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Efficient Solvent Free Synthesis and X Ray Crystal Structure of Some Cyclic Moieties Containing N-Aryl Imide and Amide

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Abstract: Substituted N-aryl Phthalimides are an important class of compounds having various types of biological and chemical applications. Some substituted anilines were reacted with phthalic anhydride and acetic anhydride to give N-substituted aryl Phthalimides (L1-L5) and Acetamides (L6-L9) respectively. The reaction is done simply by fusion method by heating the two reactants together in the absence of any solvent and or catalyst. The reaction gave excellent yields ranging from 72 to 92%. The reaction time was just 3-5 minutes. The structures were confirmed by ^{1}HNMR and ^{13}CNMR, IR spectra, m/z ratio, elemental analysis and x-ray studies.

Key words: Substituted Anilines · N-Aryl Phthalimides · Fusion · Acetamide · Acetic Anhydride

INTRODUCTION

Depending upon the type of nucleophile present in the reactant specie, variety of products are obtained when such reactants are reacted with phthalic anhydride [1-4]. Although a lot of work is reported on the reaction of anhydrides with amines but there is not much research done on the formation of cyclic or open chain products. A valuable functionality which is proved to be having considerable pharmacological activities is cyclic imides. Antimicrobial, antiviral, anti-inflammatory, anti cancer, antispasmodic and plant growth regulator activities are the major groups of interest for such kind of bioactive compounds [5-13]. Phthalimides have been used as an important precursors for the synthesis of a variety of alkaloids and other pharmacophores.

Available procedures for the synthesis of cyclic imides are still insufficient as compared to their applications and use [14]. Condensation of an amine with anhydride involving dehydration in the presence of different reagents, catalysts and/or solvents is most commonly used procedure [15-17]. Microwave assisted synthesis of cyclic imides is also been carried out [18]. Westaway and Gedye couldn't observe much difference when they compared the reaction carried out by microwave or reflux.

Phthalimides are prepared by many chemists by the reaction of phthalic anhydride and aromatic amines but they always used a medium for the reaction. For example Gustav and co workers synthesized phthalimides by using glacial acetic acid as a solvent. In 2011 and 2012 Padam Parveen Kumar and co workers introduced the PEG 600 and TBAB as reaction medium for the synthesis of phthalimides by reacting Phthalic anhydride with aromatic anilines [19-20]. Also there are two step procedures for the synthesis of imides [21]. Therefore, cyclic imides synthesis is still a good practice. In the present work we used the fusion method to synthesize N-aryl phthalimides. It is found to be a very easy, efficient, cheap, time saving and good yield process. The compounds are confirmed by the IR, ^{1}HNMR, ^{13}CNMR and GCMS, Elemental analyzer and X-Ray analysis.

Amide bond has its own importance in Pharmaceutical and chemical industries. One of the most common pharmaceutical drugs having amide bond is Acetaminophen (a very commonly used NSAID). There are so many methods applied for the formation of amide bond using different types of catalytic reactions including metal and enzyme catalysis. Also various kinds of reactants are been used in different reactions for amide bond formation. [22-28] Acetic anhydride reaction with

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aniline is one of them. In the present study we are introducing the simplest method for the synthesis of various phenyl substituted acetamides.

RESULTS AND DISCUSSION

In the present study we prepared different kinds of N-aryl substituted Phthalimides and N aryl Acetamides by using the simplest and solvent free method. First we performed the fusion reaction of phthalic anhydride with different substituted anilines. We get a good yield of the compound with comparable melting points.

The physical properties of compounds are listed here in the Table 1.

Initially we were expecting an open chain structure of carboxylate but the characterization confirmed the presence of cyclic imides. FTIR spectrum of L1-L5 proves the cyclic structure of imides as there are no absorption bands for δ (O-H) and δ (N-H) confirming success of dehydration and formation of 5 membered ring containing Nitrogen.

