

## Accepted Article

**Title:** Delineating the Mechanism of Ionic Liquids in the Synthesis of Quinazoline-2,4(1H,3H)-dione from 2-Aminobenzonitrile and CO<sub>2</sub>

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# Delineating the Mechanism of Ionic Liquids in the Synthesis of Quinazoline-2,4(1H,3H)-dione from 2-Aminobenzonitrile and CO<sub>2</sub>

Martin Hulla, Sami M. A. Chamam, Gabor Laurenczy, Shoubhik Das and Paul J. Dyson\*

**Abstract:** Ionic liquids (ILs) are versatile solvents and catalysts for the synthesis of quinazoline-2,4-dione from 2-aminobenzonitrile and CO<sub>2</sub>. However, the role of the IL in this reaction is poorly understood. Consequently, we investigated this reaction and showed that the IL cation does not play a significant role in the activation of the substrates, and instead plays a secondary role in controlling the physical properties of the IL. A linear relationship between the pK<sub>a</sub> of the IL anion (conjugate acid) and the reaction rate was identified with maximum catalyst efficiency observed at a pK<sub>a</sub> of > 14.7 in DMSO. The base catalyzed reaction is limited by the acidity of the quinazoline-2,4-dione product, which is deprotonated by more basic catalysts leading to the formation of the quinazolidine anion (conjugate acid pK<sub>a</sub> 14.7). Neutralization of the original catalyst and formation of the quinazolidine anion catalyst leads to the observed reaction limit.

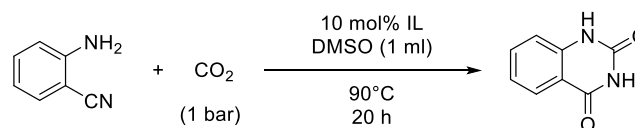
Ionic liquids (ILs) are low melting salts,<sup>[1]</sup> often composed of organic cations and inorganic anions, exhibiting diverse properties and applications.<sup>[2,3]</sup> ILs are now often used as catalysts for the transformations of CO<sub>2</sub><sup>[4-7]</sup> into fine chemicals including, for example, the cycloaddition of CO<sub>2</sub> to epoxides,<sup>[8,9]</sup> N-formylation of amines<sup>[10-12]</sup> and the synthesis of quinazoline-2,4-dione from 2-aminobenzonitrile.<sup>[13]</sup> The synthesis of quinazoline-2,4-dione is important due to its wide range biological activity and use as a precursor in the synthesis of drugs, e.g. Prazosin, Bunazosin, Doxazosin and Zenarestat.<sup>[14]</sup>

The synthesis of quinazoline-2,4-dione from 2-aminobenzonitrile and CO<sub>2</sub> was first reported with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).<sup>[15-19]</sup> Subsequently, a variety of base catalysts were used for this reaction,<sup>[20-23]</sup> as well as lanthanide complexes combined with DBU<sup>[24]</sup> and a range of polymeric, ceramic and nanocatalysts.<sup>[25-29]</sup> However, the catalysts that have attracted the most attention are ILs. The initial IL catalyst, 1-butyl-3-methylimidazolium hydroxide ([BMIm][OH]),<sup>[30]</sup> was shown to proceed via a self-deprotonation mechanism and NHC-carbene formation.<sup>[31]</sup> Other stable IL catalysts have subsequently been reported, such as 1-butyl-3-methylimidazolium acetate ([BMIm][OAc]), which catalyzes the reaction at 1 bar CO<sub>2</sub> and 90°C.<sup>[32]</sup> The discovery that ILs prepared by the protonation of DBU ([HDBU][X])<sup>[33,34]</sup> catalyze the reaction under ambient conditions led to the investigation of protic ILs including 1,1,3,3-tetramethylguanidinium imidazolidine ([HTMG][Im]), which showed similar activity.<sup>[35]</sup> Tetrabutylphosphonium 2-methylimidazolidine ([TBP][2-MIm]) can also catalyze the reaction at 1 bar CO<sub>2</sub> at slightly elevated temperatures,<sup>[36]</sup> whereas tetrabutylphosphonium arginine

([TBP][Arg]) requires high CO<sub>2</sub> pressures and temperatures.<sup>[37]</sup> Although at 1 bar CO<sub>2</sub> extended reaction times were required, tetrabutylammonium tungstate ([TBA]<sub>2</sub>[WO<sub>4</sub>]) also demonstrated relevant activity.<sup>[38,39]</sup>

With the exception of [TBA]<sub>2</sub>[WO<sub>4</sub>], all the ILs were used as dual catalyst-solvent media at high catalyst loadings (up to 500 mol%). Although this approach eliminates the need of a volatile organic solvent, it makes it difficult to assess the role of the IL. Optimized reaction conditions have been reported for each group of ILs studied, with reaction temperatures ranging from 25 to 120°C, reaction times from 6 to 144 h and CO<sub>2</sub> pressures from 1 to 100 bar. These diverse conditions make the search for the optimal IL catalyst challenging. Hence, we decided to investigate systematically the catalytic role of ILs in the conversion of 2-aminobenzonitrile to quinazoline-2,4-dione under fixed reaction conditions in order to identify the key features of the IL catalyst and the reaction mechanism.

