chemistry proceedings

MDPI

Proceedings

A New Approach for the Synthesis of *N*-Arylamides Starting from Benzonitriles †

Pradip Debnath

Department of Chemistry, Maharaja Bir Bikram College, Agartala, Tripura 799004, India; pradipchem78@gmail.com; Tel.: +91-381-2526-607; Fax: +91-381-2516-728

† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: *N*-Arylamides are a ubiquitous component of a broad range of natural products and biologically active compounds. In this paper, a new synthetic protocol for the preparation of *N*-arylamides has been developed via hypervalent iodine mediated *aza*-Hofmann type rearrangement of amidines. The reaction proceeds smoothly at 100 °C in the presence of PhINTs in toluene solvent. The requisite amidine substrates were prepared from amines and nitriles by applying Pinner reaction approach. Considering the easy access of amidines from nitriles, the overall process is the conversion of nitriles to acetanilide and *N*-arylamides. As an application of the protocol, the preparation of paracetamol from 4-cyanophenol has been also described.

Keywords: *N*-Arylamides; nitriles; amidines; paracetamol

Citation: Debnath, P. A New Approach for the Synthesis of *N*-Arylamides Starting from Benzonitriles. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Julio A. Seijas

Published: 15 November 2021

1. Introduction

Amide bond containing compounds are a ubiquitous component of a broad range of natural products and biologically active compounds [1,2]. In recent year, molecules with amide moieties have attracted considerable attention in medicinal chemistry due to their significant and diverse biological activities, including antipyretic[3], antimalarial [4], anti-inflammatory [5], and antitumor [6] agents. A recent study showed that about 25% of the known pharmaceuticals contained at least one amide bond [7]. More importantly, it constitutes the backbone of the biological crucial proteins and peptides. *N*-Arylamides are an important class of amides widely present in natural products (e.g., penicillin, paclitaxel), pharmaceuticals, and agrochemicals, as well as in a large number of industrial materials including polymers, detergents and lubricants [8,9]. The most popular and general methods for the preparation of these class of compounds rely on the reaction of activated carboxylic acid derivatives, such as chlorides, anhydrides or esters, with amines or, alternatively, the direct union of the carboxylic acids with amines assisted by stoichiometric amounts of coupling reagents [10,11]. However, these classical approaches are in low atom efficiency and generate large amounts of waste products, making their environmental profile unfavourable. New synthetic approaches that do not require activation of the carboxylic acid with a stoichiometric reagent, based on a Lewis acid (e.g. boronic acids) [12] or silica [13] as catalyst were developed. Catalyst poisoning as well as substrate scope are the main challenges remaining in this attractive approach. Among the transition-metal catalyzed synthetic methods developed so far [14], the direct formation of the C–N bond through cross-coupling reaction of arylhalides (I, Br, Cl) or pseudohalides (OTf, OTs, OMs etc.) with primary or secondary amides is one of the best method in terms of versatility [15]. These amidation methods are mainly catalyzed by the transition metal such as palladium and copper catalysts; and it is necessary to install the leaving group beforehand on the aromatic coupling partner which finally ends up with undesirable waste. It is,

therefore, highly desirable to develop an efficient and more environmental friendly method for the synthesis of *N*-arylamides.

In the recent years, hypervalent iodine compounds have emerged as environmentally friendly and efficient oxidizing reagents for various synthetically useful oxidative transformations [16]. These compounds are stable, less toxic, commercially available, and easy to handle. Now-a-days, various hypervalent iodine reagents are widely used as a green oxidant for the Hofmann rearrangement of primary amides [17]. In this context, very recently, Li and co-workers have reported the Hoffmann-type rearrangement of primary amides to secondary amides using $PhI(OAc)_2$ as an oxidizing reagent [18]. In the 1990s Ramsden and co-workers described the phenyliodine(III)diacetate (PIDA) mediated oxidative rearrangement of *N*-substituted amidines to carbodiimides.[19] Recently, we observed that carbodiimides obtained from amidines can easily be transformed into acetanilides via the reaction with acetic acid in situ generation from PhI(OAc)2 [20]. Although, this method is highly efficient for the preparation of acetanilides but there are some disadvantages associated with this protocol. The main limitation of the protocol is the limited substrate scope that is restricted to the synthesis of acetanilides only. Different hypervalent iodine reagents were required for the preparation of anilides other than acetanilide which reduces its applicability in the development of chemical project. Therefore, we envisaged that by exploring suitable oxidant systems, the *aza*-Hofmann rearrangement of amidines would lead to in situ formation of carbodiimides. Subsequent reaction of carbodiimides with a carboxylic acid may provide the easy access to *N*-arylamides (anilides) in one-pot process.

