Tetrahedron Letters 51 (2010) 4378–4381

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Metal-free one-pot oxidative conversion of benzylic alcohols and benzylic halides into aromatic amides with molecular iodine in aq ammonia, and hydrogen peroxide

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ARTICLE INFO

Article history:
Received 21 May 2010
Revised 8 June 2010
Accepted 11 June 2010
Available online 16 June 2010

ABSTRACT

Various primary alcohols, particularly benzylic alcohols, could be converted into the corresponding aromatic amides in good yields in a one-pot manner by treatment with molecular iodine in aq. NH_3, followed by reaction with ~30% aq H_2O_2. Similarly, various benzylic halides could be also converted into the corresponding aromatic amides in good yields in a one-pot manner by treatment with molecular iodine in aq NH_3, followed by reaction with ~30% aq H_2O_2. The present reactions involve the metal-free one-pot oxidative conversion of benzylic alcohols and benzylic halides into the corresponding aromatic amides, respectively.

Aromatic amides are one of the most important functional groups in organic chemistry and pharmaceuticals, some examples of which are Arotinolol hydrochloride (anti-hypertensive), Labetalol hydrochloride (anti-hypertensive), Frovatriptan (migraine headache depressant), Exalamide (antifungal), and polymers.[1] Generally, aromatic amides are prepared from aroyl halides with aq NH_3 or amines (the Schotten–Baumann reaction), and aromatic carboxylic acids with amines using dehydration reagents such as TsCl/Py, Ph_3P/CX_4 (X = Cl, Br), and $Ph_3P/(PyS)_2$, *N*-methyl-2-chloropyridinium salt.[2] As alternative practical methods, the Schmidt reaction of ketones with azides[3] and the Beckmann rearrangement of oximes derived from ketones[4] are known. On the other hand, studies of the oxidative conversion of aldehydes into amides and the oxidative conversion of primary alcohols into amides are limited in spite of the efficiency of these approaches. The former reaction includes the treatment of aldehydes with molecular iodine in aq NH_3, followed by the reaction with 33% aq H_2O_2,[5a] the treatment of aromatic aldehydes with KI-^{t}BuOOH,[5b] the treatment of aldehydes with PhI = NTs in the presence of a catalytic amount of Ru-porphyrin,[5c] the treatment of aldehydes with secondary amines in the presence of Rh catalyst,[5d] the treatment of aldehydes with primary amines in the presence of CuI–$AgIO_3$ catalyst,[5e] the treatment of aromatic aldehydes with secondary amines in the presence of ^{t}BuOOH[5f] and the treatment of aromatic aldehydes with primary amines in the presence of (diacetoxy)iodobenzene[5g] to provide the corresponding amides. The latter reaction utilizes a manganese(IV) dioxide-sodium cyanide system in a THF solution containing ammonia or primary amines for the conversion of benzylic alcohols into the corresponding aromatic amides,[6a–c] and the initial oxidation of benzylic alcohols to aldehydes with iridium catalyst, $[Ir(Cp)Cl_2]_2$ and $CsCO_3$, followed by the treatment with hydroxylamine, to provide aromatic amides.[6d] Moreover, the oxidative amidation of alcohols with amine proceeds efficiently in the presence of catalytic amounts of $Ru(COD)Cl_2$ with 1,3-diisopropylimidazolium chloride, tricyclohexylphosphine and BuOK,[6e] and in a Ru-PNN-catalyzed system,[6f] in a $[Ru(p\text{-cymene})Cl_2]_2$-catalyzed system with bis(2-diphenylphosphinophenyl)ether,[6g] and by treatment of aminoalcohols with Ru catalyst, to provide lactams.[6h] However, a majority of those approaches require metal-based oxidizing agents. Thus, a metal-free, environmentally benign, economical, and simple oxidation approach is desired.

Here, as part of our study of molecular iodine for organic synthesis,[7] we would like to report a metal-free one-pot oxidative conversion of benzylic alcohols and benzylic halides into the corresponding aromatic amides, respectively, with molecular iodine in aq NH_3, followed by the treatment with ~30% aq H_2O_2.