Table 1: Cation effects on the catalytic activity of various acetate and fluoride salts on the synthesis of quinazoline-2,4-dione.



Entry	Catalyst	Catalyst loading (mol%)	Yield (%)
1	[BMIm][OAc]	10	46
2	[BMP][OAc]	10	45
3	[TBA][OAc]	10	46
4	[HOEMIm][OAc]	10	45
5	[HDBU][OAc]	10	44
6	KOAc	10	45
7	LiF	<10 <sup>a</sup>	0
8	KF	<10 <sup>a</sup>	25
9	CsF	<10 <sup>a</sup>	46
10	[TBA]F	10	69
11	CsF	2	24
12	[TBA]F	2	24
13	-	-	0

Reaction conditions: 2-aminobenzonitrile (1 mmol), DMSO (1 ml), catalyst (10 mol%), CO<sub>2</sub> (1 bar), 90°C, 20 h, average yield of isolated product from three runs. a) 10 mol% catalyst added but salts not fully dissolved decreasing the actual catalyst loading <10 mol%.

Both the cation and the anion of the IL were proposed to synergistically activate the 2-aminobenzonitrile substrate, leading to considerably different reactivities in different ILs.<sup>[33,35]</sup>

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To verify this hypothesis we prepared a series of acetate ILs and evaluated them under standardized catalytic reaction conditions (10 mol% catalyst loading in DMSO, 1 bar CO<sub>2</sub>, 90°C, 20 h). [BMIm][OAc] yielded the desired product in 46% yield (Table 1, entry 1). Similarly, 1-butyl-1-methylpyrrolidinium acetate ([BMP][OAc]) and tetrabutylammonium acetate ([TBA][OAc]) resulted in comparable yields of 45% and 46%, respectively (Table 1, entries 2 and 3). The hydroxyl functionalized IL, 1-hydroxyethyl-3-methylimidazolium acetate ([HOEMIm][OAc]), which can potentially hydrogen bond with CO<sub>2</sub> or the proposed carbamate intermediate<sup>[40]</sup>, also resulted in 45% yield (Table 1, entry 4). The protic IL [HDBU][OAc] also yielded the product in 44% (Table 1, entry 5). Notably, even potassium acetate exhibited similar activity with the product isolated in 45% yield (Table 1, entry 6). In contrast to reactions conducted in pure ILs, where large differences in catalytic activity are observed,<sup>[32,33,35]</sup> under catalytic conditions no significant differences are observed as the IL cation is varied, indicating that the cation does not play a significant role in the activation of the substrates or in interactions with intermediates.

The lack of influence of the IL cation on the reaction does not completely mitigate its role in the overall efficiency of the catalyst. Experiments with alkali metal fluoride salts and tetrabutylammonium fluoride ([TBA]F) reveal that the cation can strongly influence catalyst performance. With 10 mol% of the fluoride salt the quinazoline-2,4-dione product was extracted in yields ranging from 0 to 69%, in the order LiF < KF < CsF < [TBA]F (Table 1, entries 7-10). However, as the alkali fluoride salts are not fully soluble, the reaction yield is a reflection of the catalysts solubility. With 2 mol% of CsF or [TBA]F, at which both salts are fully soluble, comparable catalytic activity is observed with the product isolated in 24% (Table 1, entries 11 and 12). Thus, the efficiency of the catalyst can be limited by its solubility, as proposed for metal carbonates.<sup>[20]</sup> Hence, the differences in reaction rate in pure ILs may be attributed to differences in physical properties such as viscosity or substrate solubility rather than to the synergistic activation of the substrate by the cation and anion.<sup>[33,35]</sup>

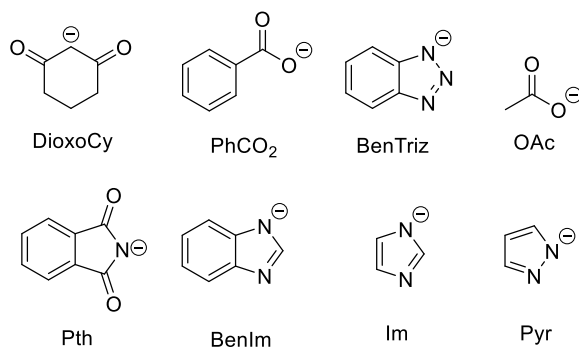


Figure 1: Structures of catalytically active organic anions for the conversion of 2-aminobenzonitrile to quinazoline-2,4-dione.

