Short Communication

Organocatalytic, rapid and facile cyclotrimerization of isocyanates using tetrabutylammonium phthalimide-N-oxyl and tetraethylammonium 2-(carbamoyl)benzoate under solvent-free conditions

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ABSTRACT

Tetrabutylammonium phthalimide-N-oxyl and tetraethylammonium 2-(carbamoyl)benzoate were found to be effective and easily accessible organocatalysts for selective cylotrimerization of aryl and alkyl isocyanates under mild reaction conditions. The reaction proceeds smoothly using very low catalyst loadings of these metal-free organocatalysts (0.025 and 0.25 mol%, respectively) under solvent-free conditions at room temperature within a very short reaction time.

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1. Introduction

The most important reaction between isocyanates is cyclotrimerization to form the heteroaromatic isocyanurate (1,3,5-trisubstituted hexahydro-s-triazinetrione) ring. This heterocycle is thermally very stable and is used to enhance the physical properties of a wide variety of polyurethanes and other coating materials such as polyureas in commercial systems. Polymeric blends of isocyanurates demonstrate increased thermal resistance, flame retardation, chemical resistance, and film-forming characteristics [1–4]. Furthermore, different derivatives of isocyanurates have recently received considerable attention in other areas such as heterogeneous catalysis [5], periodic mesoporous organosilicas (PMOs) with uniformly distributed organic and organometallic groups within the silica framework [6,7], cross-linker and glass coating agent [8–10], drug delivery [11,12] selective ion bonding [13] and chiral discrimination [14].

The general route for the preparation of isocyanurates is the catalytic cyclotrimerization of the corresponding isocyanates. However, isocyanates are very active agents which produce different products such as trimer, dimer, carbodiimide, urethane or allophanate depending on the reaction conditions [3,15]. Therefore, developing of catalysts which promote cyclotrimerization selectively is of great importance due to wide application of isocyanurate structure in both industry and academic studies [1–14]. Cyclotrimerization of isocyanates has been shown to be promoted by catalytic systems such as neutral trisaminophosphines, trialkyl arsenic oxide, tertiary amines, and anions such as carboxylates, cyanate, phenoxide [3], fluoride [16], sulfite [17] or sulfate [18]. Catalysts containing metal species such as organotin compounds, arene manganese tricarbonyl, and nickel halides have also been reported [3]. Recently, metallic catalysts such as complexes of Yb, Eu, Sm, Nd, Yb [19], Sn, Ge [20,21], and Pd [22] or zirconacyclopentanes [23] have been employed. On the other hand, organocatalysis has received great attention due to the mildness of the reaction conditions, operational simplicity, the potential for the development of large scale versions of the reaction, the ready availability, and environmental friendliness in the recent years [24]. Along this line, organocatalysts such as N-heterocyclic carbenes (NHCs) [25], calcium carbene with chelating iminophosphorane substituents [26], an electron-rich trisaminophosphine [27], potassium or sodium salts of piperidinedithiocarbamate [28], p-toluenesulfinate [29], saccharin [30], phthalimide [31], and phthalimide-N-oxyl [32] have also been introduced.

In commercial systems, alkali metal carboxylates such as potassium acetate in combination with ethylene glycol or its oligomers and potassium 2-ethylhexanoate can be considered as standard catalysts. Furthermore, the quaternary ammonium carboxylates demonstrate high performance catalytic activity that can significantly assist in processing and/or physical property modification [33]. We have recently introduced tetrabutylammonium phthalimide-N-oxyl (TBAPINO) [34] and tetraethylammonium 2-(carbamoyl)benzoate (TEACB) [24] as efficient and metal-free organocatalysts for cyanosilylation of carbonyl
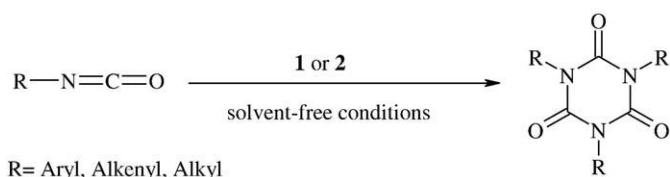
Scheme 1. Cyclotrimerization of different isocyanates catalyzed by tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO) **1** or tetraethylammonium 2-(carbamoyl)benzoate (TEACB) **2**.

compounds. In continuation of our interest on the catalytic applications of both TBAPINO and TEACB for various organic transformations, we herein disclose cyclotrimerization of aryl and alkyl isocyanates catalyzed by TBAPINO **1** and TEACB **2** as Lewis basic and bifunctional organocatalysts, respectively (Scheme 1).