At first, the one-pot oxidative conversion of benzylic alcohols into the corresponding amides was studied as follows.[8] A mixture of 4-methylbenzyl alcohol and molecular iodine in aq NH_3 (28–30%) was warmed for 2 h at 60 °C. Then, the reaction mixture was cooled to 0 °C and aq NH_3 was added again to the mixture. Finally, ~30% aq H_2O_2 was added dropwise to the reaction mixture via a dropping funnel. After being stirred for 2 h at rt, the mixture was poured into aq saturated Na_2SO_3 and then extracted with $CHCl_3$ to provide 4-methylbenzamide in 91% yield, as shown in Table 1 (entry 1). Based on these conditions, other benzylic alcohols, such as *p*-chlorobenzyl alcohol, *p*-methoxybenzyl alcohol, benzyl alcohol, *p*-nitrobenzyl alcohol, and *m*-nitrobenzyl alcohol, were treated under the same conditions to provide the corresponding

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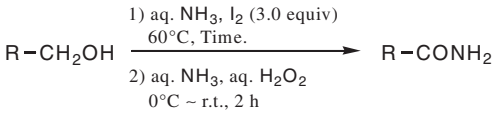
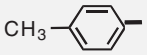
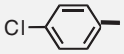
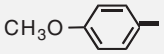
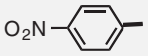
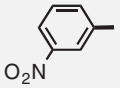
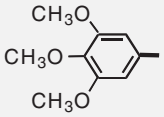
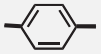
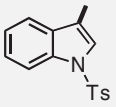
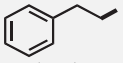
doi:10.1016/j.tetlet.2010.06.051

Table 1
Metal-free one-pot oxidative conversion of benzylic alcohols into amides with I_2 in aq NH_3, followed by treatment with H_2O_2



Entry	R–	Time (h)	Yield (%)
1		2	91
2		2	93
3		2	94
4		2	82
5		3	70
6		3	85
7		3	87
8		2	53 (39)[a]
9		3	62 (12)[a]
10		2[b]	63
11		3[b]	88
12		4	81
13		24	43 (37)[a]
14	$CH_3(CH_2)_4$–	6	78
15		8	92
16		6	61 (30)[a]

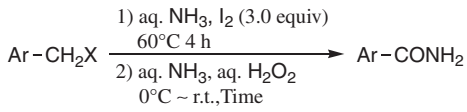
[a] Yield of nitrile.
[b] Two times of aq NH_3 and I_2 were used.

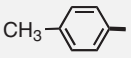
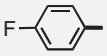
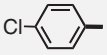
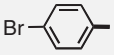
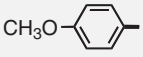
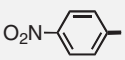
amides in good yields (entries 2–6). The yields with electron-rich alcohols, such as 3,4,5-trimethoxybenzyl alcohol and 2-(hydroxymethyl)thiophene, were moderate, due to the less reactivity of the formed aromatic nitriles against peroxide nucleophile (entries 8 and 9). The same treatment of 1,3- and 1,4-bis(hydroxymethyl)benzenes gave the corresponding benzenediamides in good yields (entries 10, 11). Heteroaromatics, such as 2-(hydroxymethyl)thiophene and 3-hydroxymethyl-1-tosylindole, provided the corresponding amides in good yields under the same conditions (entries 9 and 12). Moreover, the same treatment of primary alcohols, such as 1-hexanol, cyclohexylmethanol, and 1-adamantylmethanol, also provided the corresponding amides in good yields, respectively (entries 14–16).

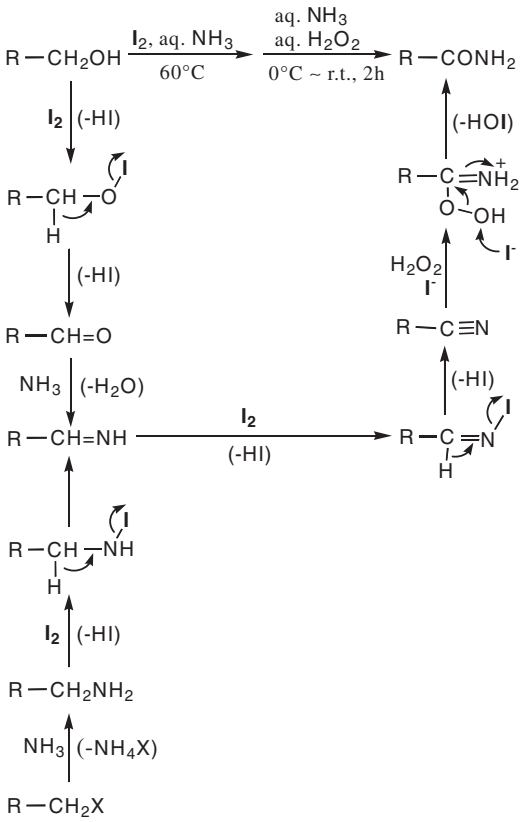
Then, the oxidative one-pot conversion of benzylic halides into amides was studied as follows.[9] A mixture of 4-methylbenzyl chloride and molecular iodine in aq NH_3 was warmed for 4 h at 60 °C. Then, the reaction mixture was cooled to 0 °C, aq NH_3 was added again, and ~30% aq H_2O_2 was slowly added dropwise via a dropping funnel. After being stirred for 2 h at rt, the reaction mixture was poured into aq saturated Na_2SO_3 and the whole was extracted with $CHCl_3$ to give 4-methylbenzamide in 81% yield, as shown in Table 2 (entry 1). The same treatment of 4-methylbenzyl bromide and 4-methylbenzyl iodide gave 4-methylbenzamide in good yields, respectively (entries 2 and 3). Other benzylic chlorides, bromides, and iodides could be also converted into the corresponding amides in good yields (entries 4–20). However, the same treatment of alkyl halides provided the corresponding amides in low yields, together with the starting alkyl halides and amines.

