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# Protic ionic liquids as catalysts for a threecomponent coupling/hydroarylation/ dehydrogenation tandem reaction

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**Abstract:** Protic ionic liquids with nitrate anions were used as solvents and catalysts for a three-component oxidative dehydrogenation tandem reaction via the coupling and hydroarylation of benzaldehyde, aniline, and phenylacetylene to a quinoline derivative. The reaction was supported by air and microwave irradiation. The presence of nitrate as counter anion in the protic ionic liquids was essential for the reaction.

**Keywords:** ammonium salts; C–H activation; multicomponent reaction; oxidation; protic ionic liquids.

## **1** Introduction

Ionic liquids (ILs) have received increased attention in recent years as novel solvents for reactions and electrochemical processes [1]. Several of these ILs, which are salts that melt below 100°C, can be considered to be "green solvents" since they can be efficiently recovered [2]. The commonly used ILs in the 1960s were composed of organic cations and chloroaluminate anions [3]. Since AlCl, was present in these liquids, the latter were also used as catalysts in Lewis acid-catalyzed reactions [3]. However, they are also highly moisture sensitive. Many of the ILs developed in the 1990s incorporated relatively inert lipophilic anions and have been used as solvents for catalytic reactions [4–9]. However, it is also known that these ILs are capable of catalyzing reactions either in substoichiometric amounts or as reaction media because of their stronger interactions with the reaction partners compared to some standard solvents [10].

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ILs can be divided into different subclasses. In addition to the more common aprotic ILs, also protic ionic liquids (PILs) have been reported. In fact, the first recognized IL was a PIL. Ethylammonium nitrate (EAN) was described in 1914 [11]. PILs are prepared via the stoichiometric neutralization reaction of Brønsted acids and Brønsted bases. In general, they possess a relatively weakly acidic proton at the cation. They should not be mistaken with Brønsted acidic ILs. The latter possess typically an acidic anion like HSO, with an aprotic cation or incorporate in the aprotic cation, for example, a sulfonic acid moiety. The field of Brønsted and PILs has been reviewed [12-14]. PILs can be directly prepared and their pH tuned by using the appropriate Brønsted acid-base combinations. This would be beneficial for many organic reactions that are catalyzed by a proton transfer or via hydrogen-bond formation. Hence, it is remarkable that there are fewer examples of PIL solvents applied for organic reactions compared to aprotic ILs in the literature.

PILs have been mainly applied for reactions catalyzed by protons. Hence, PILs have been used for esterification reactions [15–17] and aldol condensation [18]. A mixture of ammonium acetate and Bu-pyridinium nitrate was employed to catalyze a Knoevenagel condensation [19]. In addition, a Knoevenagel reaction could be carried out in EAN as solvent, which resulted in a significant improvement compared to the reaction with standard aprotic ILs [20]. EAN has also been used as a Brønsted acid catalyst in common solvents for the synthesis of imines [21]. EAN and *N*-methyl-2-pyrrolidone hydrogensulfate [NMPH]+[HSO<sub>4</sub>]<sup>-</sup> were applied as a solvent and catalyst system for a threecomponent condensation reaction [22, 23].

The specific utilization of  $NO_3$  counter anions in ILs has been limited so far. Aprotic ILs have been used with  $NO_2BF_4$  for the nitration of arenes [24]. In aprotic ILs, a mixture of  $HNO_3$  and  $Ac_2O$  gave nitroarenes in high yields [25–27]. A Brønsted acidic IL was reported for the nitration of arenes with  $HNO_3$  [28]. Aprotic ILs with a nitrate counterion supported the oxidative halogenation or oxidation of toluene to benzoic acid [29]. Brønsted acidic ILs have been reported to oxidize benzylic alcohols to aldehydes in the presence of sodium nitrate because of the oxidative behavior of the in situ formed  $HNO_3$  [30]. This

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mixture could also be used to oxidize Baylis–Hillman adducts [31]. Pyridinium nitrate catalyzed this oxidation under an oxygen atmosphere [32]. [HMIM]<sup>+</sup>[NO<sub>3</sub>]<sup>-</sup> served as a catalyst in an oxidative aromatic chlorination of mesitylene with hydrochloric acid [33] and the oxidative formation of oximes from benzyl alcohols under microwave conditions [34].