2. Experimental

2.1. General

Melting points were determined by open capillaries on an electrothermal apparatus and are uncorrected. FT IR spectra were recorded as KBr pellets on a Shimadzu FT IR-8400S spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using a Bruker DRX-500 AVANCE spectrometer. All NMR spectra were determined in CDCl$_3$ or Acetone-d_6 at ambient temperature. All chemicals were purchased from Merck, Fluka or Alfa Aesar and used as received except for 4-methoxyphenyl isocyanate which was

prepared according to a previously described procedure [30]. The catalysts were powdered and dried at 70 °C for 1 h under reduced pressure. Dry ether was freshly distilled over Na and benzophenone. All reactions were protected from air moisture using a CaCl$_2$ guard tube. Analytical TLC was carried out using Merck 0.2 mm silica gel 60 F-254 Al-plates. All compounds were well characterized using melting points, IR and NMR spectral data as compared with those obtained from authentic samples or reported in the literature [3,16,21,25,28]. *Caution*: For safety reasons, all the experiments and operations were performed in an efficient fume hood and necessary precautions were considered in order to avoid any contact with the isocyanates.

2.2. General procedure for cyclotrimerization of isocyanates catalyzed by TBAPINO **1** or TEACB **2**

2.2.1. Cyclotrimerization of aryl isocyanates

Aryl isocyanate (**3a–g**) (20 mmol) was added to TBAPINO **1** (2 mg, 0.025 mol%) or TEACB **2** (14.7 mg, 0.25 mol%) in an oven-dried 25 mL round-bottomed flask equipped with a condenser. The mixture was vigorously stirred at room temperature for liquid isocyanates. In the case of solid isocyanates, the mixture was vigorously stirred at 50 °C. After complete solidification of the reaction mixture, it was crushed and 5 mL of dry Et$_2$O was added with stirring for 10 min. The mixture was filtered and the obtained solids were suspended in 5 mL of water to extract the catalyst. The mixture was filtered and the obtained solids were recrystallized from EtOH/EtOAc to afford the desired triaryl isocyanurates (**4a–g**).

2.2.2. Cyclotrimerization of alkyl isocyanates

Allyl or ethyl isocyanate (**3i–h**) (20 mmol) was added to TBAPINO **1** (20 mg, 0.25 mol%) or TEACB **2** (14.7 mg, 0.25 mol%) in an oven-

