies and the results were presented in Table 1. From the table it was observed that $Cs_2CO_3$+$H_2O$ produce good yields in less reaction time.

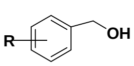
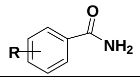
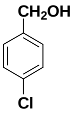
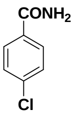
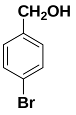
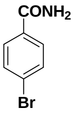
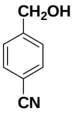
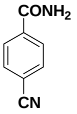
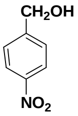
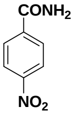
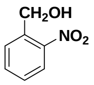
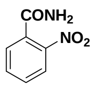
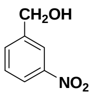
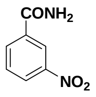
**Table 1.** Optimization of reaction conditions for the synthesis of substituted benzamides

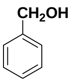
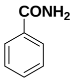
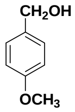
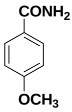
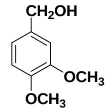
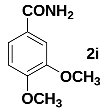
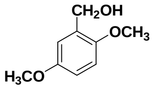
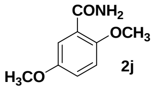
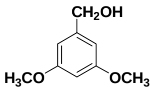
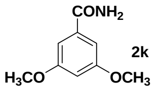
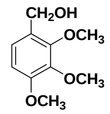
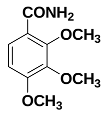
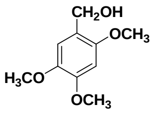
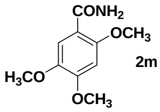
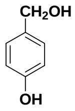
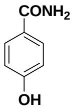


| S.No | Solvent system | Reaction time, h | Product, % |
|---|---|---|---|
| 1 | $Na_2CO_3$ +MeOH | 48 | 11 |
| 2 | $Na_2CO_3$ +DME | 42 | 25 |
| 3 | $Na_2CO_3$ +$H_2O$ | 36 | 38 |
| 4 | $K_2CO_3$ +MeOH | 28 | 42 |
| 5 | $K_2CO_3$ +DME | 25 | 57 |
| 6 | $K_2CO_3$ +$H_2O$ | 19 | 72 |
| 7 | $Cs_2CO_3$ +MeOH | 24 | 83 |
| 8 | $Cs_2CO_3$ +DME | 18 | 85 |
| 9 | $Cs_2CO_3$ +$H_2O$ | 14 | 98 |

After attaining the optimized reaction conditions, different aromatic substituted amides were prepared and the results were depicted in Table 2. It was observed from the Table 2 that electron withdrawing substituents on the aromatic ring give moderate to good yields. The presence of nitro substitution on the aromatic ring gave high yields. The reaction was proceeded by the oxidation of substituted benzyl alcohols employing TBHP to corresponding aldehydes *in situ* and then by adding hydroxyl amine in presence of cesium carbonate to yield substituted benzamides. After completion of the reaction, the products were purified and recrystallized from methanol. These pure compounds were characterized by advance spectral techniques and the results were compared with authentic samples. In IR spectra these compounds showed characteristic absorption peaks at a range 3100-3450 cm$^{-1}$ for N-H stretching in amides and 1610-1690 cm$^{-1}$ for amide carbonyl stretching. In $^1$H NMR spectral studies a chemical shift at for NH protons appear at δ 6.10-6.50.

**Table 2.** Synthesis of substituted benzamides from substituted benzyl alcohols

| S.No |  |  | Time (hrs) | Yield (%) |
|---|---|---|---|---|
| 1 | <br>1a | <br>2a | 14 | 90 |
| 2 | <br>1b | <br>2b | 15 | 91 |
| 3 | <br>1c | <br>2c | 16 | 90 |
| 4 | <br>1d | <br>2d | 12 | 98 |
| 5 | <br>1e | <br>2e | 13 | 93 |
| 6 | <br>1f | <br>2f | 14 | 92 |

| | | | | |
|---|---|---|---|---|
| 7 |  1g |  2g | 14 | 95 |
| 8 |  1h |  2h | 16 | 89 |
| 9 |  1i |  2i | 18 | 88 |
| 10 |  1j |  2j | 17 | 85 |
| 11 |  1k |  2k | 18 | 82 |
| 12 |  1l |  2l | 17 | 86 |
| 13 |  1m |  2m | 18 | 84 |
| 14 |  1n |  2n | 18 | 80 |

## Spectral data of the compounds

### *4-Chlorobenzamide (**2a**)*

IR (KBrpllet) : 3350 cm$^{-1}$, 3050 cm$^{-1}$, 1540 cm$^{-1}$, 1610 cm$^{-1}$, 610 cm$^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm : 7.79 (2H,d), 7.24(2H,d), 6.50(2H,br.s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.85, 136.22, 132.10, 130.00, 128.50; Mass-ESI: 155 (M).