Based on our work with ILs [35-45] and in threecomponent coupling/hydroarylation/dehydrogenation tandem reactions [45], we present here an investigation of the catalytic behavior of nitrate-based acidic and oxidative PILs in the synthesis of a quinoline derivative (Scheme 1). Quinoline derivatives are important structural moieties in biologically active natural products and often also starting materials for the chemical and pharmaceutical industry [46–48]. The standard method for creating quinolines is the Friedländer reaction, which is based on an aldol condensation of 2-aminobenzaldehydes with ketones. Because of their instability, these precursors are generated in situ by the reduction of 2-nitrobenzaldehyde derivatives, which are not readily available [49-52]. Hence, the development of different methods of quinoline synthesis has been attracting increasing attention recently. In addition to methods based on the use of transition-metal catalysts [53–57], also some examples using different iron salt-based catalysts have been reported [45, 58-61]. The first example of this reaction with copper(I) complexes as Lewis acid was published by Takai et al. in 2007 [54]. One report with the aprotic  $[bmim]^+[BF_{\mu}]^-$  in the presence of



Scheme 1: Reaction of benzaldehyde 8, aniline 9, and phenylacetylene 10 with 2,4-phenylquinoline 11.



Fig. 1: Applied PILs.

the rare earth salt  $Yb(OTf)_3$  has been published [62]. Yet, investigations with pure PILs have not been reported for this reaction so far.

#### 2 Results and discussion

First, PILs (Fig. 1) were prepared by the neutralization of an amine with nitric acid or acetic acid in an aqueous solution at 0°C according to the procedures in the literature [13]. Thereafter, the water was removed. Contrary to aprotic ILs, the prepared PIL systems are in equilibrium, and in addition to the protonated amine, small amounts of neutral amine and acid are present depending on the strength of the applied Brønsted base and acid. Hence, in the nitrate systems, a small amount of free HNO<sub>3</sub> can be present. The latter is known to be an oxidative agent. The prepared PILs were EAN 1 [63], which is a clear colorless liquid, and diethylammonium nitrate (DEAN) 2 [64], which forms a white gel-like solid. Pyrrolidinium nitrate (PyrN) 3 [65], piperidinium nitrate (PipN) 4 [66], und N-methylimidazolium nitrate (MethN) 5 [67] are clear yellow liquids. In addition to the nitrate-based PILs, also diethylammonium acetate (DEAA) 6 [68] and pyrrolidinium acetate (PyrA) 7 [69] were prepared in order to evaluate the influence of another anion.

The model reaction was the transformation of benzaldehyde **8**, aniline **9**, and phenylacetylene **10** to 2,4-diphenylquinoline **11** (Scheme 1). The results with different conditions and PILs are summarized in Table 1.

First the reaction was investigated with 1 equiv. EAN **1**. It was decided from the beginning to explore the reaction under microwave irradiation since ILs are very suited to be heated under such condition. However, after 20 min, no desired product could be found (Table 1, Entry 1). However, when EAN **1** was prepared in the molar ratio of 1:1.1 from ethylamine and nitric acid and applied in the reaction, a yield of 33% was achieved (Table 1, Entry 2).

Table 1: Reaction of benzaldehyde 8, aniline 9, and phenylacety-lene 10 to 2,4-phenylquinoline 11 under microwave conditions(150 W).