Also the two bands near 1780 cm-1 and 1708 cm-1 represent the asymmetric and symmetric carbonyl bands of cyclic imides. Moreover in the ^{1}HNMR spectra the two different multiplet signals at (7.07-7.55) and (7.80- 7.98) ppm represent the protons of two different aromatic rings. ^{13}CNMR spectrum also complies well with the structures assigned. GCMS data further confirms the structure and purity of compounds.

1HNMR spectrum of compound L4 showed a distinct singlet at 2.43 ppm for the H of para methyl (CH3) group and two multiplets at δ =7.33 and 7.18 ppm belong to protons of the two aromatic rings. There are no peaks for NH or OH which confirms the presence of 5 membered ring.13CNMR spectrum for L4 showed signal peaks at 20.8 and 167 for C of para methyl and C=O of imide ring. The signals for both aromatic rings lie in between (126-137) ppm. Further confirmation was done by elemental analysis.

In the second trial we synthesized amides by reacting acetic anhydride with anilines by fusion of the reactants through heating without use of any solvent or catalyst. We got good yield N-aryl acetamides which are further purified by recrystallization using chloroform.

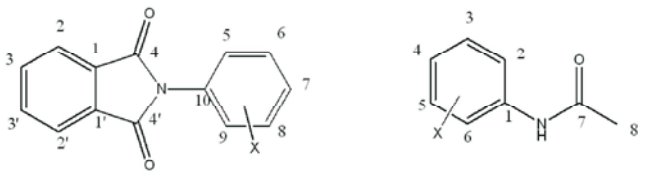
Melting points and Infra Red spectra were analogous with the literature. Further characterizations confirmed the structures assigned. X-ray structure of N- (2-methylphenyl) acetamide is also been resolved.

^{1}HNMR spectrum of compound L7 showed two distinct singlet at δ = 2.23 and 3.91 ppm for (O=C-CH3) and (O-CH3) respectively. A multiplet at δ= (6.98-7.06) ppm belongs to protons of the aromatic ring. There is peak for NH at 7.78 ppm. ^{13}CNMR results verified the structure of the compound L7. A distinct signal at 24, 55.8 and 168.9 ppm for CH_3, O-CH_3 and C=O respectively. The signals for aromatic ring appeared between (109-147) ppm.

Table 1:

S #	Anhydride	Aniline	Product Code (Empirical formula)	%Yield	Reaction time (min)	M.P (°C)
1	Phthalic anhydride	$C_6H_5NH_2$	L1 ($C_{14}H_9NO_2$)	89	3	199-202
2	Phthalic anhydride	C_7H_9N	L2 ($C_{15}H_{11}NO_2$)	90	3.5	174-175
3	Phthalic anhydride	C_7H_9NO	L3 ($C_{15}H_{11}NO_3$)	85	3	143-145
4	Phthalic anhydride	C_7H_9N	L4 ($C_{15}H_{11}NO_2$)	85	4	191-194
5	Phthalic anhydride	C_6H_6NBr	L5($C_{14}H_8BrNO_2$)	92	4	149-155
6	Acetic anhydride	$C_6H_5N\ H_2$	L6(C_8H_9NO)	79	2.5	118
7	Acetic anhydride	C_7H_9NO	L7($C_9H_{11}NO_2$)	75	3	68
8	Acetic anhydride	C_7H_9N	L8($C_9H_{11}NO$)	78	3	98
9	Acetic anhydride	C_7H_9N	L9($C_9H_{11}NO$)	72	3	180

Physical aspects of compounds



L1-L5 L6-L9

Where
X = H, CH_3, OCH_3, Br

Fig. 1:

^{1}HNMR spectrum of compound L8 showed two distinct singlet at δ= 2.22 and 2.28 ppm for (O=C-CH_3) and (-CH_3) respectively. A multiplet at δ = (7.10-7.24) ppm belongs to protons of the aromatic ring. There is peak for NH at 7.78 ppm. ^{13}CNMR results verified the structure of the compound L8. A distinct signal at 17.3, 23.93 and 167.98 ppm for CH_3, carboxy CH_3 and C=O respectively. The signals for aromatic ring appeared between (123-136.2) ppm.