A plausible reaction mechanism for the formation of aromatic amide from benzylic alcohols and benzylic halides is shown in Scheme 1. Here, the addition of molecular iodine to a solution of *p*-tolualdehyde in aq NH_3 induced the rapid formation of *p*-tolunitrile at rt, and the subsequent treatment of the reaction mixture with ~30% aq H_2O_2 provided *p*-toluamide in high yield at rt, as shown in Scheme 2. The addition of ~30% aq H_2O_2 with a dropping funnel to a mixture of *p*-tolunitrile in aq NH_3 in the presence of KI smoothly gave *p*-toluamide in high yield at rt. Once the imine was formed from the reaction of aldehyde with ammonia or the oxida-

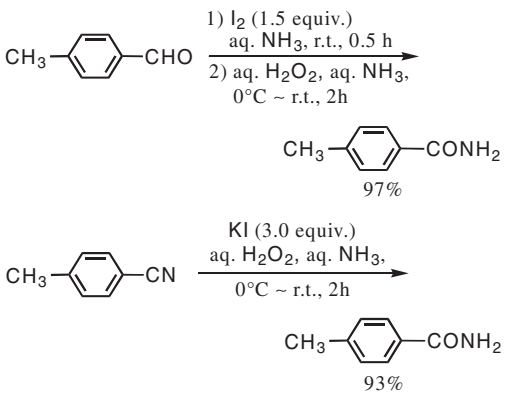
Table 2
Metal-free one-pot oxidative conversion of benzylic halides into aromatic amides with I_2 in aq NH_3, followed by treatment with H_2O_2



Entry	Ar–		Time (h)	Yield (%)
1		X = Cl	2	81
2		X = Br		72
3		X = I		69
4		X = Cl	2	93
5		X = Br		98
6		X = I		99
7		X = Cl	2	67
8		X = Br		69
9		X = I		66
10		X = Cl	2	75
11		X = Br		84
12		X = I		73
13		X = Cl	2	81
14		X = Br		73
15		X = I		89
16		X = Cl	2	85
17		X = Br		92
18		X = Cl	2	86
19		X = Br		93
20		X = I		82



Scheme 1. Plausible reaction pathway.



Scheme 2.

tion of primary amine with molecular iodine, nitrile is smoothly formed via the HI-elimination of *N*-iodoimine. The reaction of nitrile with ~30% aq H_2O_2 in the presence of iodide in aq NH_3, which works as a reducing agent of peroxide, generated the amide.

In conclusion, benzylic alcohols could be converted into the corresponding aromatic amides in good yields in a one-pot manner by the treatment with molecular iodine in aq NH_3, followed by the reaction with ~30% aq H_2O_2. Similarly, benzylic halides could be also converted into the corresponding aromatic amides in good yields in a one-pot manner with the same procedure. The present reactions involve the metal-free one-pot oxidative conversion of benzylic alcohols and benzylic halides into the corresponding aromatic amides, respectively, although excess amounts of aq NH_3 and ~30% aq H_2O_2 are required. Further study in the present reaction system is underway in this laboratory.

Acknowledgments

Financial support in the form of a Grant-in-Aid for Scientific Research (No. 20550033) from the Ministry of Education, Culture, Sports, Science, and Technology in Japan and Iodine Research Project in Chiba University is gratefully acknowledged.