Entry <sup>a</sup>	PIL (ratio of amine to acid <sup>ь</sup> )	Equiv. PIL	<i>Т</i> (°С)	t (min)	Yield (%)°
1	EAN (1:1)	1	110	20	-
2	EAN (1:1.1)	1	110	20	33
3	EAN (1:1.1)	0.1	110	20	10
4	DEAN (1:1)	1	110	20	-
5	DEAN (1:1.1)	1	110	20	40
6	DEAN (1:1.1)	1	130	20	42
7	DEAN (1:1.1)	1	110	40	26
8	PyrN (1:1.1)	1	110	20	16
9	PipN (1:1.1)	1	110	20	17
10	MethN (1:1.1)	1	110	20	-
11	DEAA (1:1.1)	1	110	20	-
12	DEAA (1:1.5)	1	110	20	-
13	PyrA (1:1.1)	1	110	20	-
14	PyrA (1:1.1)	1	110	20	-
15°	EAN (1:1.1)	1	110	24 h	11
16 <sup>c</sup>	DEAN (1:1.1)	1	110	24 h	20
17	[Bmim]⁺Cl⁻/HNO <sub>3</sub>	1	110	20	-
18	HNO <sub>3(aq)</sub>	1	110	20	-
19 <sup>d,e</sup>	DEAN (1:1.1)	1	110	24 h	29
20	DEAN (1:1.5)	1	110	20	19

<sup>a</sup>Reaction conditions: 1 equiv. benzaldehyde **8**, 1.05 equiv. aniline **9**, 1.5 equiv. phenylacetylene **10**, 150 W microwave; <sup>b</sup>HNO<sub>3</sub> or AcOH; <sup>c</sup>isolated yield; <sup>a</sup>under normal heating; <sup>e</sup>under O<sub>3</sub> atmosphere.

Obviously, the reaction benefits from a small excess of free nitric acid. When a smaller amount of 0.1 equiv. was used in this mixture, the yield decreased to 10% (Table 1, Entry 3). Thereafter, DEAN 2 was evaluated (Table 1, Entry 4). As with EAN 1, only with a slight excess of nitric acid could the desired product be isolated. However, the yield improved to 40% (Table 1, Entry 5) compared to EAN 1. A small increase of the temperature to 130°C resulted in a similar yield of 42% (Table 1, Entry 6). An extension of the reaction time to 40 min decreased the yield to 26% (Table 1, Entry 7) as a result of the decomposition of the product. Next, the other PILs were applied in the reaction under the optimized conditions. PyrN 3 gave the product in 16% yield (Table 1, Entry 8), and PipN 4 resulted in an isolated yield of 17% (Table 1, Entry 9). The aromatic PIL MethN 5 did not give the desired product (Table 1, Entry 10). In order to investigate the importance of the counter anion, DEAA 6 and PyrA 7 were also applied in reactions with different excesses of acetic acid. In all cases, no product was obtained (Table 1, Entries 11-14). Thereafter, the influence of standard heating was evaluated. With EAN 1, a yield of 11% was observed after 24 h (Table 1, Entry 15), while DEAN 2 gave a yield of 20% (Table 1,

Entry 16). The latter results show that microwave heating is favorable for the presented system. A control reaction with a mixture of  $[BMIM]^+Cl^-$  and  $HNO_3$ , as well as in water with 1 equiv.  $HNO_3$ , afforded no product (Table 1, Entries 17 and 18). The PIL was needed to obtain **11**. The important influence of oxygen was found when the reaction was performed under an oxygen atmosphere. The yield increased from 20% under normal heating in air to 29% (Table 1, Entry 19). Finally, when the amount of added  $HNO_3$  to DEAN was increased to 0.5 equiv., the yield decreased to 19% (Table 1, Entry 20). Only a slight excess of  $HNO_3$  appears to be the optimum for the reaction.

A proposed mechanism is depicted in Scheme 2. ILs are known to contain a certain amount of water, and the course of the reaction may therefore vary depending on the amount of water present in the system [1].