***2-phenyl-1H-isoindole-1,3(2H)-dione L1*:** Yield: 89%, m.p.: 199-202°C (lit. 199-201 °C), IR: 1778, 1707, 1592, 1464, 1282 cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 7.98 (dd), 7.83 (dd), 7.54 (m), 7.43 (m). ^{13}CNMR ($CDCl_3$, ppm): 131.4 (1,1'), 123.4 (2, 2'), 131.4 (3, 3'), 166.9(4, 4'), 134 (5), 127.7(6), 128.7 (7), 126.2 (8), 128.7 (9), 127.7 (10). m/z 223 [M], 179, 104, 76.

***2-(2-methylphenyl)-1H-isoindole-1,3(2H)-dione L2*:** Yield: 90%, m.p.: 174-175 °C (lit 178-180 °C), IR: 1781, 1706, 1590, 1461, 1377 cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 7.97 (dd), 7.83 (dd), 7.39 (m), 7.28 (m), 2.23 (s). ^{13}CNMR ($CDCl_3$, ppm): 130.2 (1,1'), 123.4 (2, 2'), 131 (3, 3'), 167 (4, 4'), 131 (5), 126.5 (6), 128 (7), 129 (8), 133.9 (9), 136 (10), 17.7 (11). m/z 237 [M^+],, 219, 193,180, 165, 104, 89, 76, 50.

***2-(4-methoxyphenyl)-1H-isoindole-1,3(2H)-dione L3*:** Yield: 85%, m.p.: 143-146 °C (lit. 143-145 °C), IR: 1781, 1701, 1609, 1514, 1386, 1250 cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 7.96 (dd), 7.81 (dd), 7.35 (m), 7.05 (m), 3.87 (s). ^{13}CNMR ($CDCl_3$, ppm): 133.9 (1,1'), 123.3 (2, 2'), 133.9 (3, 3'), 167.1 (4, 4'), 128.8 (5), 114.5 (6), 158.9 (7), 114.5 (8), 128.8 (9), 125 (10), 55.8 (11). m/z 253 [M^+],, 238, 210, 182, 130, 106, 76, 63, 50.

***2-(4-methylphenyl)-1H-isoindole-1,3(2H)-dione L4*:** Yield: 85%, m.p.: 191-194 °C (lit.190-192 °C), IR: 1745, 1707, 1601, 1513, 1381, 1245 cm^{-1}. ^{1}H NMR400 MHz ($CDCl_3$, ppm): 7.96 (dd), 7.81 (dd), 7.33 (m), 7.18 (m), 2.43 (s). ^{13}CNMR ($CDCl_3$, ppm): 133.9 (1,1'), 123.3 (2, 2'), 133.9 (3, 3'), 167 (4, 4'), 126 (5), 129 (6), 137.8 (7), 129 (8), 126 (9), 131 (10), 20.8 (11). m/z 237 [M^+], 193, 165, 104, 76, 50. Anal. Calcd. for $C_{15}H_{11}NO_2$ is C, 75.94; H, 4.67; N, 5.90. Found: C, 74.0; H, 4.74; N, 5.67.

***2-(3-bromophenyl)-1H-isoindole-1,3(2H)-dione L5*:** Yield: 92%, m.p.: 149-155 °C (lit. 148-150 °C), IR: 3064, 1778, 1708, 1593, 1540, 1423, 1377, 1068 cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 7.98 (dd), 7.84 (dd), 7.55 (d), 7.44 (m).