References and notes

1. (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243; (b) Kleeman, A.; Engel, J. *Pharmaceutical Substances; Syntheses, Patents, Applications*, 4th ed.; Thieme: Stuttgart, 2001; (c) Bode, J. W. *Curr. Opin. Drug Discov. Dev.* **2006**, *9*, 765; (d) Cupid, T.; Tulla-Puche, J.; Spengler, J.; Albericio, F. *Curr. Opin. Drug Discov. Dev.* **2007**, *10*, 768.
2. (a) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: Weinheim, 1999; Recent reviews: (b) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447; (c) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.
3. (a) Schmidt, R. F. *Ber.* **1924**, *57*, 704; (b) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146.
4. (a) Bechmann, E. *Ber.* **1886**, *19*, 988; (b) Beckmann, E. *Ber.* **1887**, *20*, 1507; (c) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599.
5. (a) Shie, J.; Fang, J. *J. Org. Chem.* **2003**, *68*, 1158; (b) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Prashanthi, S.; Kantam, M. L. *Tetrahedron* **2009**, *50*, 2050; (c) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1138; (d) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523; (e) Yoo, W.; Li, C. *J. Am. Chem. Soc.* **2006**, *128*, 13064; (f) Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429; (g) Fang, C.; Qian, W.; Bao, W. *Synlett* **2008**, 2529.
6. (a) Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1971**, 733; (b) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synlett* **2002**, 1293; (c) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055; (d) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 73; (e) Nordstrom, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672; (f) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790; (g) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667; (h) Naota, T.; Murahashi, S. *Synlett* **1991**, 693.
7. Reviews: (a) Togo, H.; Iida, S. *Synlett* **2006**, 2159; (b) Togo, H. *J. Synth. Org. Chem.* **2008**, *66*, 652; Papers: (c) Mori, N.; Togo, H. *Synlett* **2004**, 880; (d) Mori, N.; Togo, H. *Tetrahedron* **2005**, *61*, 5915; (e) Ishihara, M.; Togo, H. *Synlett* **2006**, 227; (f) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474; (g) Iida, S.; Togo, H. *Tetrahedron* **2007**, *63*, 8274; (h) Iida, S.; Ohmura, R.; Togo, H. *Tetrahedron* **2009**, *65*, 6257; (i) Ushijima, S.; Togo, H. *Synlett* **2010**, 1067.
8. *Typical procedure for the preparation of aromatic amides from benzylic alcohols*: To a mixture of 4-methylbenzyl alcohol (122.2 mg, 1.0 mmol) and aq NH_3 (3 mL, ca. 28%) was added I_2 (761.4 mg, 3 mmol) at rt under empty balloon. The mixture was stirred for 2 h at 60 °C. Then, the reaction mixture was cooled to 0 °C, aq NH_3 (10 mL) was added again to the mixture, and aq H_2O_2 (10 mL, ca. 30%) was slowly added to the reaction mixture via a dropping funnel. After the reaction mixture was stirred for 2 h at rt, it was poured into aq satd. Na_2SO_3 (3 mL), and was extracted with $CHCl_3$ (20 mL × 3). The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, 4-methylbenzamide was obtained in 91% yield in an almost pure state. If necessary, the amide was purified by flash column chromatography on silica gel (eluent: AcOEt) as a colorless solid.
4-Methylbenzamide: Mp 160–161 °C (commercial, mp 161–163 °C); IR (Nujol): 1618, 1661, 3177, 3345 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ = 2.40 (s, 3H), 5.97 (br s, 2H, –NH), 7.25 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H).
9. *Typical procedure for the preparation of aromatic amides from benzylic halides*: To a mixture of benzyl bromide (171.1 mg, 1.0 mmol) and aq NH_3 (3 mL, ca. 28%) was added I_2 (761.4 mg, 3 mmol) at rt under an empty balloon. The mixture was stirred for 4 h at 60 °C. Then, the reaction mixture was cooled to 0 °C, aq NH_3 (10 mL) was added again to the mixture, and aq H_2O_2 (10 mL, ca. 30%) was slowly added to the mixture via a dropping funnel. After the reaction mixture was stirred for 2 h at rt, it was poured into aq satd. Na_2SO_3 (3 mL), and was extracted with $CHCl_3$ (15 mL × 3). The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, benzamide was obtained in 98% yield in an almost pure state. If necessary, the amide was purified by flash column chromatography on silica gel (eluent: AcOEt) as a colorless solid.
Benzamide: Mp 123.3–125.5 °C (commercial, mp 128 °C); IR (Nujol): 1624, 1655, 3169, 3364 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.42 (t, J = 7.8 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 2H).
4-Chlorobenzamide: Mp 178.1–180.2 °C (commercial, mp 179 °C); IR (Nujol): 1620, 1654, 3178, 3365 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.46 (s, 1H, –NH), 7.53 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 8.05 (s, 1H, –NH).
4-Methoxybenzamide: Mp 165.8–166.4 °C (commercial, mp 166 °C); IR (Nujol): 1618, 1645, 3168, 3389 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 3.81 (s, 3H), 6.98 (d, J = 8.6 Hz, 2H), 7.19 (br s, 1H, –NH), 7.83 (br s, 1H, –NH), 7.85 (d, J = 8.6 Hz, 2H).
4-Nitrobenzamide: Mp 199.3–202.0 °C (commercial, mp 203 °C); IR (Nujol): 1595, 1677, 3162, 3476 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ = 7.73 (br s, 1H, –NH), 8.11 (d, J = 8.4 Hz, 2H), 8.30 (br s, 1H, –NH), 8.31 (d, J = 8.4 Hz, 2H).
2,5-Dimethylbenzamide: Mp 182.2–183.0 °C (lit.[10] mp 185–186 °C); IR (Nujol): 1605, 1650, 3177, 3359 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 2.33 (s, 3H), 2.45 (s, 3H), 7.12–7.16 (m, 2H), 7.28 (s, 1H).