Since the reported organocatalysts are all bases<sup>[15–19,22]</sup> and the cation has limited influence on the catalytic cycle, we hypothesized that the catalytic activity of ILs is determined by the basicity of the anion. We prepared and tested a series of ILs with anions of varying basicity. ILs with anions derived from strong acids are inactive (Table 2, entries 1 and 2). In contrast, ILs with

anions generated from weak acids (Figure 1) demonstrated some catalytic activity towards the formation of quinazoline-2,4-dione (Table 3, entries 7-11 and 13-16). A plot of the IL anion pK<sub>a</sub> versus the product yield reveals a linear relationship with an onset pK<sub>a</sub> value of 9.2 (Figure 2). A conversion limit of 68-69% (under the conditions used), obtained with a number of stronger bases, e.g. [TBA]F, tetrabutylphosphonium benzoimidazolide ([TBP][BenIm]) and imidazolide ([TBP][Im]), is marked by a plateau (Figure 2). Notably, even uncharged bases such as DBU fit the linear relationship indicating that the dependency of 2-aminobenzonitrile conversion (and mechanism) is the same for both ILs and uncharged bases. In addition, it should be noted that bases with pK<sub>a</sub> values close to the observed reaction onset, e.g. triethylamine and diphenylguanidine, were found to only catalyze the reaction at elevated CO<sub>2</sub> pressures,<sup>[18,22]</sup> and weaker bases with pK<sub>a</sub> values much lower than the onset value, e.g. pyridine, were inactive even in supercritical CO<sub>2</sub>.<sup>[18]</sup> The positive effect of CO<sub>2</sub> pressure together with the observed pK<sub>a</sub> dependency supports a proposed reaction mechanism, where the catalyst promotes carbamate salt formation via partial amine deprotonation and nucleophilic attack on CO<sub>2</sub>.<sup>[40]</sup>

Table 2: Dependency of the yield of quinazoline-2,4-dione on the basicity (characterized by pK<sub>a</sub>) of the catalyst.

Entry	Catalyst	pK <sub>a</sub> of Conjugate Acid (BH <sup>+</sup> ) <sup>[a]</sup>	Yield (%)
1	[TBA]Br	0.9	0
2	[TBA]Cl	1.8	0
3	Pyridine	3.4	0
4	[TBA][NO <sub>2</sub> ]	7.5	0
5	Diphenylguanidine	8.6	0
6	Et <sub>3</sub> N	9.0	0
7	[HDBU][DioxoCy]	10.3	16
8	[TBA][PhCO <sub>2</sub> ]	11.1	22
9	[TBP][BenTriz]	11.9	38
10	[X][OAc]	12.6	45 <sup>[b]</sup>
11	[TBA][Pth]	13.4	55
12	DBU	13.9	65
13	[TBA]F	15.0	69
14	[TBP][BenIm]	16.4	69
15	[TBP][Im]	18.6	68
16	[TBP][Pyr]	19.8	68

Reaction conditions: 2-aminobenzonitrile (1 mmol), DMSO (1 ml), catalyst (10 mol%), CO<sub>2</sub> (1 bar), 90°C, 20 h, average yield of isolated product from three runs. [a] Values were taken from Bordwell's pK<sub>a</sub> tables, for ILs only the basicity of the anion in DMSO was considered. [b] Average value for all acetate ILs and KOAc.

The base catalyzed reaction yield reaches a limit with a maximum efficiency between pK<sub>a</sub> 13.9 and 15, marked by a plateau (Figure 2). From a linear extrapolation, the most efficient catalysts will have a pK<sub>a</sub> around 14.4 or above in DMSO. Although full deprotonation of the 2-aminobenzonitrile starting material (pK<sub>a</sub> 24.3)<sup>[41]</sup> cannot be achieved with such a catalyst, higher yields are not observed with substantially stronger bases. To rationalize this limit we determined the acidity of the

quinazoline-2,4-dione product using UV-vis spectroscopy (SI).<sup>[42]</sup> The measured pKa of 14.7 is in excellent agreement with the estimated pKa limit of the catalyst of 14.4. Presumably, the acidity of quinazoline-2,4-dione results in its deprotonation by ILs and bases with pKa values above 14.7. Hence, the original base catalyst is neutralized and a new IL catalyst containing a quinazolidone anion is formed (Scheme 1). Thus, all catalysts with pKa values above 14.7 only act as pre-catalysts towards the formation of the quinazolidone IL catalysts explaining the uniform reaction yield observed for all ILs with a pKa above this value.

