Sulfate catalysed multicomponent cyclisation reaction of aryl isocyanates under green conditions

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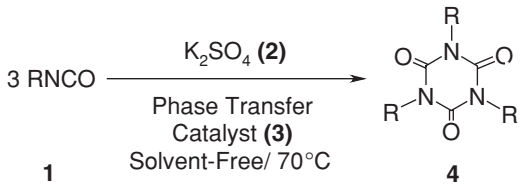
Sulfate anion, as a novel anionic catalyst, promotes the multicomponent cyclisation of aryl isocyantes to give heterocyclic symmetrical isocyanurates selectively under solvent-free conditions. The use of phase transfer catalysts reduces reaction times by 4-16 times.

Keywords: isocyanate cyclisation, sulfate anion, phase-transfer catalysis, 1,3,5-triaryl isocyanurate, green chemistry

Isocyanurates, the corresponding trimers of isocyanates, have found many interesting applications especially in the polymer industry because of their unique properties.[1-5] Recent studies have highlighted their inflexibility, similarity with natural rhodotorulic acid and symmetry. These properties have led to applications in the fields of enantiomeric discrimination, low toxicity drug delivery and nonlinear-optical properties, respectively.[6-8]

Although some laborious protocols have been used for the synthesis of isocyanurates,[7,9] the most popular and industrial routes rely on catalytic cyclotrimerisation of isocyanates.[4,5] Catalytic activity has been observed for many compounds since the initial works by Hoffman and Michael in the last decades of 19th century[10] and one can classify them in five major groups: (a) anionic such as metal alkoxides,[10] various metal salts of carboxylic acids,[4,5] fluoride[3] and cyanate[11,2] salts; (b) neutral Lewis bases such as proazaphosphatrane and quasi-azaphosphatrane,[2] phosphines and tertiary amines;[12] (c) Lewis acids and weak Bronsted acids such as $AlCl_3$[13a] and phenols or alcohols;[13b] (d) Organometallics especially with tin species in their structures[14] or transition metal complexes; and (e) combination catalysts such as pyridine and epoxides,[15a,b] 2-tributylstannylpropanol and quaternary ammonium halides,[15c] ethyl alcohol and N-methylmorpholine[15d] and carboxylate salts along with quaternary ammonium salt.[5a,15e] However, most of these conventional methods usually require severe conditions due to the low activity of the catalyst, formation of byproducts such as dimer or carbodiimides because of poor selectivity of the catalyst, lengthy reactions, the use of reagents and solvents which are not readily available, toxic, or difficult to separate. Therefore, methods are needed to prepare isocyanurates in high yields, which require little or no purification of the final product are needed[2,14,15c] and use mild conditions *i.e.* green chemistry.[16]

Recently, we have demonstrated the selective catalytic activity of sodium or potassium salts of piperidinedithiocarbamate and nitrite,[17a] sodium *p*-toluenesulfinate,[17b] sodium saccharin,[17c] and potassium sulfite[17d] as novel anionic catalysts, on their own or in the presence of phase-transfer catalysts (PTCs), mainly tetraalkylammonium halides with soft anions, in solvent-free condition. Isocyanates have been classified as hard heterophiles and according to Hard-Soft Acid and Base (HSAB) theory, react preferably with hard nucleophiles.[3,18] Comparing different Lewis bases and anionic catalysts which exert their catalytic activity by the same mechanism also shows that nucleophiles must be sufficiently hard to be able to starting catalytic cycle, but leave the final intermediate to produce the aromatic isocyanurate. On the other hand, solubility of the catalyst in the reaction medium has a vital effect on the rate of the reaction especially under solvent-free condition. This is in agreement with the observed literature results, *i.e.* the catalytic activity decreases in the following series: quaternary ammonium salts of fluoride > organic acid salts > tertiary amines.[15e]



Scheme 1

In the course of our study about cyclotrimerisation of isocyantes catalysed by potassium sulfite to prepare novel isocyanurates useful for dendrimer or medicinal chemistry, we compared its activity with potassium sulfate to evaluate the *alpha* effect from the sulfite lone pair on the sulfur atom.[17d, 18b] Although we expected less catalytic activity for the sulfate anion, however better activity in the terms of reaction time and yield was observed. This implies that solubility of the catalyst has a great effect on the rate of reaction. Therefore, it was found when phenyl isocyanate (**1a**) as a model compound is heated with 0.33 mol% of potassium sulfate (**2**) at 70 °C, 1,3,5-triphenyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (1,3,5-triphenyl isocyanurate) (**4a**) appeared after 66 min in 95% yield (Scheme 1) while a mixture containing sulfite remains intact even at higher temperature after 24 h (Table 1, entries 1-3).

