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Green synthesis and molinspiration analysis of novel N-Unsubstituted imide derivatives

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A series of novel *N*-unsubstituted cyclic imides have been synthesized using solvent free conditions using bentonite as a catalyst from anhydrides with urea. As a nitrogen source, urea gives the benefits of a smooth reaction, simple product separation, easy recovery, and bentonite recycling. The synthesized compounds have been analysed using TLC, FT-IR, and ^{1}H NMR to determine their characteristics. The molinspiration online programme has been used to predict the molecular characteristics and bioactivity of the compounds.

Keywords: Cyclic imides, Molinspiration, Bentonite, Polar surface area, Montmorillonites

Because of their distinctive pharmacological characteristics and biological activity, N-unsubstituted cyclic imides are significant intermediates that are frequently employed in the synthesis of drug molecules[1-6].

Reactive acyl transfer agents called cyclic amide derivatives are also employed in the C–N activation/ cross-coupling reaction[7,8].

Traditionally, excess ammonia[1], urea[9], thiourea[10], lithium nitride[11], or formamide[12] will further react with cyclic anhydride in the presence or absence of a solvent to generate imides.

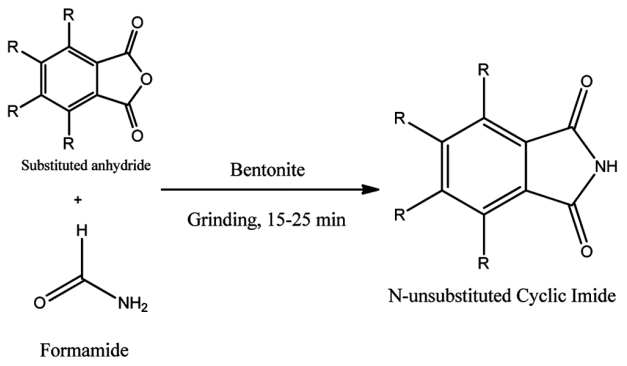
Even so, the majority of these techniques have the drawbacks of having strong reaction conditions, a lengthy reaction time, and laborious post-processing. Furthermore, when ammonia was used as the nitrogen source, a significant amount of effluent was produced.

Environment friendly ways to synthesize cyclic imides have been worked on continuously; examples include utilizing a solvent-free grindstone process and conducting the reaction in a microwave[13–17].

Imide preparation entails the conventional reaction of amides with carboxylic esters, anhydrides, and acyl chlorides[18]. The described procedures involve the following reactions: the combination of azalactones with O_2 and Pd/C[19]the aminocarbonylation[20] of aryl bromide using pentafluorophenyl (PFP) esters and deprotonated amides[21], the coupling of amides and thioesters using $FeCl_2$/NBS[22], the amidation of an aldehyde using CuBr/NBS[23], and the oxidation of N-alkyl amides[24]. The majority of the aforementioned procedures have several disadvantages, such as elevated temperatures, extended reaction durations, reliance on solvents or two-phase systems, employment of toxic reagents, corrosive and dangerous oxidizing agents, laborious purification processes, and occurrence of side reactions such as nitrile elimination, and formation of triacyl amides.

However, the oldest reaction that uses the well-established reaction mechanism, the imidation reaction, still draws the interest of chemists because of fascinating synthetic and mechanistic challenges. Solid acids that are naturally occurring alumosilicates, such zeolites and clays, have the potential to be a suitable substitute for liquid acids. Because of their immense promise in green chemistry and incredibly variable properties, clays, both natural and modified, have received attention. Clay-based catalysts come in a variety of commercial forms, such as hectorite, bentonite, kaolin, envirocat, KSF and K-10 montmorillonites, *etc*. KSF and K-10 clays are the two most common types of clay used in organic synthesis processes. Despite having identical physic-chemical parameters, the clays differ in their BET (Brunauer–Emmett–Teller) surface areas.

This work presents a cost-effective and environment friendly method for converting cyclic anhydrides into N-unsubstituted imides. The methodology involves



Scheme 1 — A green and solvent-free method for synthesizing N-unsubstituted cyclic imides utilizing the grindstone process

employing smectite clays as catalysts, which can be easily reused (Scheme 1).

This study is an extension of ongoing studies on the use of montmorillonites as solid substrates for organic compound synthesis and reactivity. The clay can thereafter be eliminated and used once more in the various processes.

Phthalic anhydrides and their derivatives were demonstrated to provide high product yields. Instead of the intended imide, dark brown polymeric by-products were produced when maleic anhydride was used.

We have, in summary, generated a simple and effective process for the synthesis of cyclic imides. Numerous benefits come with the current process, including a straightforward work-up process, excellent yields, broad application, and readily available reagents.

Experimental Section

All chemicals were used as such without any further purification. The ^{1}H NMR spectra were obtained using a Bruker AC-P-400 spectrometer, with TMS (trimethylsilane) as internal standard. Melting points were determined using a digital melting point apparatus without any modifications and are uncorrected. The FT-IR spectra were acquired using a Bruker Vector-22 infrared spectrometer with the use of KBr discs. The water used in the experiments was subjected to the process of distillation.

