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Short communication

SHORT COMMUNICATION

Ultrasound-assisted catalytic synthesis of acyclic imides in the presence of *p*-toluenesulfonic acid under solvent-free conditions

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Abstract: A rapid and convenient preparation of acyclic imides by the reaction of aliphatic and aromatic nitriles with acyclic carboxylic anhydride in the presence of catalytic amounts of *p*-toluenesulfonic acid under thermal or ultrasonic conditions is reported. The advantages of this procedure are moderate reaction times, good to excellent yields, and use of an inexpensive and eco-friendly catalyst. The reaction of nitriles with aliphatic anhydrides proceeds under thermal conditions, while they are accelerated by the use of ultrasound irradiation.

Keywords: linear carboxylic anhydride; unsymmetrical acyclic imide; nitrile; *p*-toluenesulfonic acid; ultrasound.

INTRODUCTION

The imide group is an interesting functionality due to its wide presence in natural products and pharmacologically active compounds. Mixed acyclic imide functionality is shared by a growing class of natural products with diverse activities, such as dolastatin 15, a cytotoxic anticancer agent,[1] althiomycin, a potent antibiotic,[2] and antifeedant.[3] Acyclic imides have also been used in the diastereoselective intramolecular photocycloaddition reactions,[4] as bleach activators[5] and asymmetric oxetane synthesis.[6]

Classically, imides are prepared by the reaction of amides with acyl chlorides, anhydrides and carboxylic esters or acids.[7] However, these methods are not as straightforward as they may seem to be at first sight, and several side reactions, such as elimination to nitriles, formation of triacyl amides, or acyl group scrambling, can occur. The best yields were reported for acid-catalyzed reactions of anhydrides with amides. Other procedures for the synthesis of acyclic imides

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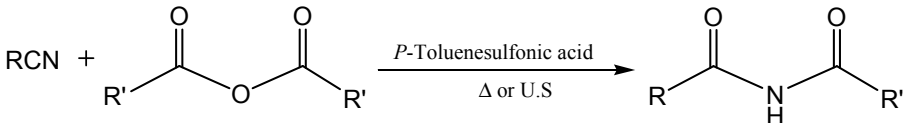
involve aminocarbonylation of aryl bromides,[8] and reaction of pentafluorophenyl esters with deprotonated amides.[9] The available methods for the synthesis of unsymmetrical acyclic imides suffer from low yields, high temperature or scrambling of the groups to give symmetrical imides.

The use of ultrasonic waves in organic synthesis has been elevated during the last few years.[10–17] Most of the observed effects are due to cavitation, the formation, growth and collapse of bubbles in an irradiated liquid, which makes sonochemistry unique. Cavitation induces very high local temperatures and pressures or strong electric fields[13,18] inside the bubbles (cavities) and enhances mass transfer and turbulent flow in the liquid.[19] Their specificity has been exhibited in homogeneous and heterogeneous reactions.[15,16] They are defined as acoustic waves with frequencies in the 20 kHz to 100 MHz range.[11] Ultrasound is known to accelerate different types of organic reactions and it is established as an important technique in organic synthesis.[13,20,21]

p-Toluenesulfonic acid (*p*-TSA) is a strong organic acid, about a million times stronger than benzoic acid. It is one of the few strong acids that are solid and, hence, conveniently weighed. In addition, unlike some of the strong mineral acids (especially nitric acid, sulfuric acid, and perchloric acid), *p*-TSA is non-oxidizing. The application of *p*-toluenesulfonic acid is feasible because of its easy preparation, easy handling, stability and good activity, and it is inexpensive and eco-friendly.

Herein, an efficient procedure for the catalytic synthesis of unsymmetrical acyclic imides using *p*-toluenesulfonic acid under thermal or ultrasound irradiation conditions is presented (Scheme 1).



Scheme 1. Reaction for the catalytic synthesis of unsymmetrical acyclic imides using *p*-toluenesulfonic acid under thermal or ultrasound irradiation conditions.

EXPERIMENTAL

All chemicals were purchased from Merck, Fluka or Sigma–Aldrich chemical companies. The reactions were monitored by thin layer chromatography (TLC). The products were isolated and identified by comparison of their physical and spectral data with authentic samples. Sonication was performed in Bandelin Sonorex D12207 type: RK 1028H ultrasonic cleaner (with a frequency of 35 kHz and a power of 1000 W). The IR spectra were recorded on a JASCO-680 FT-IR instrument, the ^{1}H-NMR spectra were obtained on a Bruker-Avance AQS 300 MHz or a Bruker 400 Ultrasheild (400 MHz) instrument. The melting points were measured on a Barnstead Electrothermal (BI 9300) apparatus.