3,4,5-Trimethoxybenzamide: Mp 176.6–178.1 °C (commercial, mp 180 °C); IR (Nujol): 1618, 1661, 3185, 3359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.92 (s, 9H), 7.05 (s, 2H).

2-Thiophenecarboxamide: Mp 179.1–180.2 °C (commercial, mp 182 °C); IR (Nujol): 1607, 1650, 3170, 3361 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.31 (t, J = 4.3 Hz, 1H), 7.38 (br s, 1H, –NH), 7.73 (d, J = 4.1 Hz, 1H), 7.74 (d, J = 4.1 Hz, 1H), 7.97 (br s, 1H, –NH).

Terephthalamide: Mp >250 °C (lit.[11] mp 320–323 °C); IR (Nujol): 1621, 1661, 3166, 3360 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 8.42 (br s, 2H, –NH), 8.84 (s, 4H), 9.01 (br s, 2H, –NH).

3-Phenylpropionamide: Mp 96.1–97.6 °C (commercial, mp 101 °C); IR (Nujol): 1626, 1649, 3182, 3389 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.54 (t, J = 15.5 Hz, 2H), 2.98 (t, J = 15.5 Hz, 2H), 5.27 (br s, 2H, –NH), 7.19–7.32 (m, 5H).

Hexanamide: Mp 95.3–97.0 °C (commercial, mp 100 °C); IR (Nujol): 1632, 3191, 3358 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 0.86 (t, J = 7.0 Hz, 3H), 1.28–1.32 (m, 4H), 1.47 (quintet, J = 7.5 Hz, 2H), 2.02 (t, J = 7.5 Hz, 2H), 6.68 (br s, 1H, –NH), 7.22 (br s, 1H, –NH).

Cyclohexanecarboxamide: Mp 180.5–182.8 °C (commercial, mp 186–188 °C); IR (Nujol): 1635, 3168, 3338 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.20–1.33 (m, 3H), 1.38–1.44 (m, 2H), 1.70 (m, 1H), 1.79–1.82 (m, 2H), 1.89–1.92 (m, 2H), 2.11–2.18 (m, 1H).

1-Adamantanecarboxamide: Mp 185.5–191.7 °C (commercial, mp 188 °C); IR (Nujol): 1635, 3422, 3512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.70–1.76 (m, 6H), 1.84–1.95 (m, 9H), 5.66 (br s, 2H, –NH).

3-Nitrobenzamide: Mp 147.0–150.5 °C (commercial, mp 143 °C); IR (Nujol): 1624, 1690, 3176, 3325 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 7.76 (s, 1H, –NH), 7.84 (t, J = 7.9 Hz, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.40 (s, 1H, –NH), 8.44 (d, J = 7.9 Hz, 1H), 8.75 (s, 1H).

Isophthalamide: Mp >250 °C (lit.[12] mp 286 °C); IR (Nujol): 1626, 1658, 3153, 3362 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 7.48 (s, 2H, –NH), 7.54 (t, J = 7.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 2H), 8.21 (s, 2H, –NH), 8.52 (s, 1H).

10. Chakraborty, D. P.; Mandal, A. K.; Roy, Swapan K. *Synthesis* **1981**, 977.
11. Theodorou, V.; Karkatsoulis, A.; Kinigopoulou, M.; Ragoussis, V.; Skobridis, K. *Arkivoc* **2009**, *11*, 277.
12. Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, 949.