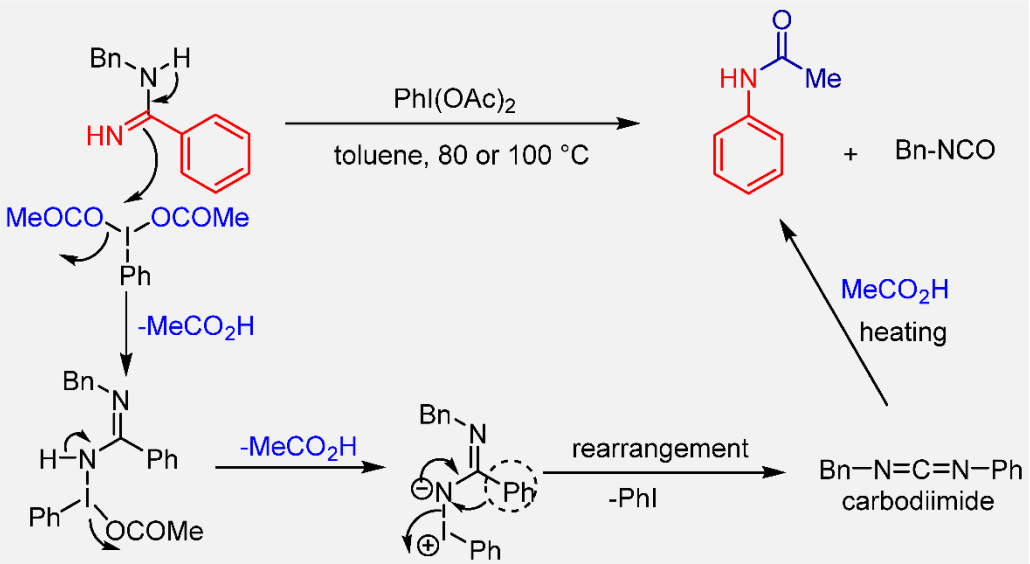
In this paper, we have demonstrated a new synthetic protocol for the preparation of *N*-arylamides including paracetamol via hypervalent iodine mediated *aza*-Hofmann type rearrangement of amidines. The requisite amidine substrates were prepared from amines and nitriles by applying Pinner reaction approach [21]. Considering the easy access of amidines from nitriles, the overall process is the conversion of nitriles to anilides. As an application of the protocol, we have synthesized paracetamol from 4-cyanophenol.

2. Materials and Methods

In our previous work, we have demonstrated the synthesis of secondary amides from *N*-substituted amidines by tandem oxidative rearrangement and isocyanate elimination. In that approach, $PhI(OAc)_2$ mediated oxidative rearrangement of *N*-substituted amidines in-situ generated an carbodiimide intermediate, which was subsequently trapped by an in situ generated acetic acid from $PhI(OAc)_2$ to provide the corresponding acetanilides (Scheme 1). The main disadvantage of this protocol is that different hypervalent iodine reagents are required for the synthesis of anilides other than acetanilide which reduces its applicability in the development of chemical project. Therefore, we envisaged that by exploring suitable oxidant systems other than $PhI(OAc)_2$, the oxidative rearrangement of amidines would lead to in situ formation of carbodiimides. Subsequent reaction of carbodiimide with a carboxylic acid would provide the access to anilides in one-pot process. The efficient oxidative rearrangement of amidines without competitive nucleophilic addition of in situ generated nucleophiles may be an efficient approach for the success of this transformation. Moreover, the reactivity of hypervalent iodines can be modulated by changing the substituents and the nucleophile in situ generated can be selected.