The chemistry of imidation reactions involves the synthesis of imides, which are molecules defined by the functional group R-CO-NR`-CO-R. These reactions are essential in organic synthesis and medicinal chemistry due to the ubiquity of imides in different physiologically active chemicals and medicines.

Imidation typically happens by the interaction of anhydrides or carboxylic acids with amines or ammonia. The process can be catalyzed by acids, bases or other catalysts, and it often needs activation of carboxylic acid moiety. Sustainable approaches for amidation have been developed to reduce waste and enhance efficiency, including the use of boron based reagents, metallic and organometallic catalysts, and metal free methods employing milder oxidants.

The grindstone method is a solvent free technique that can be used for imidation reactions, providing a more eco-friendly approach compared to standard approaches.

General synthetic procedure

For 15 min, a mortar and pestle were used to crush a mixture of 1 g of clay, 1 mmol of anhydride, and 2 mmol of formamide. It warmed the reaction mixture. Following the completion of the reaction, which was seen by TLC to be devoid of anhydrides, the product was extracted with chloroform (2×15 mL). The resultant mixture was then concentrated under vacuum to obtain the necessary N-unsubstituted cyclic imides. After thorough water wash, the solid imide was dried and purified by recrystallization from ethanol. To be employed again in the next operations, the washing of the clay was done twice with methanol and after that dried at 120°C (under low pressure). Melting point, FT-IR, and ^{1}H NMR data were used to describe the isolated products, which were then compared to authentic samples or the literature.

Results

The synthesis of N-unsubstituted cyclic imides was assisted by clay and involved a solvent free reaction between anhydrides and formamide. Table 1 provides the spectral data, melting point, reaction time and percentage yield of the synthesized derivatives.

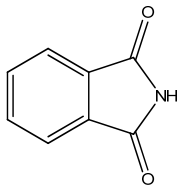
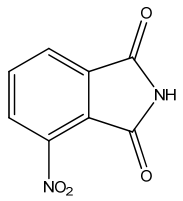
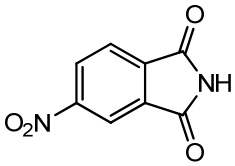
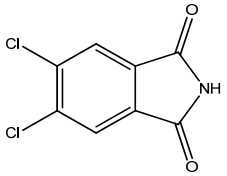
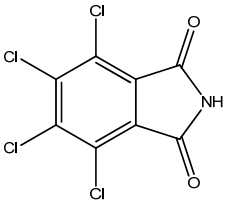
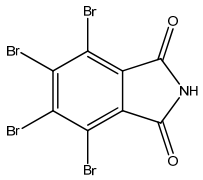
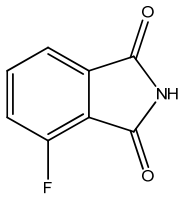
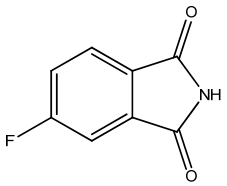
Molinspiration Analysis

Molinspiration is a freely accessible web-based program that computes important molecular metrics, including LogP, PSA (polar surface area), the count of hydrogen bond donors and acceptors, and forecasts the bioactivity score for the most relevant therapeutic targets. The data are presented in a Table 2 and Table 3.

Discussion

The synthesis of N-unsubstituted cyclic imides was assisted by clay and involved a solvent-free reaction between anhydrides and formamide (Scheme 1). The

Table 1 — Percentage yield, physical and spectral data of synthesized compounds

Compd	Product	Reaction time (min)	m.p. (°C)	Spectral Data	Yield (%)
1		15	230-234	^{1}H NMR: δ 11.74 (bs, 1H), 7.27 (s, 4H); IR (KBr): 3335, 3020, 1749, 1796, 1612, 1375, 1315 cm^{-1}.	90
2		20	213-216	^{1}H NMR: δ 11.64 (bs,1H), 8.13 (m, 1H), 8.04 (m, 1H), 7.94 (m, 1H); IR (KBr): 3212, 3041, 1763, 1702, 1626, 1544, 1357 cm^{-1}.	91
3		15	196-199	^{1}H NMR: δ 11.80 (bs, 1H), 8.21 (m, 1H), 8.10 (m, 1H), 8.09 (m, 1H); IR (KBr): 3292, 3072, 1757, 1734, 1639, 1517, 1357 cm^{-1}	91
4		15	217-220	^{1}H NMR: δ 11.78 (bs, 1H), 8.24 (s, 2H); IR (KBr): 3263, 3042,1761, 1725, 1675, 1316,1301 cm^{-1}.	93
5		15	337-342	^{1}H NMR: δ 11.85 (bs, 1H); IR (KBr): 3235, 3052, 1745, 1772, 1708, 1355, 1314 cm^{-1}.	93
6		20	>339	^{1}H NMR: δ 11.92 (bs, 1H); IR (KBr): 3242, 3013, 1740, 1745, 1721, 1386, 1359 cm^{-1}.	89
7		20	179-182	^{1}H NMR: δ 11.84 (bs, 1H), 8.21 (m, 1H), 8.18 (m, 1H), 8.03 (m, 1H); IR (KBr): 3275, 3047, 1785, 1714, 1616, 1327, 1048, 886 cm^{-1}.	91
8		25	175-177	^{1}H NMR: δ 11.82 (bs, 1H), 8.28 (m, 1H), 8.15 (m, 1H), 8.14 (m, 1H); IR (KBr): 3273, 3043, 1779, 1711, 1647, 1321, 1072, 874 cm^{-1}.	91