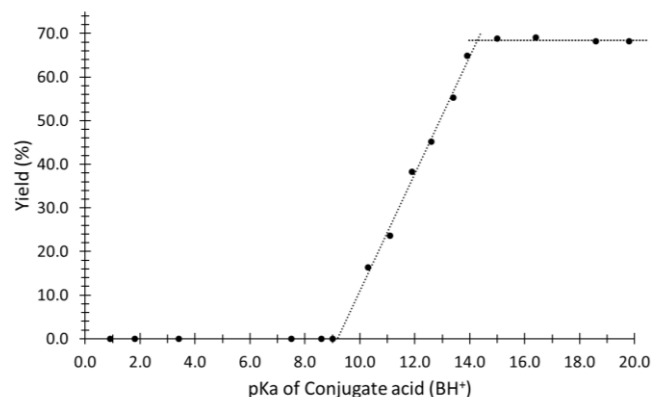
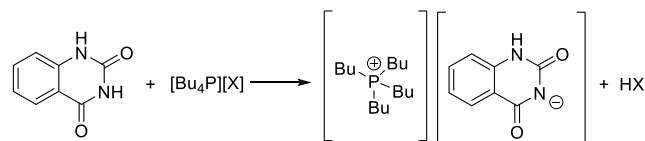


Figure 2: Reaction yield dependency on the pKa of the catalyst in DMSO. Linear dependency is observed in the range 9.2-14.4; R = 0.99

Once the product quinazolidone-2,4-dione starts to form [TBP][BenIm], [TBP][Im], [TBP][Pyr] and [TBA]F are transformed into the tetrabutylphosphonium or tetrabutylammonium quinazolidone ([TBP][Quinazolidone] and [TBA][Quinazolidone]) ILs with comparable activity. Some of the quinazolidone-2,4-dione product is lost (equivalent to the catalyst loading), which is only partially recovered during aqueous work-up. Hence, using [TBP][BenIm] as a pre-catalyst followed by an acidic work-up

gives the product in 73% yield (cf. 69% is without acid). To confirm the proposed transformation, the [TBP][Quinazolidone] IL was prepared and evaluated as a catalyst, resulting in a 74% yield even with an aqueous work-up.