Table 1
Cyclotrimerization of aryl and alkyl isocyanates catalyzed by TBAPINO **1**.
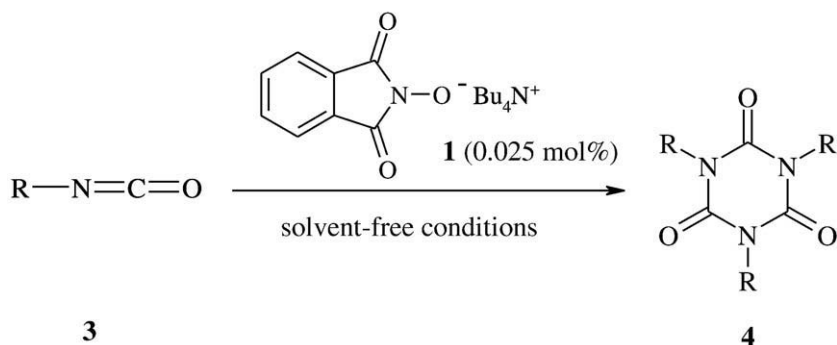
Entry	Isocyanate (R)	Mol (%)	T (°C)	Time (min)	Product	Yield[a] (%)	TON	TOF (h^{-1})	m.p. (°C) [Lit.]
1	Phenyl (**3a**)	0.1	r.t.	13	**4a**	99	990	4569	279–281 [3,23]
2	Phenyl (**3a**)	0.05	r.t.	14	**4a**	98	1960	8400	279–281 [3,23]
3	Phenyl (**3a**)	0.025	r.t.	14	**4a**	98	3920	16,800	279–281 [3,23]
4	Phenyl (**3a**)	0.0125	r.t.	35	**4a**	81	6480	11,109	279–281 [3,23]
5	Phenyl (**3a**)	0.025	50	8	**4a**	70	2800	21,000	279–281 [3,23]
6	4-Chlorophenyl (**3b**)[b]	0.025	50	0.5	**4b**	98	3920	470,400	317–318 [23]
7	3,4-Dichlorophenyl (**3c**)[b]	0.025	50	0.5	**4c**	99	3960	475,200	277–279 [18]
8	4-Methylphenyl (**3d**)	0.025	r.t.	30	**4d**	92	3680	7360	262–264 [16]
9	2-Methylphenyl (**3e**)	0.025	r.t.	50	**4e**	98	3920	4704	178–180 [25]
10	4-Methoxyphenyl (**3f**)	0.025	r.t.	13	**4f**	98	3920	18,092	261–262 [3,25]
11	1-Naphthyl (**3g**)	0.025	r.t.	16	**4g**	94	3760	14,100	339–341 [23]
12[c]	Allyl (**3i**)	0.25	r.t.	540	**4i**	88	352	39	24–26 [3,25]
13[c]	Ethyl (**3h**)	0.25	r.t.	1200	**4h**	86	348	17	93–95 [3,23]

[a] Isolated yields (average of at least two runs).
[b] Solid substrate.
[c] Performed with 0.25 mol% of TBAPINO loading.

Table 2
Cyclotrimerization of aryl and alkyl isocyanates catalyzed by TEACB **2**.
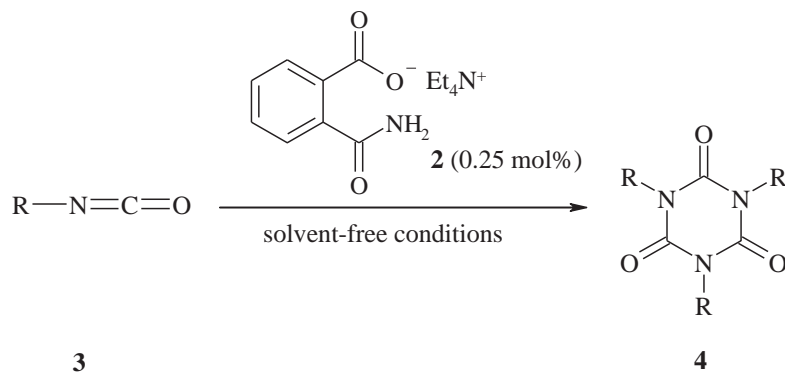
Entry	Isocyanate (R)	Mol (%)	Temp (°C)	Time (min)	Yield [a] (%)	Product	TON	TOF (h^{-1})
1	Phenyl (**3**a)	1	r.t.	0.25	97	**4**a	97	23,280
2	Phenyl (**3**a)	0.5	r.t.	0.5	96	**4**a	192	23,040
3	Phenyl (**3**a)	0.25	r.t.	0.83	98	**4**a	392	28,337
4	Phenyl (**3**a)	0.125	r.t.	1.17	85	**4**a	680	34,872
5	4-Chlorophenyl (**3**b)[b]	0.25	50	0.17	98	**4**b	392	138,353
6	3,4-Dichlorophenyl (**3**c)[b]	0.25	50	0.083	97	**4**c	388	280,482
7	4-Methylphenyl (**3**d)	0.25	r.t.	1.3	96	**4**d	384	17,723
8	2-Methylphenyl (**3**e)	0.25	r.t.	3	92	**4**e	368	7360
9	1-Naphthyl (**3**g)	0.25	r.t.	4	96	**4**g	384	5760
10	Allyl (**3**h)	0.25	50	360	95	**4**h	380	63
11	Ethyl (**3**i)	0.25	50	900	87	**4**i	348	23