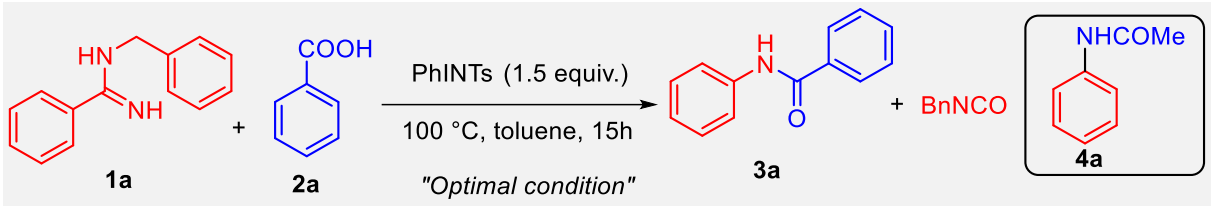
Based on these elegant ideas, we started our investigation with *N*-benzylbenzamidine (**1a**) as model substrate for the generation of carbodiimide. Benzoic acid (**2a**) was selected for the reaction with carbodiimide. When **1a** and **2a** were heated with 1.5 equiv. $PhI(OAc)_2$ in toluene at 100 °C for 15h, a mixture of two anilides, benzanilide (**3a**) and acetanilide (**4a**) was obtained in 48% and 40% yields, respectively (Table 1, entry 1). Unfortunately, we didn't obtained any product when the reaction was performed with $PhI(OCOCF_3)$ as oxidant (Table 1, entry 2). Interestingly, by switching the hypervalent iodine reagent from $PhI(OAc)_2$ to PhINTs, a full conversion was achieved in an overnight reaction (15 h) and only one product, benzanilide was obtained in 86% yield (Table 1,

entry 3). In this reaction *N*-tosyl aniline was eliminated as by-product from PhINTs. Due to the lower nucleophilicity of *N*-tosyl aniline, benzoic acid attacks the carbodiimide leading to the formation of benzanilide product. Screening of solvent revealed that toluene is to be the best solvent for this transformation (entries 4–6). Next, we investigated the influence of base on this tandem reaction. It was observed that additive (base) either has no influence or negative influence on the yield of product (Table 1, entries 7–10). Thus, the optimal reaction conditions for this transformation as follow amidine (0.5 mmol), carboxylic acid (1 mmol), PhINTs (0.75 mmol), and toluene (1 mL), at 100 °C for 15h.



Scheme 1. Synthesis of secondary amides via PhI(OAc)$_2$-mediated oxidative rearrangement of *N*-substituted amidines.

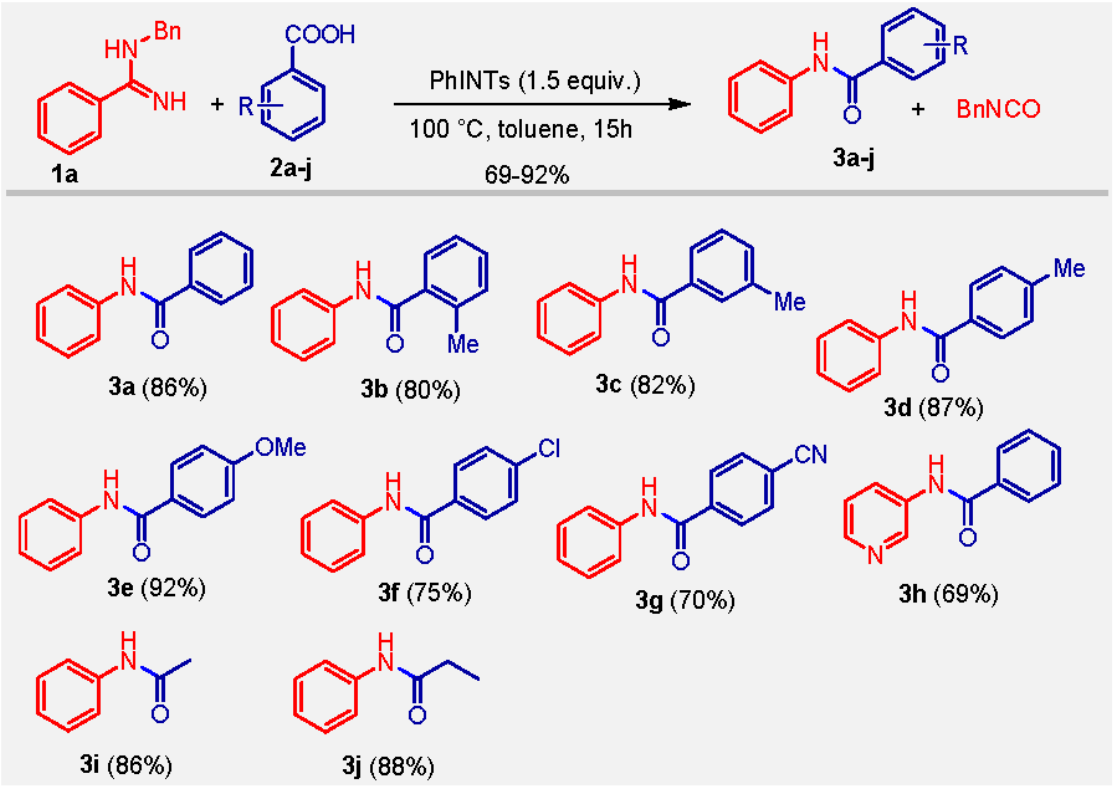
Table 1. Optimization reactions for the preparation of benzanilide from *N*-benzylbenzamidine.



