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ONE POT REACTION FOR THE SYNTHESIS OF AMIDES FROM TOLUENE USING TERTIARY BUTYL AMMONIUM IODIDE

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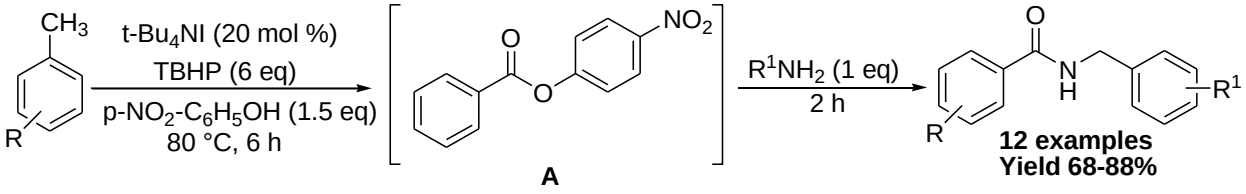
ABSTRACT:
An efficient one pot synthesis of amides from toluene through the activation of p-nitro phenolester using tetra butyl ammonium iodide (TBAI) and tetra butyl hydrogen peroxide (TBHP) indecane has been developed. We have also explored the wide substrate scope. In addition to this we have also studied the effect of electronic and steric factors on the yield by selecting appropriate substrates.

GRAPHICAL ABSTRACT



Keywords: P-nitro phenol ester, TBAI, TBHP, Steric factor, Substrate.

INTRODUCTION:

Polymers, natural products and pharmaceuticals contain amide functional group, which is important in synthetic organic chemistry. Therefore many researchers have developed methodologies for the synthesis of amides using both classical and modern methods. Amides are produced by a classical condensation reaction of carboxylic acids with nucleophilic amines. In addition the condensation reaction is in between alcohols and amino acids to obtain esters and peptides respectively.[2] Furthermore, amides have been prepared using acyl chlorides,[3] azides,[4] mixed anhydride[5], activated esters[6], coupling reagents[7] and carbonyl diimidazole (CDI).[8]iInterestingly, activation of carboxylic acids into an activated form followed by nucleophilic acylation takes place in most of the above methods.In extend amides have also been synthesized using transition metal catalysis and organo catalysis.[9]The reported methods having drawbacks such as using harsh temperature, expensive reagents, produce stoichiometric amount of waste.[10]Acylation of aldehydes has been recently achieved by converting them into activated form through transition metal catalysis and organocatlysis. But, for the synthesis of amides an important activating auxiliary i.e. *para* nitro phenolic esters, has notbeen attempted.[11] In this connection our group recently developed amidation from aldehydes using *para* nitro phenol as activating reagent. In continuation to our on-going research on amidation and esterification, we wish to demonstrate herein convenient synthesis of amides from toluene using TBHP and TBAI under ambient conditions *via*insitu formation of aldehydes and esters.

Experimental:

General

Before using the glassware was dried in an oven and cooled. Unless stated otherwise, all chemicals and solvents were used as suppliedwithout any extra purification. Reactions weremonitored by TLC onsilica gel plates and components were visualised using combination of UV-light and Iodine. Solvents were evaporated under reduced pressure at 50°C. NMR spectrawere recorded on a Bruker 400 MHz NMR spectrometer. Chemical shifts (d) and coupling constants(J)are given in ppm (parts per million) and Hz (Hertz), respectively.

Typical Procedure for Amidation of Toluene:

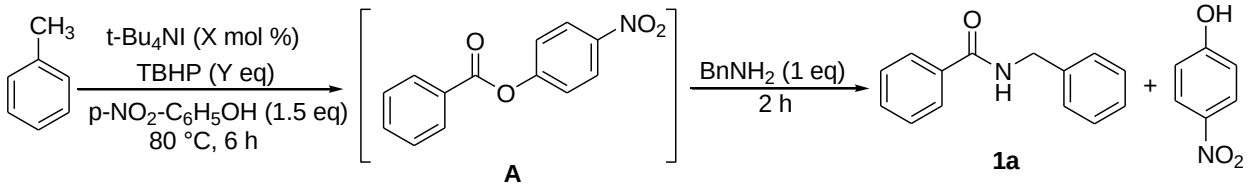
The toluene (1 mmol, 1 equiv.) and *para*nitrophenol (1.5 mmol, 1.5 equiv.) were mixed well with a magnetic stirrer. To this mixture*n*-Bu_4NI (20 mol% , 0.2equiv) and *tert*-butyl hydroperoxide (5.5 M) in decane (6.0equiv) were added at room temperature. The reaction mixture was heated at 80°C to accelerate the reaction. After completion of the reaction, thereaction mixture was cooled to room temperature and then the respective amine (1 equiv.) was added. Thereaction mixture was stirred at room temperature for 2 h and it was further diluted with 10 mL EtOAc, washed with 5% $NaHCO_3$(3×10 mL). The isolated product was almost pure, though it was recrystallized as per necessity.