General procedure for liquid nitriles

A mixture of nitrile (1.0 mmol), carboxylic anhydride (1.0 mmol), and *p*-toluenesulfonic acid monohydrate (30 mol %, equal to 0.30 mmol H^+) was heated in a 10 mL round-bottomed flask at 70–80°C with concomitant stirring (or ultrasound irradiation). The reactions were completed within 30–120 min, as monitored by TLC (eluent, EtOAc:*n*-hexane, 1:2). After completion of the reaction, diethyl ether (15 mL) was added, the solid catalyst was separated, and then the pure crude products were obtained by short column chromatography.

General procedure for solid nitriles

The solid nitrile (1 mmol), carboxylic anhydride (2 mmol) and *p*-TSA monohydrate (50 mol %) were mixed thoroughly in a round-bottomed flask**.** The flask was heated at 80 °C with concomitant stirring (or ultrasound irradiation). After completion of the reaction, confirmed by TLC (eluent: EtOAc/*n*-hexane, 1:6), EtOAc (15 mL) was added and the solution was filtered to separate the solid catalyst. Then the pure products were obtained by column chromatography. The products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and *via* comparison of their melting points with reported ones.

RESULTS AND DISCUSSION

The amidation of alcohols with nitriles in the presence of acidic catalyst is known as the Ritter reaction.[9] By careful investigation of this reaction, this method was simulated for the one-pot synthesis of a wide variety of linear imides in fair to excellent yields using acid anhydrides instead of alcohols under thermal conditions or ultrasound irradiation (Scheme 1).

For investigation of the effect of different amounts of *p*-TSA monohydrate in the synthesis of unsymmetrical acyclic imides, various amounts of catalyst were used and it was found that 0.057 g (equal to 30 mol %) of *p*-TSA monohydrate for liquid nitriles and 0.095 g (equal to 50 mol %) for solid nitriles were the best amounts of the catalyst. These amounts were used to study the effects of various parameters on the reaction yields.

Synthesis of unsymmetrical acyclic imides catalyzed by p-*toluenesulfonic acid*

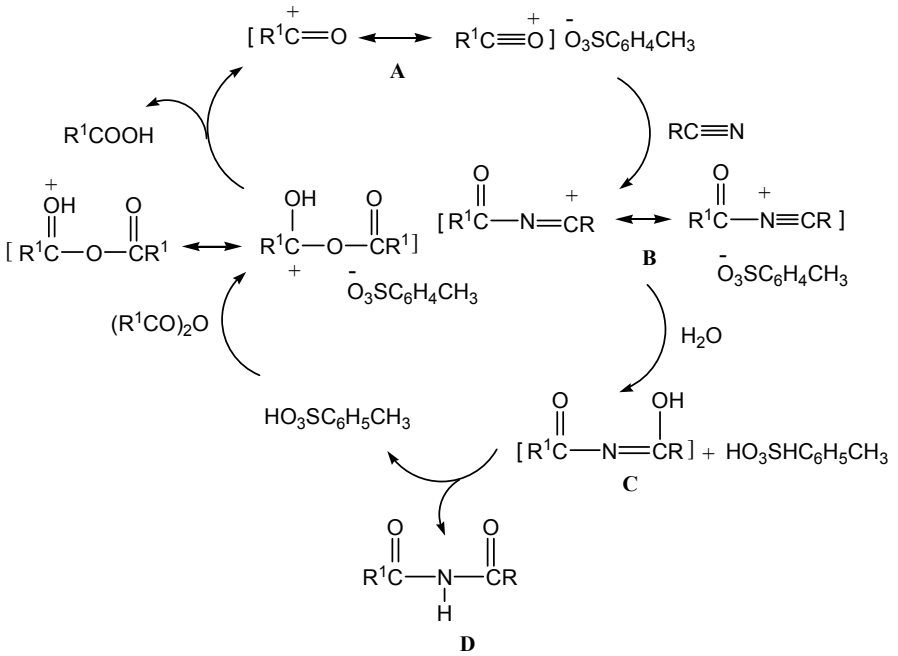
These reaction conditions were extended to a series of aromatic and aliphatic nitriles with acyclic carboxylic anhydrides under solvent-free conditions in the presence of *p*-TSA as an active reagent. The results from the reaction of various nitriles and carboxylic anhydrides in the presence of the optimized amount of *p*-TSA are summarized in Table I. As shown, good to excellent yields were obtained in the reaction of aromatic nitriles (Entries **4**–**16**). The reaction of the nitriles with the aliphatic anhydrides proceeded within 30–120 min in the presence of *p*-TSA under thermal conditions, while by employment of ultrasound irradiation, these reactions were accelerated to within 5–28 min.