The procedure is very simple and separation of the catalyst from reaction mixture is convenient. This reactivity yielding high conversion is very notable for sulfate as an inorganic anion. The time of reaction could be reduced 4–16 times by adding an equivalent amount of PTCs (**3**) while conversions

Table 1 Cyclotrimerisation of Phenyl Isocyanate (**1a**) catalysed by (**2**) (0.33 mol%, 70 °C) and its combination with equivalent amount of different PTCs (**3**) under solvent-free condition

Entry	PTC **3**	Time/min	Yield[a]/%
1[b]	–	24 h	0.0
2[b]	TBAB[c]	24	86
3	–	66	95
4	TBAB	15	94
5	TBAI[d]	10	90
6	TEAB[e]	10	94
7	CTAB[f]	8	88
8	$Bu_4N[BF_4]$	4	87
9	$Bu_4N[ClO_4]$	11	92
10	$Bu_4N[HSO_4]$	48 h	0.0
11	$(NH_4)_2SO_4$	48 h	0.0
12	$(NH_4)_2CO_3$	48 h	0.0

[a]Yields of isolated product. [b]Potassium sulfite as catalyst at 120 °C.[17d] [c]Tetrabutylammonium bromide. [d] Tetrabutylammonium iodide. [e]Tetraethylammonium bromide. [f]Cetyltrimethylammonium bromide.

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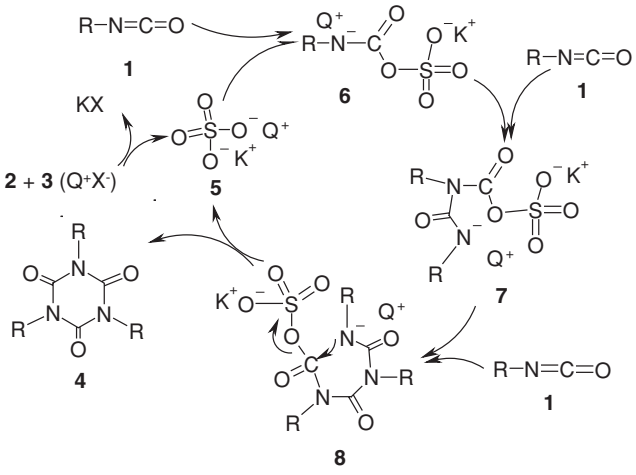
do not change substantially (entries 4–9). In this context, PTCs containing soft anions such as bromide and iodide were investigated. TBAI displays faster reaction times than TBAB. Both increasing and decreasing the size of ammonium part of PTC has the same effect on the reaction time (entries 4–7). $Bu_4N[BF_4]$ and $Bu_4N[ClO_4]$ which show no catalytic activity even after 24 h alone, also demonstrate fast reaction times by adding (**2**) to the reaction mixture (entries 8,9). On the other hand $Bu_4N[HSO_4]$, $(NH_4)_2SO_4$ and $(NH_4)_2CO_3$ prohibit catalytic activity of sulfate anion which may be attributed to their acidic protons (entries 10–12).

These findings are in consistence with the following proposed mechanism not only for sulfate anion but also for *p*-toluenesulfinate and sulfite anions:[17b,d] (1) Initial nucleophilic attack of negative oxygen atoms upon the first molecule of isocyanate to produce the intermediate (**6**). (2) Successive attacks of (**6**) and its product upon the second and third molecules of isocyanate to produce the intermediates (**7**) and (**8**), respectively. (3) Ring closure and leaving the catalyst to start new catalytic cycle (Scheme 2).

Further confirmation of the purposed mechanism could be deduced from reactivity of 4-substituted aryl isocyanates under the reaction conditions (Table 2). In this context, isocyanates containing electron-withdrawing groups react much faster than ones with electron-donating groups. The yields are good to excellent. Another advantage of the combination catalyst could be observed for trimerisation of electron-donating substituted isocyanates, especially 4-metoxyphenyl isocyanate (**1f**)**,** which most of the so far introduced catalysts failed to trimerise, or even 4-methylphenyl isocyanate (entries 1–6).[2]

On the other hand, like the most of reported catalysts which are unable to promote cyclisation of alkyl isocyanates and aryl isothio-cyanates, the combination of sulfite anion and PTC has no effect on butyl and cyclohexyl isocyanate or phenyl isothiocyanate as representative of these kinds of substrates.[2]