Crystal Structure

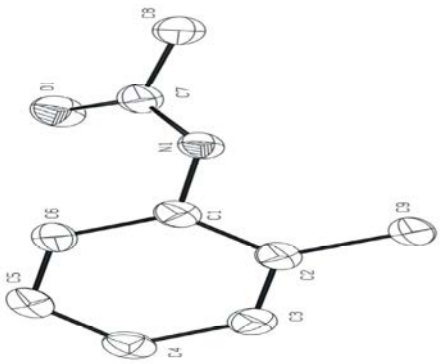


Fig. 2: ORTEP diagrams for compound L8. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity.

^{13}CNMR ($CDCl_3$, ppm): 132.5 (1,1'), 123.7 (2, 2'), 132.5 (3, 3'), 166.5 (4, 4'), 129.7 (5), 131 (6), 130.7 (7), 123.5 (8), 122 (9), 134.9 (10). m/z 303 [M^{+1}],, 257, 207, 197, 178, 166, 151, 104, 90, 76, 67, 57.

***N- Phenylacetamide L6*:** Yield: 79%, m.p.: 118 °C (lit. 116.5-118 °C), IR: 3291(N-H), 1661 (C=O), 1596, 1486 (aromatic C=C), 745 & 692 (mono substituted) cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 7.11(t), 7.31 (t), 7.51(d), 2.17(s), 7.96 (s)representing NH. ^{13}CNMR 400 MHz ($CDCl_3$, ppm): 137 (1), 119 (2,6), 123 (3,5), 128.5 (4), 168.4 (7), 24.2(8). m/z: 135 [M^+], 93, 65, 51, 43.

***N-(2-methoxyphenyl) Acetamide L7*:** Yield: 75%, m.p.: 68 °C (lit. 71-93), IR: 3245(N-H), 1654 (C=O), 1595, 1494 (aromatic C=C), 746 (ortho substituted) cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 6.98-7.06 (m), 7.78(s), 3.91(s), 2.23 (s). ^{13}CNMR 400 MHz ($CDCl_3$, ppm): 127 (1), 147 (2), 109 (3), 123 (4), 120 (5), 119 (6), 167 (7), 24 (8) 55.8 (9). m/z: 165 [M^+], 123, 108, 80, 65.

***N- (2-methylphenyl) acetamide L8*:** Yield: 78 %, m.p: 98°C (lit. 98-101 °C), IR: 3289(N-H), 1641 (C=O), 1587, 1457 (aromatic C=C), 747 (ortho substituted) cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 7.0-7.30 (m), 7.76(s), 2.28 (s), 2.22 (s). ^{13}CNMR 400 MHz ($CDCl_3$, ppm): 135.2 (1), 130.6 (2), 128.9 (3), 126.3 (4), 124.9 (5), 123 (6), 168 (7), 23.9 (8) 17.4 (9). m/z: 149 [M^+], 107, 91, 77, 43.

Crystal data: CCDC 948447

Fig 2: ORTEP diagrams for compound 3D. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity.

Table 2: Bond Lengths

C(2)-C(3)	1.390(3)	C(3)-C(4)	1.390(3)
C(2)-C(1)	1.393(3)	C(7)-O(1)	1.237(3)
C(2)-C(9)	1.508(3)	C(7)-N(1)	1.349(3)
C(1)-C(6)	1.395(3)	C(7)-C(8)	1.498(3)
C(1)-N(1)	1.428(3)	C(6)-C(5)	1.386(3)
		C(5)-C(4)	1.386(3)
Bond Angles			
C(3)-C(2)-C(1)	117.99(19)	O(1)-C(7)-N(1)	122.9(2)
C(3)-C(2)-C(9)	120.78(19)	O(1)-C(7)-C(8)	121.04(19)
C(1)-C(2)-C(9)	121.23(18)	N(1)-C(7)-C(8)	116.10(17)
C(2)-C(1)-C(6)	120.77(19)	C(5)-C(6)-C(1)	120.2(2)
C(2)-C(1)-N(1)	119.48(18)	C(4)-C(5)-C(6)	119.70(19)
C(6)-C(1)-N(1)	119.75(18)	C(5)-C(4)-C(3)	119.61(19)
C(4)-C(3)-C(2)	121.7(2)	C(7)-N(1)-C(1)	123.72(17)