A plausible mechanism for the formation of acyclic imides is shown in Scheme 2. The mechanism may involve acylinium ion (A) from protonated carboxylic anhydride. On further reaction with nitrile, it affords the corresponding acyliminium cation (B) that will react with water to afford the intermediate acyliminol (C), which then yields the acyclic imide (D).

TABLE I. Products from reaction of nitriles and anhydrides under thermal or ultrasonic conditions

Entry	R	R'	Thermal	Ultrasonic	m.p.[a] / °C	
			Time, min	Time, min	Found	Reported
			Yield[b], %	Yield, %		
1	CH_3	CH_3	100/80	20/90	72–73	73–74
2	CH_3	CH_3CH_2	120/82	25/92	88–89	85–86
3	CH_3	$CH_3CH_2CH_2$	120/75	25/90	107–108	109–110
4	2-Thiophene	CH_3CH_2	80/85	13/92	135–137	137–138
5	C_6H_5	CH_3	35/88	5/97	110–112	112–114
6	$(CH_3)_2CH$	CH_3CH_2	80/86	8/95	110–111	124–126
7	4-ClC_6H_4	CH_3	30/86	6/94	133–135	136–137
8	4-ClC_6H_4	CH_3CH_2	50/87	10/96	155–157	157–158
9	4-$CH_3OC_6H_4$	CH_3	40/78	7/85	111–113	119–119.5
10	4-$CH_3OC_6H_4$	CH_3CH_2	35/75	5/78	137–139	133–134
11	4-$CH_3OC_6H_4$	$CH_3CH_2CH_2$	40/82	8/90	162–163	–
12	4-FC_6H_4	CH_3	85/84	15/93	112–113	111–112
13	4-FC_6H_4	CH_3CH_2	80/82	15/90	113–115	115
14	4-FC_6H_4	$CH_3CH_2CH_2$	70/75	12/83	106–108	108–109
15	3-$NO_2C_6H_4$	CH_3	120/65	23/80	197–198	195–196
16	3-$NO_2C_6H_4$	$CH_3CH_2CH_2$	150/68	28/85	107–109	108–110

[a]All products were fully characterized by their IR, ^{1}H-NMR and physical data and comparison with these reported in the literature;[22–26] [b]yields of pure isolated products



Scheme 2. A plausible mechanism for the formation of acyclic imides by the proposed method.

Spectral and physical data for the synthesized compounds

2-Methyl-N-*propionylpropionamide (entry **6**)*. White solid, m.p.: 110–111 °C; Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78 %. Found: C, 68.6; H, 9.20; N, 9.70 %; IR (KBr, cm^{-1}): 3266, 3180, 2969, 2930, 1734, 1273, 1174; ^{1}H-NMR (400 MHz, $CDCl_3$, δ / ppm): 0.91 (6H, *d*, *J* = 6.5 Hz), 1.42 (3H, *t*, *J* = = 7.0 Hz), 2.76 (2H, *q*, *J* = 7.2 Hz), 4.20–4.23 (1H, *m*), 8.4 (1H, *brs*).

N-*Acetyl-4-methoxybenzamide (entry **9**)*. White solid, m.p.: 111–113 °C; Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25 %. Found: C, 62.3; H, 5.80; N, 7.20 %; IR (KBr, cm^{-1}): 3240, 3140, 2940, 1720, 1690, 1605; ^{1}H-NMR (400 MHz, $CDCl_3$, δ / ppm): 2.62 (3H, *s*), 3.89 (3H, *s*), 6.98 (2H, *d*, *J* = 7.8 Hz), 7.88 (2H, *d*, *J* = 7.5 Hz), 9.04 (1H, *brs*); ^{13}C-NMR (100 MHz, $CDCl_3$, δ / ppm): 25.52, 55.55, 114.21, 125.00, 129.94, 132.21, 165.12, 173.03.