### *4-Bromobenzamide (**2b**)*

IR (KBr pellet) : 3150 cm$^{-1}$, 1670 cm$^{-1}$, 1580 cm$^{-1}$, 1150 cm$^{-1}$, 650 cm$^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm : 7.92 (2H,d), 7.65 (2H,d), 6.49(2H,br.s); $^{13}$C NMR (22.5 MHz/ CDCl3) δ ppm : 167.50, 132.50, 130.90, 128.20, 125.75; Mass-ESI: 198 (M).

### *4- Cyanobenzamide (**2c**)*

IR (KBr pellet) : 3200 cm$^{-1}$, 3050 cm$^{-1}$, 2230 cm$^{-1}$, 1640 cm$^{-1}$, 1550 cm $^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm : 8.10(2H,d), 7.50 (2H,d), 6.45(2H,br.s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.25, 135.59, 131.95, 128.20, 116.00, 115.25; Mass-ESI: 146 (M).

### *4-Nitro benzamide (**2d**)*

IR (KBr pellet) : 3350 cm$^{-1}$, 3050 cm$^{-1}$, 1650 cm$^{-1}$, 1600 cm$^{-1}$, 1350 cm$^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm : 8.29(2H,d), 8.10(2H,d), 6.45(2H,br.s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.50, 150.20, 139.50, 127.00, 120.30; Mass-ESI: 166 (M).

### *2-Nitrobenzamide **(2e)***

IR (KBr pellet) : 3200 cm$^{-1}$, 1690 cm$^{-1}$, 1600 cm$^{-1}$, 1550 cm$^{-1}$, 1350 cm$^{-1}$, 1200 cm$^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm : 8.29(1H,d), 8.18(1H,d), 7.62(1H,m), 7.60(1H,m), 6.42 (2H,br.s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.00, 146.12, 133.00, 132.11, 130.19, 130.12 120.13; Mass-ESI:166 (M).

### *3-Nitrobenzamide **(2f)***

IR (KBr pellet) : 3300 cm$^{-1}$, 3150 cm$^{-1}$, 1660 cm$^{-1}$, 1650 cm$^{-1}$, 1580 cm$^{-1}$ 1350 cm$^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm : 8.92 (1H,s), 8.56(1H,d), 8.10(1H,d), 7.62(1H,m), 6.40 (2H,br.s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.12, 145.00, 139.62, 128.82, 124.22, 120.9; Mass-ESI: 166 (M).

### *Benzamide (**2g**)*

IR (KBr pellet) **:** 3200 cm$^{-1}$, 1680 cm$^{-1}$ , 1600 cm$^{-1}$, 1200 cm$^{-1}$; $^{1}$NMR (400 MHz/ CDCl3) δ ppm :7.75 (2H,s), 7.49 (2H,m), 7.41(2H,m), 6.2 (2H,br.s);$^{13}$C NMR (22.5 MHz/CDCl3) δ ppm: 167.00, 133.22, 131.20, 129.85, 127.10; Mass-ESI: 121 (M).

### *4- Methoxybenzamide **(2h)***

IR (KBr pellet) : 3300 cm$^{-1}$, 3100 cm $^{-1}$, 1660 cm$^{-1}$, 1600 cm$^{-1}$, 1100 cm$^{-1}$; $^{1}$H NMR (400 MHz/CDCl3) δ ppm : 7.59(2H,d), 6.85(2H,d), 6.40 (2H,br.s);$^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 168.10, 165.21, 127.56, 126.12, 113.10, 55.12**;** Mass-ESI: 151 (M).

### *3,4-Dimethoxybenzamide (**2i**)*

IR (KBr pellet) : 3250 cm$^{-1}$, 3100 cm$^{-1}$, 1650 cm$^{-1}$, 1600 cm$^{-1}$, 1250 cm$^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm : 7.30(1H,d), 7.25(1H,s), 6.80(1H,d), 6.38 (2H,br.s), 3.79(6H,s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm :167.40, 152.00, 150.20, 126.50, 120.00, 116.10, 110.50, 55.25; Mass-ESI: 181 (M).