Entry	Oxidant (1.5 eq)	Solvent (1 mL)	Additives (1.1 eq)	Yield (%) 3a/4a
1	PhI(OAc)$_2$	toluene	-	48/40
2	PhI(OCOCF$_3$)	toluene	-	0/0
3	**PhINTs**	**toluene**	**-**	**86/0**
4	PhINTs	THF	-	74/0
5	PhINTs	DMF	-	35/0
6	PhINTs	o-xylene	-	68/0
7	PhINTs	toluene	Et$_3$N	77/0
8	PhINTs	toluene	AcOK	58/34
9	PhINTs	toluene	Cs$_2$CO$_3$	42/0
10	PhINTs	toluene	Pyridine	58/0

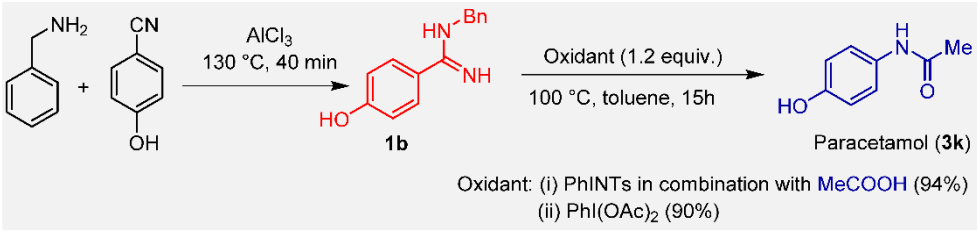
3. Results and Discussion

We then explored the substrate scope and limitation of the protocol. Various aliphatic and aromatic carboxylic acids bearing electron-donating as well as electron-withdrawing group were reacted with the carbodiimide generated from *N*-benzylbenzamidine (**1a**), affording benzanilides (**3**) in good to excellent yields. Various functional groups such as Me, OMe, Cl, CN substituted at *ortho*-, *meta*-, and *para*-positions of aromatic carboxylic acids were well tolerated under the reaction conditions and furnished desired products in high yields (Scheme 2).



Scheme 2. PhINTs-mediated synthesis of benzanilides from *N*-benzylbenzamidine.

N-Acetyl-para-aminophenol (APAP), commonly known as paracetamol or acetaminophen, is a representative of the *N*-arylamide class drug. This drug is one of the most consumed worldwide with a global production of more than 100,000 tons per year. Over the last century, many routes have been explored for the preparation of paracetamol [22–24] but all those which have emerged industrially are based on the acetylation of para-aminophenol (PAP) as final stage [25,26]. We applied this protocol for the preparation of paracetamol stating from 4-cyanophenol. The reaction of 4-cyanophenol with benzylamine in the presence of 1.2 equiv. of anhydrous $AlCl_3$ at 130 °C to give the corresponding amidine (**1b**). The oxidative rearrangement of **1b** with $PhI(OAc)_2$ (1.5 equiv.) in toluene at 100 °C for 15 h to give the paracetamol (**3k**) in 90% yield. When the same reaction is carried out with PhINTs, 94% of paracetamol is obtained. The overall process is to be considered as the conversion of 4-cyanophenol into paracetamol.



Scheme 3. Synthesis of paracetamol from amidine.

4. Conclusions

In conclusion, we have developed an efficient and sustainable protocol for the preparation of *N*-arylamides (anilides) from *N*-substituted amidines. All the reaction proceeded smoothly with PhINTs at 100 °C in toluene solvent. Various substituted *N*-arylamides were obtained in high yields under oxidative reaction conditions. As an application of this protocol we have synthesized paracetamol in high yield starting from 4-cyanophenol.