RESULTS AND DISCUSSION:

Initially, the optimization of reaction conditions was conducted with toluene as a model substrate with various mol % of TBAI and different eq of TBHP at 80 °C. We could observe that the substrate proceeded reactions in the presence of TBAI (20 mol %), TBHP (6 eq) and p-nitro phenol (1.5 eq) at 80 °C to give corresponding ester **A**(which was observed in TLC) in complete conversion, that, gratifyingly reacts with benzyl amine to produce target product **1a**in complete conversion (Table 1, entry 4).

Having optimization reaction conditions in our hand, we explored the substrate scope. Benzyl amine bearing substituents such as 4-Me, 4-OMe and 4-Cl could produce their respective target products in 86%, 88% and 74% yields. Other substrates like *n*-butyl and *n*-pentyl amines proceeded reactions to afford their final products in good yield. We have also tried the reaction with tertiary butyl amine and very interestingly it gave target product in moderate yield. In order to extend the substrate scope, the reactions were conducted with cyclic amines and ester linkage amines. Both of them gave desired products in moderate yield. Finally, toluene possess both electron donating and electron withdrawing groups were also performed the reaction under optimized conditions. In this connection, toluene having electron donating group like 4-OMe gave desired product in excellent yield (Table 2, entry 10). Toluene bearing electron withdrawing groups like 4-Cl and 4-NO_2 proceeded reactions to provide target products in good yield (Table2, entry 11, 12).

Table 1: Optimization reaction conditions[a]



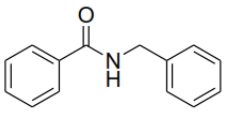
Entry	t-Bu_4NI (X)	TBHP (Y)	Conversion (**1a**)
1	20 mol %	2 eq	42
2	20 mol %	3 eq	58
3	20 mol %	4 eq	65
4	**20 mol %**	**6 eq**	**89**
5	10 mol%	6 eq	66
6	-	-	n.d.

[a]Reaction conditions:Toluene (1 mmol), t-Bu_4NI (20 mol %), TBHP (6 eq), p-NO_2-C_6H_5OH (1.5 eq), 80 °C, 6 h, $BnNH_2$ (1 eq), 2 h.

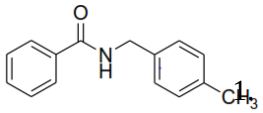
CONCLUSION

An efficient method for the one pot synthesis of amides from toluenes through the activation of p-nitro phenol ester using cheap catalyst has been developed. All the reactions are neat, general, simple and efficient. All the substrates readily underwent optimized reaction conditions to produce target products in moderate to excellent yield. The reaction is simple, carried out on a gram scale and high yield making the method a valuable to the existing method.

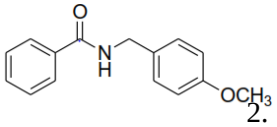
Spectral Data



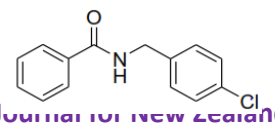
***N*-Benzylbenzamide**: yield 85%, white solid;^{1}H NMR (400 MHz, $CDCl_3$) d 7.75-7.72 (m,2H), 7.44-7.32 (m, 4H), 7.36-7.28 (m, 4H), 4.60 (d, *J* = 4.0 Hz, 2H).



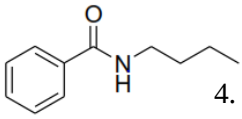
1. ***N*-(4-Methylbenzyl)benzamide**: yield 86%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.797.74(m,2H), 7.49-7.34(m,3H), 7.21-7.02(m,4H),4.52 (d, *J*=4.0 Hz,2H),2.23 (s,3H).