Selected bond lengths [$A] and Bond angles [deg.] for compound 3D

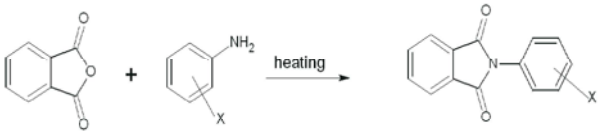
Selected bond lengths and bond angles are illustrated in Table 2.

***N-(4-methylphenyl) acetamide L9*:** Yield: 72%, m.p.: 180 °C (lit.185 °C), IR: 3297 (N-H), 1662 (C=O), 1600, 1505 (aromatic C=C), 830 (para substituted) cm^{-1}. ^{1}H NMR 400 MHz ($CDCl_3$, ppm): 7.14(dd),7.40 (dd), 7.28(s), 2.33(s), 2.17 (s). $^{13}CNMR$ 400 MHz ($CDCl_3$, ppm): 133.5 (1), 119.6 (2), 129 (3), 134.9 (4), 129 (5), 119.6 (6), 167.8 (7), 24 (8) 20.5 (9). m/z: 149 [M^+], 107, 91, 77, 51.

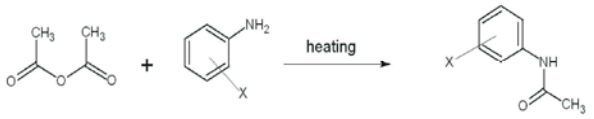
MATERIALS AND METHODS

General Procedure for Synthesis of Ligands: 1mMol of anhydride and 1m Mol of substituted aniline were weighed accurately and separately. The compound having low melting point was taken in the China dish and started heating, as soon as the solid get melted (in case of liquid just heated not boiled), the other reactant was then added with continuous stirring. The reaction may evolve some fumes and may change the color and phase. Then heated for a while until a homogenous phase formed, allowed to cool at room temperature. The product obtained is recrystallized by using chloroform.

Schemes 1and 2 describe the general reaction for L1-L5 and L6-L9 respectively.

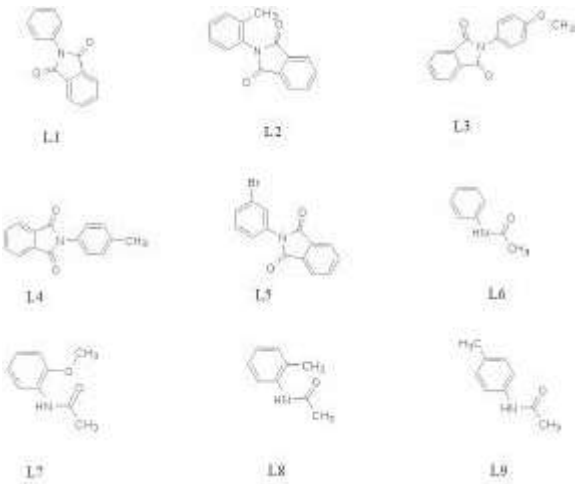


Scheme 1 (synthesis of N-Aryl Phthalimides)



Scheme II (Synthesis of Acetamides)

Structures of Ligands (Figure 3)



CONCLUSION

The synthesis of N-aryl phthalimides and phenyl acetamides is even possible in the absence of solvents, any other medium or catalyst, just heating and fusion of reactants is required.

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Supporting Information: Complete details of the X-ray analysis for compound N4 have also been deposited at the Cambridge Crystallographic Data Centre (CCDC) and can be retrieved with the following reference number: 948447. These data can be obtained free of charge via www.ccdc.cam.ac.uk/ data_request/cif, by emailing data_request@ccdc. cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033).

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