5. Experimental

General procedure for the synthesis of *N*-substituted amidines from amines and carbonitriles: A pressure flask (50 mL) equipped with a small stirring bar was charged with the amine (5.5 mmol, 1.1 equiv.) and the carbonitrile (5.0 mmol, 1.0 equiv). $AlCl_3$ (0.7 g, 0.5 equiv.) was added in one portion. The flask was tightly sealed with a Teflon screw cap and placed into a preheated oil bath at 130 °C. The reaction mixture was stirred for 40 min, and subsequently taken out of the oil bath. Ice-water (50 mL) was added and under vigorous stirring concentrated aqueous NaOH (2 M) was added until a pH of 14 was reached. The aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with water and then brine, and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified using chromatography with heptane/ ethyl acetate-7N NH_3 in MeOH (19:1) eluent.

General procedure for the PhINTs-medidated oxidative rearrangement of *N*-substituted amidines to anilides: In an oven-dried microwave vial (10 mL) equipped with a magnetic stirring bar the *N*-benzylbenzamidine (0.5 mmol), carboxylic acid (1 mmol) and PhINTs (0.75 mmol) were charged. The vessel was flushed with N_2 and then sealed with septum. 1 mL of dry toluene was added to the vessel and the reaction mixture was heated at 100 °C for 15 h. After completion of the reaction, the toluene was evaporated under reduced pressure. The crude product was purified by chromatography using hexane and ethylacetate (19:1) as eluent.

***N*-Phenylbenzamide (3a)**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.07 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 8.1 Hz, 2H), 7.48–7.56 (m, 3H), 7.75 (d, *J* = 7.7 Hz, 2H), 7.92 (d, *J* = 7.0 Hz, 2H), 10.18 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 120.8, 124.1, 128.1, 128.8, 129.0, 132.0, 135.5, 139.6, 166.0.

***N*-(4-hydroxyphenyl)acetamide (3k):** ^{1}H NMR (400 MHz, DMSO-d_6) = 1.98 (s, 3H), 6.68 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 2H), 9.12 (brs, 1H, OH), 9.65 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) = 24.2, 115.4, 121.2, 131.5, 153.5, 166.9 ppm.