### *2,5-Dimethoxybenzamide **( 2j)***

IR (KBr pellet) : 3100 cm$^{-1}$, 3050 cm$^{-1}$, 1640 cm$^{-1}$, 1580 cm$^{-1}$, 1200 cm$^{-1}$; $^{1}$H NMR (400 MHz/CDCl3) δ ppm : 7.12(1H,s), 6.98(1H,d), 6.70(1H,d), 6.38 (2H,br.s) 3.82(6H,s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.20, 150.80, 149.50, 118.50, 116.10, 114.90, 113.30, 55.20; Mass-ESI: 181 (M).

### *3,5-Dimethoxy benzamide **(2k)***

IR (KBr pellet) : 3150 cm$^{-1}$, 1640 cm$^{-1}$, 1600 cm$^{-1}$, 1510 cm$^{-1}$, 1330 cm$^{-1}$, 1200 cm$^{-1}$, 1150 cm$^{-1}$ $^{1}$HNMR (400 MHz/ CDCl3) δ ppm : 7.12(2H,s), 6.42(1H,s), 6.39(2H,br.s), 3.85(6H,s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.20, 159.82, 135.92, 103.60, 102.94, 55.82; Mass-ESI: 181 (M).

### *2,3,4- Trimethoxybenzamide (**2l**)*

IR (KBr pellet) : 3350 cm$^{-1}$, 3050 cm$^{-1}$, 1650 cm$^{-1}$, 1540 cm$^{-1}$, 1150 cm$^{-1}$; $^{1}$H NMR (400 MHz/CDCl3) δ ppm : 7.12(1H,d), 6.32(1H,d), 6.32(2H,br.s), 3.82(9H,s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.20, 152.10, 151.92, 120.10, 119.50, 110.20, 55.85, 53.30; Mass-ESI: 211 (M).

### *2,4,5-Trimethoxybenzamide (**2m**)*

IR (KBr pellet) :3400 cm$^{-1}$, 3050 cm$^{-1}$, 1640 cm$^{-1}$, 1530 cm$^{-1}$, 1200 cm$^{-1}$; $^{1}$H NMR (400 MHz/CDCl3) δ ppm : 7.16 (1H,s), 6.20 (2H,br.s), 3.92(3H,s ), 3.85 (3H,s), 3.82 (3H,s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.50, 153.10, 151.50, 139.20, 112.90, 110.30, 99.40, 56.00, 54.85; Mass-ESI: 211 (M).

### *4-Hydroxy benzamide (**2n**)*

IR (KBr pellet) : 3100 cm$^{-1}$ 3200 cm$^{-1}$, 3300 cm$^{-1}$ 1630 cm$^{-1}$, 1600 cm$^{-1}$, 1200 cm$^{-1}$; $^{1}$H NMR (400 MHz/ CDCl3) δ ppm :7.85(2H,d), 6.82(2H,d), 6.10 (2H,br.s), 5.15(1H,br.s); $^{13}$C NMR (22.5 MHz/CDCl3) δ ppm : 167.12, 160.00, 127.16. 125.96, 115.00; Mass-ESI: 137 (M).

## Conclusion

An efficient protocol for the synthesis of aromatic substituted benzamides was prepared by the oxidation of benzyl alcohols employing TBHP as promissive catalyst. The advantages of TBHP are nontoxic, ease of handling, ecofriendly and inexpensive.

### *Acknowledgement*

The authors are thankful to Defence Research Development Organization (DRDO), New Delhi, India for their financial support. The authors are also grateful to the Committee on Strengthening Infrastructure for Science & Technology (COSIST) Labs in Department of Organic Chemistry, Andhra University for providing necessary facilities.