[a] Isolated yields (average of at least two runs).
[b] Solid substrate.

dried 20 mL round-bottomed flask equipped with a condenser. The mixture was vigorously stirred at room temperature or 50 °C for the time indicated in Table 1 or 2. After cooling to room temperature, 15 mL of dry ether was added and the mixture was stirred for 10 min. On adding of ether, any urea formed by hydrolysis of the substrates is separated as white crystals. The mixture was filtered on a Buchner funnel and the crystals washed with additional 5 mL ether. The filtrate was evaporated at reduced pressure to afford the desired isocyanurates **4**i–h. Further purification of triethyl isocyanurate (**4**h) could be performed by its recrystallization from EtOH.

2.2.3. Selected spectroscopic data

*2.2.3.1. 1,3,5-Triphenyl-1,3,5-triazine-2,4,6(1H,3H,5H)trione (Triphenyl isocyanurate, **4**a).* m.p. 279–281 °C; IR (KBr): υ 3065, 1709, 1491, 1415 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.44–7.52 (m, 15H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 128.2, 128.6, 129.0, 133.3, 148.7 [3,23].

*2.2.3.2. 1,3,5-Tris-(4-chlorophenyl)-1,3,5-triazine-2,4,6(1H,3H,5H) trione (Tris-(4-chlorophenyl) isocyanurate, **4**b).* m.p. 317–318 °C; IR (KBr): υ 3277, 1720, 1692, 1593, 1491, 1422, 1089, 812 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.42–7.44 (d, $J = 8.8$, 6H), 7.58–7.60 (d, $J = 8.8$, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 129.9, 130.0, 131.9, 135.8, 148.2 [23,27].

*2.2.3.3. 1,3,5-Tris-(4-methoxyphenyl)-1,3,5-triazine-2,4,6(1H,3H,5H) trione (Tris-(4-methoxyphenyl) isocyanurate, **4**f).* m.p. 261–262 °C; IR (KBr): υ 3030, 2963, 2841, 1770, 1715, 1695, 1609, 1420, 1175 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6): δ 3.83 (s, 9H), 7.00–7.02 (d, $J = 9.0$ Hz, 6H), 7.33–7.35 (d, $J = 9.0$ Hz, 6H); ^{13}C NMR (125 MHz, Acetone-d_6): δ 55.8, 114.9, 126.6, 129.7, 149.4, 160.1 [3,25].

*2.2.3.4. 1,3,5-Triallyl-1,3,5-triazine-2,4,6(1H,3H,5H)trione (Triallyl isocyanurate, **4**i).*
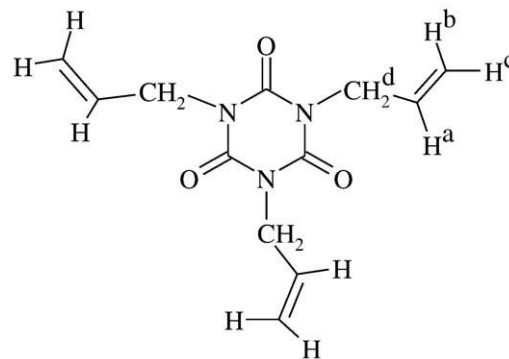
m.p. 24–26 °C; IR (KBr): υ 3085, 2987, 2958, 1690, 1457, 1413, 1318, 993, 933 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.46–4.47(td, $^3J_{H^aH^d} = 6.0$ Hz, $^4J_{H^bH^d} = {^4}J_{H^cH^d} = 1.2$ Hz, 6H^d), 5.20–5.23 (dd, $^3J_{H^aH^c} = 10.2$ Hz, $^2J_{H^bH^c} = 1.1$ Hz, 3H^c), 5.26–5.30 (dd, $^3J_{H^aH^b} = 17.1$ Hz, $^2J_{H^bH^c} = 1.1$ Hz, 3H^b), 5.81–5.89 (tdd, $^3J_{H^aH^b} = 17.1$ Hz, $^3J_{H^aH^c} = 10.2$ Hz, $^3J_{H^aH^d} = 6.0$ Hz, 3H^a); ^{13}C NMR (125 MHz, Acetone-d_6): δ 45.2, 119.2, 131.1, 148.5 [3,25].