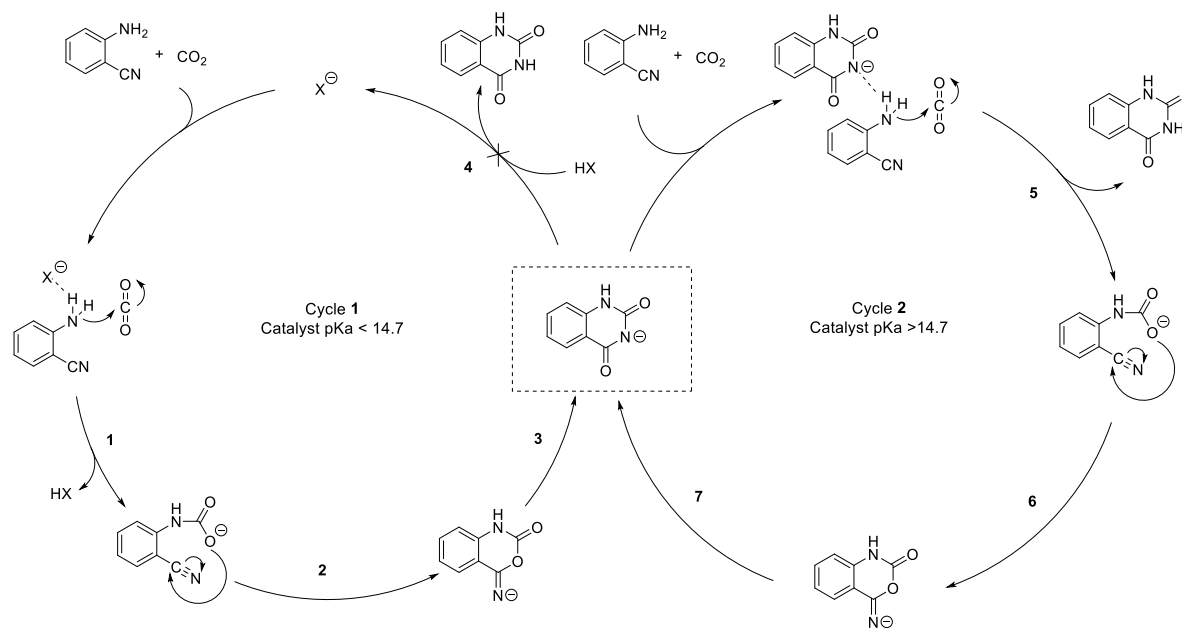


Scheme 1 Reaction of quinazoline-2,4-dione with a tetrabutylphosphonium IL, X = fluoride, benzoimidazole, imidazole, pyrrolide and other anions with pKa >14.7 in DMSO.

The pKa of a compound is solvent dependent and a linear relationship between acidities in DMSO and a range of ILs was recently demonstrated.<sup>[43–46]</sup> Hence, while the limiting pKa value of 14.7 is only valid in DMSO, the pKa value is readily convertible to ILs. Consequently, unless a base is present in excess, the deprotonation of quinazoline-2,4-dione to the quinazolidone anion leads to the strongest base available in both organic solvents and ILs. Similarly, in the case of substituted quinazoline-2,4-diones the strongest available base would be the respective quinazolidone anion. Due to the linear relationship between pKa and the yield (see above), bases stronger than quinazoline-2,4-dione (or the quinazolidone anion) are the most active catalysts for the synthesis of quinazoline-2,4-dione (assuming they proceed via a base-catalyzed mechanism (Scheme 2)).

Based on calculations a reaction mechanism was proposed for the base catalyzed synthesis of quinazoline-2,4-diones from CO<sub>2</sub> and 2-aminobenzonitrile (Scheme 2, cycle 1).<sup>[40]</sup> In the first step (1), a carbamate salt is formed via a base promoted reaction between 2-aminobenzonitrile and CO<sub>2</sub>. The observed pKa dependency further supports the proposed carbamate salt formation step as stronger bases enhance the nucleophilicity of the amine favoring its reaction with CO<sub>2</sub>.

Scheme 2: Proposed catalytic cycle for the preparation of quinazoline-2,4-diones by catalysts with a pKa <14.7 (cycle 1, adapted from reference [40]) and the cycle for catalysts with a pKa >14.7 (cycle 2). The IL cation was omitted for clarity.



Intramolecular cyclisation (2), followed by a series of intramolecular rearrangement steps (3), leads to the formation of a quinazolide anion. However, the final step (4), where the quinazolide anion is protonated by the conjugate acid of the base catalyst (eliminated in step 1), is only possible for catalysts with a  $pK_a < 14.7$ . For catalysts with  $pK_a > 14.7$  the quinazolide anion is insufficiently basic to extract a proton from the original catalyst. Presumably, the quinazolide anion then becomes the new base catalyst in a second cycle (Scheme 2, cycle 2). The second cycle follows the same steps, as the quinazolide anion is also a base, with the exception that the product is formed simultaneously with the carbamate salt in step (5) and the catalyst is regenerated by a series of intramolecular rearrangement steps (7).<sup>[40]</sup>

We have demonstrated that IL cations do not play a significant (direct) role in the catalytic activation of 2-aminobenzonitrile,  $CO_2$  or the intermediates in the catalytic cycle. Instead, the cation contributes toward the required physical properties of the IL, such as its solubility, to ensure homogeneous reaction conditions. Catalytic activity is dependent on the anion and, in particular, on the basicity of the anion, with a linear relationship between  $pK_a$  and activity, and the most active catalyst correlating to the strongest base. However, the acidity of the product results in its deprotonation by the catalyst leading to a limit in the maximum base strength. Unless present in excess, the strongest base available in the presence of quinazoline-2,4-dione is the corresponding quinazolide anion, and for substituted quinazoline-2,4-diones, ILs containing the corresponding quinazolide anion should be the most active catalysts.

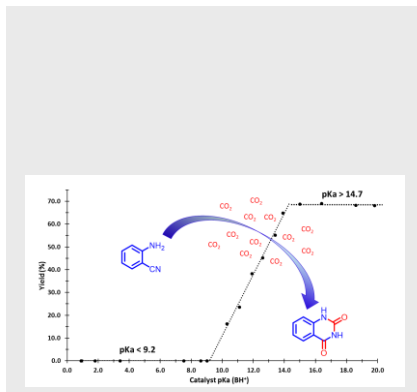
## ACKNOWLEDGMENT

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## COMMUNICATION

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