## References

1. (a) Han S Y and Kim Y A, *Tetrahedron*, 2004, **60(11)**, 2447-2467; DOI:10.1016/j.tet.2004.01.020 (b) Montalbetti C A G N and Falque V, *Tetrahedron*, 2005, **61(46)**, 10827-10852; DOI:10.1016/j.tet.2005.08.031 (*c*) Valeur E and Bradley M, *Chem Soc Rev.*, 2009, **38**, 606-631; DOI:10.1039/B701677H
2. (*a*) K¨ohn M and Breinbauer R, *Angew Chem Int Ed.*, 2004, **43(24)**, 3106-3116; DOI:10.1002/anie.200401744 (b) Damkaci F and DeShong P, *J Am Chem Soc.*, 2003, **125(15)**, 4408-4409; DOI:10.1021/ja028694u (c) Gololobov Y G and Kasukhin L F, *Tetrahedron*, 1992, **48(8)**, 1353-1406; DOI:10.1016/S0040-4020(01)92229-X
3. (*a*) Ribelin T, Katz C E, English D G, Smith S, Manukyan A K, Day V W, Neuenswander B, Poutsma J L and Aub´e J, *Angew Chem Int Ed.*, 2008, **47(33)**, 6233-6235; DOI:10.1002/anie.200801591 (b) Lang S and Murphy J A, *Chem Soc Rev.*, 2006, **35**, 146-156; DOI:10.1039/B505080D (c) K. Tani and Stoltz B M, *Nature*, 2006, **441(7094)**, 731-734; DOI:10.1038/nature04842 (d) Aub´e J and Milligan G L, *J Am Chem Soc.*, 1991, **113(23)**, 8965-8966; DOI:10.1021/ja00023a065
4. (*a*) Owston N A, Parker A J and Williams J M J, *Org Lett.*, 2007, **9(18)**, 3599–3601; DOI:10.1021/ol701445n (b) Hashimoto M, Obora Y, Sakaguchi S and Ishii Y, *J Org Chem.*, 2008, **73(7)**, 2894–2897; DOI:10.1021/jo702277g
5. Allen C L and Williams J M J, *Chem Soc Rev.*, 2011, **40**, 3405-3415; DOI:10.1039/C0CS00196A
6. Chen C and Hong S H, *Org Biomol Chem.*, 2011, **9**, 20-26; DOI:10.1039/C0OB00342E
7. Dobereiner G E and Crabtree R H, *Chem Rev.*, 2010, **110(2)**, 681-793; DOI:10.1021/cr900202j
8. Gunanathan C, Ben-David Y and Milstein D, *Science*, 2007, **317**, 790.
9. Nordstrom L U, Vogt H and Madsen R, *J Am Chem Soc.*, 2008, **130(52)**, 17672-17673; DOI:10.1021/ja808129p

10. Watson A J A, Maxwell A C and Williams J M J, *Org Lett.*, 2009, **11(12)**, 2667-2670; DOI:10.1021/ol900723v
11. Zhang Y, Chen C, Ghosh S C, Li Y and Hong H S, *Organometallics*, 2010, **29**, 1374-1378; DOI:10.1021/om901020h
12. Zweifel T, Naubron J V and Grützmacher H, *Angew Chem Int Ed.*, 2009, **48(3)**, 559-563; DOI:10.1002/anie.200804757
13. Shimizu K, Ohshima K and Satsuma A, *Chem; A Eur J.,* 2009, **15(39)**, 9977-9980; DOI:10.1002/chem.200901896
14. (a) Wang Y, Zhu D, Tang L, Wang S and Wang Z, *Angew Chem Int Ed.*, 2011, **50(38)**, 8917-8921; DOI:10.1002/anie.201102374 (b) Soulé J F, Miyamuraand H and Kobayashi S, *J Am Chem Soc.*, 2011, **133(46)**, 18550-18553; DOI:10.1021/ja2080086 (c) Zhu J, Zhang Y, Shi F and Deng Y, *Tetrahedron Lett.,* 2012, **53(25)**, 3178-3180; DOI:10.1016/j.tetlet.2012.04.048
15. Mallot T and Baiker A, *Chem Rev.*, 2004, **104(6)**, 3037-3058; DOI:10.1021/cr0200116
16. Holum J R, *J Org Chem.,* 1961, **26(12)**, 4814-4816; DOI:10.1021/jo01070a009
17. Collins J C, Hess W W and Frank F J, *Tetrahedron Lett.,* 1968, **9(30)**, 3363-3366; DOI:10.1016/S0040-4039(00)89494-0
18. Corey E J and Suggs J W, *Tetrahedron Lett.,* 1975, **16(31)**, 2647-2650; DOI:10.1016/S0040-4039(00)75204-X
19. Highet R J and Wildma W C, *J Am Soc Chem.,* 1955, **77(16)**, 4399-4401; DOI:10.1021/ja01621a062
20. Lee D G and Spitzer U A, *J Org Chem.,* 1970, **35(10)**, 3589-3590; DOI:10.1021/jo00835a101
21. Stevens R V, Chapman K T and Weller H N, *J Org Chem.,* 1980, **45(10)**, 2030-2032; DOI:10.1021/jo01298a066
22. Menger F M and Lee C, *J Org Chem.,* 1979, **44(19)**, 3446-3448; DOI:10.1021/jo01333a051