3. Results and discussion

At first, phenyl isocyanate **3**a was used as a model substrate and the effect of different catalyst loading of TBAPINO was studied from 0.1 to 0.025 mol% under solvent-free conditions at room temperature. After completion of the reaction (a crystalline white solid precipitated out of the reaction mixture and monitored by TLC), a simple work up afforded the desired product in excellent yields. The reaction proceeded very cleanly and the obtained solid was free of any side products such as
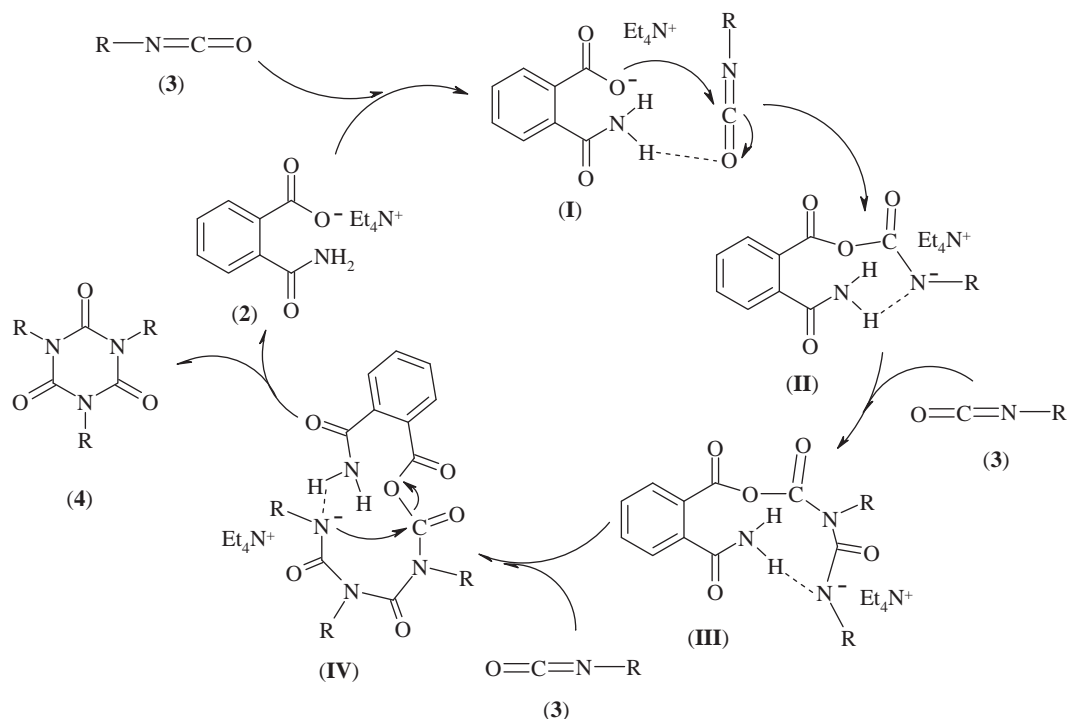
Scheme 2. Plausible mechanism for cyclotrimerization of isocyanates catalyzed by TEACB.