However, taking into consideration that the first step of the reaction is the formation of an imine species T (Scheme 2), water is formed during the reaction. Since the imine was present after the reaction and could also be isolated, it can be concluded that the imine formation is not the limiting step in the reaction. The ammonium cation coordinates to this imine T and activates it via a hydrogen bond. Phenylacetylene 10 is then added to the adduct to form the intermediate X. Evidence for the ammonium cation $-\pi$  interactions with alkynes has been reported recently [70]. The propargylamine **Y** is formed through the addition of acetylene 10 to the imine T. It forms the dihydroquinoline intermediate Z by performing an intermolecular hydroarylation. Z is oxidized by the nitrate, which is reduced to nitrite in this process. The nitrite can be regenerated by oxygen in the air or in an enriched oxygen atmosphere.

# **3** Conclusion

In this work, the influence of PILs based on nitrate counter anions in the oxidative tandem and hydroarylation reaction of benzaldehyde **8**, aniline **9**, and phenylacetylene **10** was investigated. It was possible to use PILs as catalysts and solvents. Compared to other ILs, higher yields were obtained. The reaction could be performed under normal atmosphere. The PIL is a hydrogen-bond-activating catalyst and oxidant while atmospheric oxygen is a co-oxidant. Although the maximum yield was a moderate 42%, this study will allow the development of more reactions involving an oxidation step with PILs as catalysts and solvents.



Scheme 2: Proposed mechanism.

### 4 Experimental section

All chemicals were commercially available and used without further purification. The solvents were purified prior to use by standard procedures. Thin-layer chromatography was performed on plates from Merck (Silica gel 60, F254), and the substances were detected under UV light at 254 nm. NMR spectra were recorded at 30°C on a Bruker Avance 500 instrument (<sup>1</sup>H: 500 MHz; <sup>13</sup>C: 125 MHz) referenced to the residual proton or carbon signals of the deuterated solvent (<sup>1</sup>H and <sup>13</sup>C NMR). The NMR signals are reported as ppm relative to TMS. Compounds **1** [63], **2** [64], **3** [65], **4** [66], **5** [67], **6** [68], and **7** [69] were synthesized according to literature procedures.

# 4.1 General experimental for the preparation of 2,4-diphenylquinoline (11)

Benzaldehyde **8** (1.0 mmol), aniline **9** (1.05 mmol), phenylacetylene **3** (1.5 mmol), and the PIL as indicated in Table 1 were added to a 10-mL flask under an atmosphere of air. The reaction mixture was stirred at 110°C for 20 min in a microwave oven (150 W). Afterward, the reaction mixture was cooled to room temperature. Purification was performed by flash chromatography (petroleum ether/AcOEt 20:1) to afford **11.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz, ppm):  $\delta$  = 8.31–8.29 (d, *J*=10 Hz, 1H), 8.25–8.24 (m, 2H), 7.95–7.93 (d, *J*=10 Hz, 1H), 7.86 (s, 1H), 7.78–7.75 (m, 1H), 7.60–7.48 (m, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz, ppm):  $\delta$  = 156.8, 149.1, 148.8, 139.6, 138.4, 130.1, 129.5, 129.4, 129.3, 128.8, 128.5, 128.4, 127.6, 126.3, 125.8, 125.6, 119.3. The spectral data of the product were consistent with their literature values [58].

### References

- P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, 2<sup>nd</sup> edition, Vol. 1–2, Wiley-VCH, Weinheim, 2008.
- [2] R. D. Rogers, K. R. Seddon, *lonic Liquids as Green Solvents: Progress and Prospects*, American Chemical Society, Washington, DC, **2003**, p. 2.
- [3] T. Welton, Chem. Rev. 1999, 99, 2071.