To summarise, novel, nontoxic, nonmetallic and readily available sulfate anion on its own or in the presence of PTCs has been explored for multicomponent cyclisation of aryl isocyanates. Achieving high turnover numbers, increasing the catalyst efficiency by the use of PTCs and avoiding toxic solvents such as benzene, DMSO and DMF make the reaction conditions green.[16]



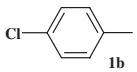
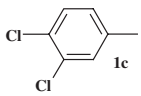
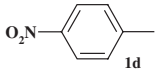
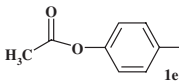
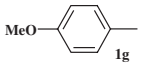
Scheme 2

Experimental

General methods: Melting points were determined on a Gallenkamp apparatus and are uncorrected. FT IR spectra were recorded as KBr pellets on a spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and referenced to TMS or residual $CDCl_3$. Mass spectra were obtained on a Fissions Trio 1000 with an ionising voltage of 70 eV. Analytical TLC was carried out using Fluka aluminium-backed 0.2 mm silica gel 60 F-254 plates. The end of reactions were determined on solidification of the reaction mixture in the case of aryl isocyanates or substantial condensation of alkyl isocyanates. All reactions were monitored by TLC chromatography after suspension of the reaction mixture in dry ether and its filtering on a Buchner funnel.[19a] Dry ether was distilled freshly either on sodium and benzophenone. (**2**) and PTCs were dried under reduced pressure at 70 °C for 2 h prior to use and then kept in a dessicator. 4-nitrophenyl, 4-methoxyphenyl and 4-acetoxyphenyl derivatives were prepared by known literature procedures from 4-nitrobenzoyl chloride, 4-methoxybenzoic acid and 4-hydroxybenzoic acid respectively,[19,20] all substrates were used as received from Merck. All cyclotrimerisation reactions were carried out using carefully oven-dried glassware and were protected from moisture

CAUTION: For safety reasons, all the experiments must be performed in an efficient fume hood and necessary precautions considered in order to avoid any contact with substrates during the operation.

Table 2 Cyclotrimerisation of isocyantes at optimised condition [(**2**), 0.33 mol%, TBAB (**3**), 0.33 mol%, 70 °C]

Entry	Isocyanate **1**	Time /min	Product **4**[a]	Yield /%[b]	M.p. °C Found (Lit)
1	 **1a**	15	**4a**	94	580–282 (279)2
2	 **1b**	10	**4b**	89	317–318 (318)
3	 **1c**	5	**4c**	86	277–279 (279)15
4	 **1d**	4	**4d**	84	348–349 (350)15
5	 **1e**	14	**4e**	91	278–280
6	 **1g**	68	**4f**	96	261–266 (261)[2]

[a]All products, except **4f**, are known and gave spectroscopic data similar to the literature.[2,15] [b]Yields of isolated products.

by a $CaCl_2$ guard tube. All products were crystallised from EtOH or EtOH/ EtOAc and yields refer to isolated pure products.

Typical isocyanate cyclotrimerisation: The general procedure is illustrated with 4-acetoxyphenyl isocyanate (**1f**): A mixture of (**1f**) (0.5000 g, 2.823 mmol), (**2**) (0.0016 g, 9.315 μmol) and TBAB (0.0030g, 9.315 μmol) in a 20 ml flask attached to a condenser and drying tube was heated at 70 °C in an oil bath. After solidification of the reaction mixture (See Table 2 for required time), dry Et_2O (2 ml) was added and the mixture was refluxed for 10 min in the oil bath. The reaction mixture was then cooled to r.t. and after complete crushing of the reaction mixture, an additional dry Et_2O (15 ml) was added. The suspension was stirred for 10 min and filtered by a Buchner funnel to yield a powdery crude product which in the most cases is sufficient pure. Further purification by crystallisation from EtOH/ EtOAc gave 0.455 g (91%) of 1,3,5-tris-(4-acetoxyphenyl) isocyanurate(**4f**) as white crystals: m.p.= 278–280 °C ; IR (KBr pellet) 2968, 2935, 1762, 1709, 1601, 1507, 1409, 1196 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.42 (d, *J*= 8.74 Hz, 6 H), 7.30–7.27 (d, *J*= 8.74 Hz, 6 H), 2.34 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.25, 151.52, 148.88, 131.17, 129.96, 122.88, 21.54; MS (EI) for $C_{27}H_{21}N_3O_9$ (M) calcd. 531.43, found 531.42.

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