dimer [25] or even catalyst (entries 1–4, Table 1). Interestingly, TBAPINO is more soluble in water comparing to solvents with low to medium polarity such as CH₂Cl₂, Et₂O and EtOAc. Therefore, it substantially partitions in the aqueous phase and this allows very convenient separation of the catalyst from the reaction mixture. Furthermore, TBAPINO can be easily prepared from N-hydroxyphthalimide and tetrabutylammonium hydroxide. It has good lifetime and is resistant to moisture and air. TBAPINO could be used for months without loss of performance [34,35]. It was found that the best result could be obtained with catalyst loading of 0.025 mol% (entry 3). Encouraged by these results, different isocyanates were subjected to cyclotrimerization under the optimized reaction conditions (TBAPINO; 0.025 mol%, solvent-free conditions, r.t.). Table 1 shows the scope of the reaction using a number of representative isocyanates wherein high to quantitative yields of the corresponding isocyanurates (4a–h) were obtained within short reaction time in all the cases studied (entries 6–13, Table 1). It is noteworthy that allyl isocyanate 3i afforded its corresponding isocyanurate (4i) as a commercially important compound [25].

As shown in Table 1, aryl isocyanates react much faster under similar reaction conditions comparing to allyl and alkyl derivatives. Furthermore, the nature of the substituents on the aromatic ring showed relatively strong effects on the reaction time (entries 4, 6–13). On the other hand, isocyanates 3b and 3c (entries 6 and 7) are solid at room temperature. Since the reaction takes place under solvent-free conditions, the reactivity of these isocyanates was studied at 50 °C. At this temperature, these isocyanates melt and the catalysts dissolve in the obtained melts. Consequently, these substrates involved in the reaction conditions very well.

These encouraging findings prompted us to further investigate the use of a more efficient organocatalyst for cyclotrimerization of isocyanates. This tactic would be more useful for isocyanates such as allyl isocyanate which require longer reaction time. Therefore, we decided to investigate the use of tetraethylammonium 2-(carbamoyl) benzoate (TEACB) which demonstrated higher catalytic activity comparing to TBAPINO in the cyanosilylation of carbonyl compounds [24,34]. The results of this remarkably accelerated isocyanate cyclo-trimerization methodology have been summarized in Table 2. This improved catalytic activity can be attributed to an additional hydrogen bonding interaction of TEACB with the oxygen atom of the isocyanate functionality in the complex or intermediates (I–IV), comparing to TBAPINO, whereas the later catalyst activates isocyanates only by its negatively charged oxygen atom (Scheme 2).

Table 3
Comparison of some of the results obtained by cyclotrimerization of isocyanates in the presence of TBAPINO (1) and TEACB (2), with some of those reported by proazaphosphatrane (3), 1,3-Bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr, 4), tetrasulfido complexes of Sn (5) and palladium(0) (dibenzylideneacetone) complex bearing 1,10-phenanthroline (6).

Entry	Substrate	Method [temperature (°C)/TOF (h⁻¹)]					
		1[a]	2[a]	3 [3]	4[b] [25]	5[a] [21]	6[c] [22]
1	PhNCO	r.t./16,800 50/21,000	r.t./28,377	r.t./8545[a]	r.t./980	r.t./238	r.t./238
2	4-ClPhNCO	50/470,400	50/138,353	–	–	–	–
3	4-MePhNCO	r.t./7360	r.t./17,723	–	–	–	r.t./0.23
4	4-MeOPhNCO	r.t./18,092	–	r.t./3418[a]	r.t./850	r.t./407	r.t./0.52
5	Allyl	r.t./39	50/63	r.t./3[b]	1.0/980	–	–

[a] The reactions were carried out under solvent-free conditions.
[b] The reactions were carried out in THF as solvent.
[c] The reaction was carried out in PhNO₂ as solvent.

To illustrate the efficiency of the proposed method, Table 3 is shown to compare our results with those reported in the literature [3,21,22,25].

4. Conclusion

In summary, we have developed new, mild and highly efficient protocols for the synthesis of a wide range of aryl and alkyl isocyanurates catalyzed by tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO) or tetraethylammonium 2-(carbamoyl) benzoate (TEACB). The reported procedures clearly demonstrated that TBA-PINO and especially TEACB are suitable metal-free organocatalysts for the preparation of isocyanurates. The important features of our method are: the mild reaction conditions, low catalysts loading, high to quantitative yields of the products, chemical stability and the simple preparation of the catalysts or their removal from the reaction mixture.

Acknowledgement

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