- [4] D. Zhao, M. Wu, Y. Kou, E. Min, Catal. Today 2002, 74, 157.
- [5] C. Baudequin, J. Baudoux, J. Levillain, D. Cahard, A. C. Gaumont, J. C. Plaquevent, *Tetrahedron: Asymmetry* 2003, 14, 3081.
- [6] N. Jain, A. Kumar, S. Chauhan, S. M. S. Chauhan, *Tetrahedron* 2005, 61, 1015.
- [7] V. I. Parvulescu, C. Hardacre, Chem. Rev. 2007, 107, 2615.
- [8] J. Durand, E. Teuma, M. Goez, C. R. Chim. 2007, 10, 152.
- [9] J. Muzart, Adv. Synth. Catal. 2006, 348, 275.
- [10] O. Sereda, S. Tabassum, R. Wilhelm, Top. Curr. Chem. 2010, 291, 349.
- [11] P. Walden, Bull. Acad. Imper. Sci. 1914, 1800.
- [12] T. L. Greaves, C. J. Drummond, Chem. Rev. 2008, 108, 206.
- [13] T. L. Greaves, C. J. Drummond, Chem. Rev. 2015, 115, 11379.
- [14] A. R. Hajipour, F. Rafiee, Org. Prep. Proc. Int. 2010, 42, 285.
- [15] H.-P. Zhu, F. Yang, J. Tang, M.-Y. He, Green Chem. 2003, 5, 38.
- [16] H. Zhang, F. Xu, X. Zhou, G. Zhang, C. Wang, *Green Chem.* 2007, 9, 1208.
- [17] P. A. Ganeshpure, G. George, J. Das, J. Mol. Catal. A: Chem. 2008, 279, 182.
- [18] I. Cota, R. Gonzalez-Olmos, M. Iglesias, F. Medina, J. Phys. Chem. B 2007, 111, 12468.
- [19] Y. Q. Li, X. M. Xu, M. Y. Zhou, Chin. Chem. Lett. 2003, 14, 448.
- [20] R. V. Hangarge, D. V. Jarikote, M. S. Shingare, *Green Chem.* 2002, 4, 266.
- [21] C. G. Adam, G. G. Fortunato, P. M. Mancini, J. Phys. Org. Chem. 2009, 22, 460.
- [22] S. A. R. Mulla, T. A. Salama, M. Y. Pathan, S. M. Inamdar, S. S. Chavan, *Tetrahedron Lett.* **2013**, *54*, 672.
- [23] K. M. Deshmukh, Z. S. Qureshi, Y. P. Patil, B. M. Bhanage, Synth. Commun. 2012, 42, 93.
- [24] K. K. Laali, V. J. Gettwert, J. Org. Chem. 2001, 66, 35.
- [25] N. L. Lancaster, V. Llopis-Mestre, Chem. Commun. 2003, 2812.
- [26] E. Dal, N. L. Lancaster, Org. Biomol. Chem. 2005, 3, 682.
- [27] K. Smith, S. Liu, G. A. El-Hiti, *Ind. Eng. Chem. Res.* **2005**, 44, 8611.
- [28] Q. Kun, Y. Chiaki, Chem. Lett. 2004, 33, 808.
- [29] M. J. Earle, S. P. Katdare, K. R. Seddon, Org. Lett. 2004, 6, 707.
- [30] A. R. Hajipour, F. Rafiee, A. E. Ruoho, Synlett 2007, 1118.
- [31] L. D. S. Yadav, C. Awashti, A. Rai, *Tetrahedron Lett.* 2008, 49, 6360.
- [32] S. Shi, A. Kong, X. Zhao, Y. Shan, *Synth. Commun.* **2011**, *41*, 3066.
- [33] C. Chiappe, E. Leandri, M. Tebano, Green Chem. 2006, 8, 742.
- [34] A. Mirjafari, N. Mobarrez, R. A. O'Brien, J. H. Davis Jr, J. Noei, C. R. Chim. 2011, 14, 1065.
- [35] V. Jurčík, R. Wilhelm, Green Chem. 2005, 7, 844.
- [36] V. Jurčík, R. Wilhelm, *Tetrahedron: Asymmetry* **2006**, *17*, 801.
- [37] V. Jurčík, M. Gilani, R. Wilhelm, Eur. J. Org. Chem. 2006, 5103.
- [38] A. Winkel, R. Wilhelm, *Tetrahedron: Asymmetry* 2009, 20, 2344.
- [39] A. Winkel, R. Wilhelm, Eur. J. Org. Chem. 2010, 5817.