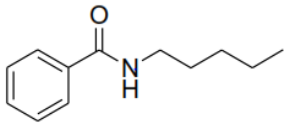
2. ***N*-(4-Methoxylbenzyl)benzamide**: yield 88%, white solid; ^{1}H NMR (400 MHz, CDCl3) d7.76-7.72 (m, 2H), 7.47-7.33 (m, 3H), 7.21-7.02 (m, 4H), 4.49 (d, *J* = 4.0 Hz, 2H), 3.71 (s, 3H).



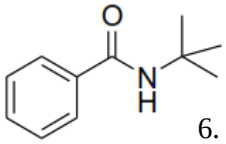
3. ***N*-(4-Chlorobenzyl)benzamide**: yield 74%, white solid; ^{1}H NMR (400 MHz, CDCl3) d7.827.69 (m, 2H), 7.50-7.39 (m, 3H), 7.18-7.05 (m, 4H), 4.49 (d, *J* = 4.0 Hz, 2H).



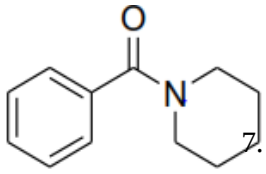
4. ***N*-Butylbenzamide**: yield 85%, white solid; ^{1}H NMR (400 MHz, CDCl3) 7.76-7.74 (d, *J* = 8.3 Hz, 2H), 7.37 - 7.51 (m, 3H), 6.35(br, s, 1H,), 3.72-3.42 (m, *J* = 12.84, 2H,), 1.62-1.50 (m, 2H,), 1.36-1.48 (m, 2H), 0.99 (t, *J* = 6.79, 3H).



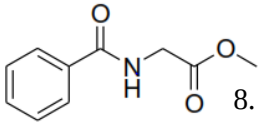
***N*-Pentylbenzamide**: yield 87%, white solid; ^{1}H NMR (400 MHz, CDCl3) 7.79-7.72 (d, *J* =8.3 Hz, 2H), 7.51 - 7.42 (m, 3H), 6.42 (br, 1NH, 1H), 3.73-3.45 (m, 2H,), 1.60-1.48 (m, 2H,), 1.42-1.21 (m, 4H), 0.99 (t, *J* = 6.79, 3H).



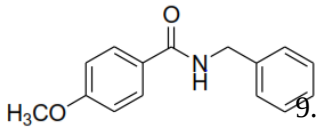
6. ***N*-*t*-Butylbenzamide**: yield 70%, white solid; ^{1}H NMR (400 MHz, CDCl3) 7.72-7.70 (d, *J* = 8.1 Hz, 2H), 7.37 - 7.45 (m, 3H), 5.84 (br, s, 1H,), 1.46 (s, 9H).



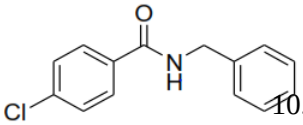
7. **Phenyl(piperidin-1-yl)methanone:** yield 72%, white solid; ^{1}H NMR (400 MHz, CDCl3) d 7.79-7.69 (m, 2H), 7.48-7.37 (m, 3H), 3.35-1.25 (m, 10H).



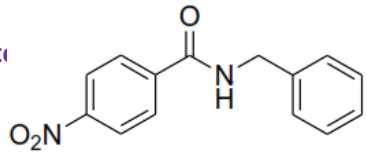
8. **Methyl 2-benzamidoacetate**: yield 68%, white solid; H NMR (400 MHz, CDCl3) 7.80-7.69 (m, 2H), 7.51-7.47 (m, 3H), 6.98 (br s, 1H, 1NH), 4.18 (d, 2H, *J* = 6.8 Hz), 3.67 (s, 3H).



9. ***N*-Benzyl-4-methoxybenzamide**: yield 85%, white solid; H NMR (400 MHz, CDCl3) 6.84 - 6.87 (d, 2H, *J* = 7.5 Hz), 7.26 - 7.30 (m, 5H), 7.69 - 7.72 (d, 2H, *J* = 7.5 Hz) 3.72 (s, 3H), 4.54 -4.56 (d, 2H, *J* = 5.5 Hz).