4-Methoxy-N-*propionylbenzamide (entry **10**)*. White solid, m.p.: 137–139 °C; Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76 %. Found: C, 63.8; H, 6.2; N, 6.9 %; IR (KBr, cm^{-1}): 3280, 3160, 2930, 1710, 1685, 1600, 1250; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 1.23 (3H, *t*, *J* = 6.8 Hz), 3.04 (2H, *q*, *J* = = 7.2 Hz), 3.89 (3H, *s*), 6.98 (2H, *d*, *J* = 7.5 Hz), 7.87 (2H, *d*, *J* = 7.6 Hz), 8.88 (1H, *brs*); ^{13}C-NMR (100 MHz, $CDCl_3$, δ / ppm): 18.28, 31.07, 55.54, 114.17 124.91, 128.10, 129.86, 163.56, 177.42.

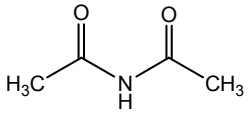
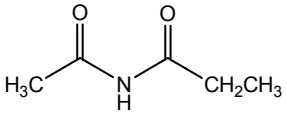
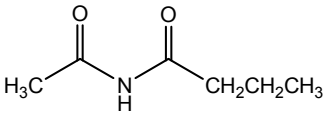
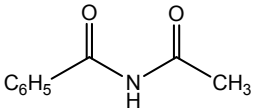
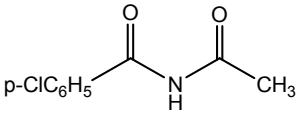
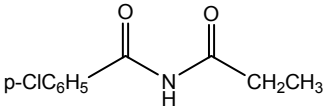
N-*Butyryl-4-methoxybenzamide (entry **11**)*. White solid, m.p.: 162–163 °C; Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33 %. Found: C, 65.20; H, 6.90; N, 6.40 %; IR (KBr, cm^{-1}): 3285, 2960, 2930, 1710, 1680, 1610, 1470, 1265; ^{1}H-NMR (400 MHz, $CDCl_3$, δ / ppm): 1.03 (3H, *t*, *J* = 7.6 Hz), 1.74–1.80 (2H, *m*), 3.01 (2H, *t*, *J* = 7.4 Hz), 3.89 (3H, *s*), 7.89 (2H, *d*, *J* = 7.6 Hz), 8.08 (2H, *d*, *J* = 7.2 Hz), 9.06 (1H, *brs*); ^{13}C-NMR (100 MHz, $CDCl_3$, δ / ppm): 13.74, 17.66, 39.40, 55.46, 113.72, 114.17, 129.95, 132.30, 163.96, 177.01.

Comparative results

In order to show the ability of the employed method with respect to those previously reported, some of the present results in comparison to some other methods are summarized in Table II. As can be seen, the yield/time ratio of the present method is better than or comparable with the other reported results.

In conclusion, an efficient, inexpensive and straightforward procedure for a one-pot synthesis of unsymmetrical acyclic imides using *p*-TSA as catalyst has been found. To the best of our knowledge, this is one of the simplest procedures for the preparation of a wide variety of imides as a valuable class of organic compounds.

TABLE II. Comparison of some of the results obtained in the present study with those reported in the literature (values refer to yield (in %)/time (in min for A and C and in h for B) ratios. In the methods A, B and C, different catalysts were used with the same substrates. A: the present method with *p*-toluenesulfonic acid as catalyst under ultrasonic conditions. B: silica sulfuric acid at 60–70 °C,[22] and C: tungstophosphoric acid as an acidic catalyst at 70 °C[23])

Entry	Product	A	B	C
1		90/20	96/5.9	96/40
2		92/25	93/5.9	94/50
3		90/25	92/6.1	89/50
4		97/5	35/7.1	73/40
5		94/6	–	86/85
6		96/10	–	81/80

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И З В О Д

СИНТЕЗА АЦИКЛИЧНИХ ИМИДА У ПРИСУСТВУ *p*-ТОЛУЕНСУЛФОНСКЕ КИСЕЛИНЕ БЕЗ РАСТВАРАЧА ПОД УСЛОВИМА ОЗРАЧИВАЊА УЛТРАЗВУКОМ

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Приказана је брза синтеза ацикличних имида реакцијом алифатичних и ароматичних нитрила и анхидрида ацикличних карбоксилних киселина у присуству *p*-толуенсулфонске киселине под термалним и ултразвучним условима. Предности описане методе су релативно кратко реакционо време, добар до одличан принос и употреба еколошких и јефтиних катализатора. Реакција нитрила и алифатичних анхидрида одвија се и под термичким условима, али је убрзана уколико се врши озрачивање ултразвуком.

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