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Acknowledgments: The author is thankful to Tripura University, Suryamaninar, Tripura, India for providing the Bruker-400 spectrometer facility for spectral analysis.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Humphrey, J.M.; Chamberlin, A.R. Chemical synthesis of natural product peptides: coupling methods for the incorporation of noncoded amino acids into peptides. *Chem. Rev.* **1997**, *97*, 2243–2266.
2. Greenberg, A.; Breneman C. M.; Liebman, J.F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; John Wiley & Sons: New York, NY, USA, 2000.
3. Sullivan, J.E.; Farrar, H.C. Fever and antipyretic use in children. *Pediatrics* **2011**, **127**, 580–587
4. Zhang, Y.K.; Plattner, J.J.; Easom, E.E.; Jacobs, R.T.; Guo, D.; Freund, Y.R.; Berry, P.; Ciaravino, V.; Erve, J.C.L.; Rosenthal, P.J.; et al. Benzoxaborole antimalarial agents. Part 5. Lead optimization of novel amide pyrazinyloxy benzoxaboroles and identification of a preclinical candidate. *Med. Chem*. **2017**, *60*, 5889–5908.
5. Walesa, K.G.; Stec, A.P. *Med Acad. Lub.* **2003**, *9*, 118–125.
6. Warnecke, A.; Fichtner, I.; Sab, G.; Kratz, F. Synthesis, cleavage profile, and antitumor efficacy of an albumin-binding prodrug of methotrexate that is cleaved by plasmin and cathepsin B. *Arch. Pharm. Chem. Life Sci*. **2007**, *340*, 389–395.
7. Ghose, A.K.; Viswanadhan, V.N.; Wendoloski, J.J.J. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. *Comb. Chem*. **1999**, *1*, 55–68.
8. Chen, Y.; Pienkowski, E.W.; Ju, J.; Lin, S.; Rajski, S.R.; Shen, B.J. Characterization of FdmV as an amide synthetase for frederi-camycin A biosynthesis in *Streptomyces griseus* ATCC 43944. *Biol. Chem*. **2010**, *285*, 38853–38860.
9. Lakouraj, M.; Mokhtary, M.J. Synthesis of polyamides from p-Xylylene glycol and dinitriles. *Polym. Res*. **2009**, *16*, 681–686.
10. Bailey, P.D.; Mills, T.J.; Pettecrew, R.; Price, R.A. In *Comprehensive Organic Functional Group Transformations II*; Katrizky, A.R., Taylor, R.J.K., Eds.; Elsevier: Oxford, UK, 2005; Volume 5, p. 201.
11. El-Faham, A.; Albericio, F. Peptide coupling reagents, more than a letter soup. *Chem. Rev*. **2011**, *111*, 6557–6602.
12. Charville, H.; Jackson, D.; Hodges, G. Whiting, A. Boronic acid catalyzed amide bond formation. *Chem. Commun*. **2010**, *46*, 1813–1823.
13. Comerford, J.W.; Farmer, T.J.; MacQuarrie, D.J.; Breeden, S.W.; Clark, J.H. Silica-catalyzed amide bond formation. *Arkivoc* **2012**, 282–293.
14. Review on transition metal catalyzed amide bond formation: (a) Allen, C.L.; Williams, J.M.J. Metal-catalysed approaches to amide bond formation. *Chem. Soc. Rev.* **2011**, *40*, 3405–3415. (b) Pattabiraman, V.R.; Bode, J.W. Rethinking amide bond synthesis. *Nature* **2011**, *480*, 471–479.
15. (a) Yin, J.; Buchwald, S.L.J. Pd-catalyzed intermolecular amidation of aryl halides: the discovery that xantphos can be trans-chelating in a palladium complex. *Am. Chem. Soc*. **2002**, *124*, 6043–6048. (b) Jiang L.; Buchwald, S.L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
16. Yoshimura, A.; Zhdankin, V.V. Advances in synthetic applications of hypervalent iodine compounds. *Chem. Rev*. **2016**, *116*, 3328–3435.
17. Debnath, P. *Curr. Org. Synth.* **2018**, *15*, 666–706.
18. Wang, X.; Yang, P.; Hu, B.; Zhanga, Q.; Li, D.J. *Org. Chem.* **2020**, *86*, 2820–2826.
19. Ramsden, C.A.; Rose, H.L.J. Oxidative rearrangement and cyclisation of N-substituted amidines using iodine (III) reagents and the influence of leaving group on mode of reaction. *Chem. Soc. Perkin Trans. 1* **1997**, 2319–2327.
20. Debnath, P.; Baeten, M.; LefÀvre, N.; Daele, S.V.; Maes, B.U.W. Synthesis of Secondary Amides from N-Substituted Amidines by Tandem Oxidative Rearrangement and Isocyanate Elimination. *Adv. Synth. Catal*. **2015**, *357*, 197–209.
21. Noe, M.; Perosa, A.; Selva, M. A flexible Pinner preparation of orthoesters: the model case of trimethylorthobenzoate. *Green Chem*. **2013**, *15*, 2252–2260.
22. Caskey, D.C.; Chapman, D.W. Process for Preparing p-Aminophenol and Alkyl Substituted p-Aminophenol. US 4,571,437, 18 February 1986.
23. Rode, C.V.; Vaidya, M.J.; Chaudhari, R.V. Synthesis of p-aminophenol by catalytic hydrogenation of nitrobenzene. Organic process research & development. *Org. Process Res. Dev*. **1999**, *3*, 465–470.
24. Joncour, R.; Duguet, N.; Metay, E.; Ferreira, A.; Lemaire, M. Amidation of phenol derivatives: a direct synthesis of paracetamol (acetaminophen) from hydroquinone. *Green Chem*. **2014**, *16*, 2997–3002.
25. Wang, S.; Ma, Y.; Wang, Y.; Xue, W.; Zhao, X.J. Synthesis of p-aminophenol from the hydrogenation of nitrobenzene over metal–solid acid bifunctional catalyst. *Chem. Technol. Biotechnol*. **2008**, *83*, 1466–1471.
26. Liu, P.; Hu, Y.; Ni, M.; You, K.; Luo, H. Liquid phase hydrogenation of nitrobenzene to para-aminophenol over Pt/ZrO 2 catalyst and $SO_4^{2-}/ZrO_2–Al_2O_3$ solid acid. *Catal. Lett*. **2010**, *140*, 65–68.