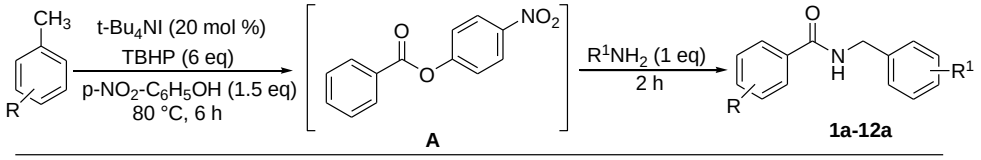


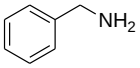
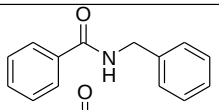
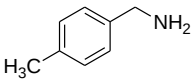
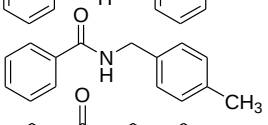
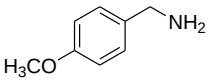
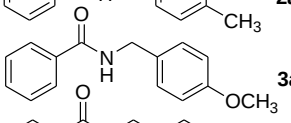
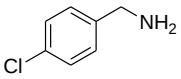
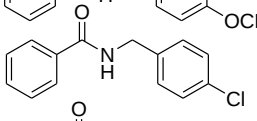
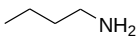
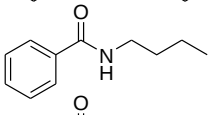
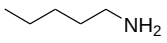
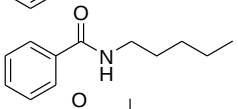
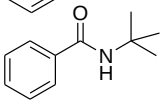
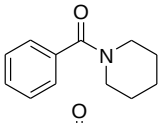
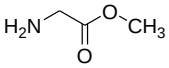
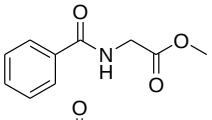
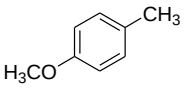
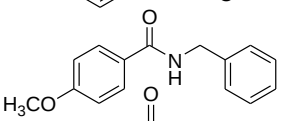
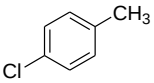
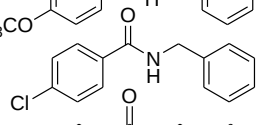
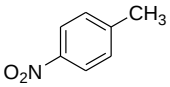
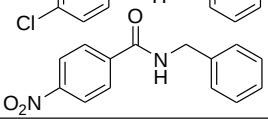
10. ***N*-Benzyl-4-chlorobenzamide**: yield 86%, white solid; ^{1}H NMR (400 MHz, CDCl3) d 7.82 7.69 (m, 2H), 7.50-7.39 (m, 3H), 7.18-7.05 (m, 4H), 4.49 (d, *J* = 4.0 Hz, 2H).



***N*-(4-Chlorobenzyl)benzamide**: yield 88%, white solid; ^{1}H NMR (400 MHz, CDCl3) 8.21 8.00 (m, 2H), 7.91 (d, *J* = 8.3, 2H), 7.21-711 (m, 5H), 6.25 (br, s, 1H, 1NH).

Table 2: Substrate scope



Entry	RNH_2	Product		Yield (%)
1			**1a**	85
2			**2a**	86
3			**3a**	88
4			**4a**	74
5			**5a**	85
6			**6a**	87
7			**7a**	70
8			**8a**	72
9			**9a**	68
10			**10a**	85
11			**11a**	86
12			**12a**	88

[a]Reaction conditions:Substrate (1 mmol), t-Bu_4NI (20 mol %), TBHP (6 eq), p-NO_2-C_6H_5OH (1.5 eq), 80 °C, 6 h, $BnNH_2$ (1 eq), 2 h.

References:

1. (a.)M. J. Humphrey, R. A. Chamberlin, *Chem. Rev*., 97,224 (1997); (b.)R. M.Wilson, J. L. Stockdill, X.Wu, X. Li, P. A. Vadola, P. K. Park, P. Wang, S. J. Danishefsky, *Angew. ChemInt. Ed*., 124, 2888 (2012); (c.) V. R. Pattabiraman, J.W. Bode, *Nature*, 480, 471 (2012); (d.) M. Bodanzsky, *Principles of Peptide Synthesis* 2nd ed., Springer, New York, 199.
2. (a.) L. A. Carpino, *J. Am. Chem. Soc*., 115, 4397 (1993); (b.) J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* 77, 1067 (1955); (c.) A. El- Faham, F. Albericio, *Chem. Rev*., 111, 6557 (2011); (d.) C. Najera, *Syn. let.*, 9, 1388 (2002).
3. R. C. Larock, In Comprehensive Organic Transformations; VCH Publisher Inc.; New York, 1989, p 980.
4 a) E. Saxon, C. R. Bertozzi, Science. 287 (2000), 2007. b) Damkaci, F.; DeShong, P. J. Am. Chem. Soc. 125 (2003), 4408.
5 a) Chen, C. T.; Kuo, J. H.; Li, C. H.; Barhate, N. B.; Hon, S.W.; Li, T. W.; Chao, S. D.; Liu, C. C.; Li, Y. C.; Chang, I. H.; Lin, J. S.; Liu, C. J.; Chou, Y. C.; Org. Lett.3(2001),3729. b) Chen, C.T.; Kuo, J. H.; Pawar, V. D.; Munot, M. S.; Weng, S. S. S.; Ku C. H.; Liu, C. Y. J. Org. Chem. 70 (2005), 1188.c) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M.; J. Org. Chem. 69 (2004), 1822. (d) Shiina, I.; Kawakita, Y. Tetrahedron, 60 (2004), 4729.
6 For a recent activation, see: Hardee, D. J.; Kovalchuke, L.; Lambert, T. H. J. Am. Chem. Soc.132 (2010), 5002.
7 Valeur, E.; Bradley, M. Chem. Soc. Rev.38 (2009), 606.
8. a) Aboussafy, C. L.; Jones, B. P.; Price, K. E.; Hardink, M. A.; McLaughlin, R. W.; Lillie, B. M.; Hawkins, J. M.; Vaidyanathan, R. Org. Lett. 12 **(**2010**),** 324. b) Rannard P. S.; Davis, N. J.; Org. Lett. 14 (2000),2117.
9. (a.)W. Yoo, C. Li, *J. Am. Chem. Soc*. 128, 13064 (2006); (b.) K. Ekoue-Kovi, C.Wolf, *Org.Lett*. 9,3429 (2007); (c.) C. L. Allen, S. Davulcu, J. M. J. Williams, *Org. Lett*. 12, 5096 (2010);(d.) C. Zhang, Z. Xu, L. Zhang, N. Jiao.*Angew. Chem. Int. Ed*. 50, 11088 (2011); (e.) S. C.Ghosh, J. S. Y.Ngiam, C. L. L. Chai, A. M. Seayad, T. T. Dang, A. Chen, *Adv. Synth. Catal*. 354, 1407 (2012).
10. (a.)I. Abdelmoty, F. Albericio, L.A. Carpino, B. M. Foxman, S.A. Kates, *Lett. Pept. Sci*., 1,57(1994); (b.) A. El-Faham, F. Albericio, *J. Org. Chem*. 73, 2731 (2008).
11. (a.) K. Y. K. Chow, J.W. Bode, *J. Am. Chem. Soc.*126, 8126 (2004); (b.) N. Y. Reynolds, J.R.deAlaniz, T. Rovis, *J. Am. Chem. Soc*. 126, 9518 (2004); (c.) R. M. Al-Zoubi, O. Marion, D. G. Hall.*Angew. Chem. Int. Ed*. 47, 2876 (2008); (d.) S. D. Sarkar, S. Grimme, A. Studer, *J. Am.Chem.Soc*.132, 1190 (2010); (e.) C. L. Allen, B. N. Atkinson, J. M. J. Williams. *Angew. Chem. Int. Ed*. 51,1383 (2012); (f.) T. B. Nguyen, J. Sorres, M. Q. Tran, L. Ermolenko, A. Al-Mourabit, *Org. Lett*. 14,3202 (2012); (g.) E. E. Finney, K. A. Ogawa, A. J. Boydston, *J. Am. Chem. Soc*. 134, 12374 (2012);(h.) B. Tan, N. Toda, C. F. Barbas III. *Angew. Chem. Int. Ed*. 51, 12538 (2012); (i.) G. Majji, S. Guin,A. Gogoi, S. K. Rout, B. K. Patel. *Chem. Commun.*49, 3031 (2013); (j.) D. Leow. *Org. Lett.*, 16,5812 (2014).