(*Contd.*)

Table 1 — Percentage yield, physical and spectral data of synthesized compounds

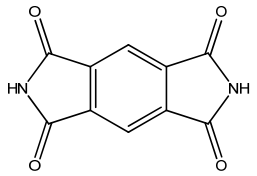
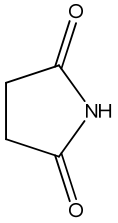
Compd	Product	Reaction time (min)	m.p. (°C)	Spectral Data	Yield (%)
9		20	124-126	^{1}H NMR: δ 11.85 (bs, 2H), 8.10 (s, 2H); IR (KBr): 3198, 3069, 1772, 1698, 1378, 1357, 1156, 1061, 860, 728 cm^{-1}.	90
10		25	124-127	^{1}H NMR: δ 10.28 (bs, 1H), 2.84 (s, 4H,CH_2); IR (KBr): 3395, 3058, 2963, 2924, 1774, 1692, 1329, 1179, 845 cm^{-1}.	92

Table 2 — Computation of the synthetic compounds molecular characteristics

Compd	miLogP	TPSA	nAtoms	MW	nON	nOHNH	n violations	n rotb	Volume
1	1.46	49.93	11	147.13	3	1	0	0	123.57
2	1.05	95.76	14	192.13	6	1	0	1	146.91
3	1.39	95.76	14	192.13	6	1	0	1	146.91
4	2.72	49.93	13	216.02	3	1	0	0	150.64
5	3.30	49.93	15	284.91	3	1	0	0	177.71
6	3.83	49.93	15	462.72	3	1	0	0	195.11
7	1.26	49.93	12	165.12	3	1	0	0	128.50
8	0.62	49.93	12	165.12	3	1	0	0	128.50
9	0.93	99.87	16	216.15	6	2	0	0	163.10
10	–0.86	46.17	7	99.09	3	1	0	0	85.77

Table 3 — Computation of the bioactivity of synthetic compounds

Compd	GPCR	Ion Channel modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
1	–1.07	–0.73	–0.48	–1.51	–1.23	–0.31
2	–1.00	–0.72	–0.49	–1.27	–1.27	–0.32
3	–0.92	–0.53	–0.38	–1.15	–1.06	–0.27
4	–0.79	–0.53	–0.29	–1.16	–0.98	–0.21
5	–0.72	–0.69	–0.29	–0.60	–1.05	–0.01
6	–0.68	–0.46	–0.02	–0.84	–0.83	0.03
7	–0.75	–0.67	–0.29	–1.24	–1.13	–0.24
8	–0.86	–0.64	–0.30	–1.23	–1.14	–0.22
9	–0.49	–0.34	–0.00	–0.74	–0.56	0.01
10	–3.56	–3.60	–3.76	–3.83	–3.61	–3.47

extent and generality of the reaction with reference to the distinct anhydrides are revealed by the results. Different aspects are controlled by the kind of substituent on the aromatic ring of anhydrides. Compared to phthalic anhydride, the introduction of electron-withdrawing groups like fluorine and nitro generates better product yields.

The catalysts under research were laminar silicates of the smectite type. Bentonite sandwiched between two tetrahedral layers of SiO_4 tetrahedral makes up the structure of an elementary sheet of these materials. NH_3 adsorption was utilized to quantify the overall concentration of acid sites on the catalyst surface, and the BET technique was employed to estimate the

surface area. The clay's acidity is the principal catalyst for the reaction; surface area appears to have less of an impact. Every kind of clay shows activity in the reaction, however the most effective catalyst out of all the catalysts studied is bentonite bieliaca, which has the greatest level of total acidity. This technique offers the benefits of rapid reaction, simple manipulation, high yield, and purity in the synthesis of these chemicals.

The reaction time has also been lowered. When compared to previous procedures, the exploitation of the solid clay catalyst in this methodology delivers improved product yields. One of the method's extra benefits is that solid clay may be recycled. Following filtering and a methanol wash, the first cycle's utilized clay catalysts were recovered. When comparing the findings of this approach to those reported earlier, a significantly larger isolated yield was discovered. The molecular properties and bioactivity of the synthesized compounds were analyzed by using the molinspiration online software.

Conclusion

Ultimately, a straightforward and efficient approach was developed for the production of N-unsubstituted cyclic imides, using bentonite as a catalyst. Urea-containing anhydrides produced significant amounts of cyclic imides without nitrogen substitution. This method is advantageous because it utilizes urea as a nitrogen source, which enables a consistent reaction, easy separation of the product, and straightforward recovery and reuse of bentonite. From the molinspiration online software we get to know about the molecular properties as well as the bioactivity of the synthesized compounds.

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