- [40] A. Blanrue, R. Wilhelm, Synthesis 2009, 583.
- [41] V. Jurčík, R. Wilhelm, Org. Biomol. Chem. 2005, 3, 239.
- [42] O. Sereda, N. Clemens, T. Heckel, R. Wilhelm, *Beilstein J. Org. Chem.* 2012, *8*, 1798.
- [43] T. Heckel, D. D. Konieczna, R. Wilhelm, Catalysts 2013, 3, 914.
- [44] T. Heckel, A. Winkel, R. Wilhelm, *Tetrahedron: Asymmetry* 2013, 24, 1127.
- [45] M. Muntzeck, R. Wilhelm, Int. J. Mol. Sci. 2016, 17, 860.
- [46] Y. L. Chen, K. C. Fang, J. Y. Sheu, S. L. Hsu, C. C. Tzeng, J. Med. Chem. 2001, 44, 2374.
- [47] J. P. Michael, Nat. Prod. Rep. 1997, 14, 605.
- [48] I. Solomonov, M. Osipova, Y. Feldman, C. Baehtz, K. Kjaer,
  I. K. Robinson, G. T. Webster, D. McNaughton, B. R. Wood,
  I. Weissbuch, L. Leiserowitz, J. Am. Chem. Soc. 2007, 129, 2615.
- [49] P. G. Dormer, K. K. Eng, R. N. Farr, G. R. Humphrey,
  J. C. McWilliams, P. J. Reider, J. W. Sager, R. P. Volante, *J. Org. Chem.* 2003, *68*, 467.
- [50] Y. Hsiao, N. R. Rivera, N. Yasuda, D. L. Hughes, P. J. Reider, Org. Lett. 2001, 3, 1101.
- [51] Y. Z. Hu, D. Zhang, R. P. Thumme, Org. Lett. 2003, 5, 2251.
- [52] B. R. McNaughton, B. L. Miller, Org. Lett. 2003, 5, 4257.
- [53] H. Cho, F. Torok, B. Torok, *Green Chem.* 2014, 16, 3623.
- [54] Y. Kuninobu, Y. Inoue, K. Takai, Chem. Lett. 2007, 36, 1422.
- [55] J. Tang, L. M. Wang, D. Mao, W. B. Wang, L. Zhang, S. Y. Wu, Y. S. Xie, *Tetrahedron* **2011**, *67*, 8465.
- [56] F. P. Xiao, Y. L. Chen, Y. Liu, J. B. Wang, *Tetrahedron* 2008, 64, 2755.
- [57] X. Zhang, B. Q. Liu, X. Shu, Y. Gao, H. P. Lv, J. Zhu, J. Org. Chem. 2012, 77, 501.
- [58] K. Cao, F. M. Zhang, Y. Q. Tu, X. T. Zhuo, C. A. Fan, *Chem. Eur. J.* 2009, 15, 6332.
- [59] S. S. Patil, S. V. Patil, V. D. Bobade, Synlett 2011, 2379.
- [60] C. S. Yao, B. B. Qin, H. H. Zhang, J. Lu, D. L. Wang, S. J. Tu, RSC Adv. 2012, 2, 3759.
- [61] I. Bauer, H. J. Knölker, Chem. Rev. 2015, 115, 3170.
- [62] A. Kumar, V. K. Rao, Synlett 2011, 2157.
- [63] S. Thomaier, W. Kunz, J. Mol. Liq. 2007, 130, 104.
- [64] T. L. Greaves, A. Weerawardena, I. Krodkiewska, C. J. Drummond, J. Phys. Chem. B 2008, 112, 896.
- [65] J.-H. Lin, C.-P. Zhang, Z.-Q. Zhu, Q.-Y. Chen, J.-C. Xiao, J. Fluor. Chem. 2009, 130, 394.
- [66] H. Ono, S. Ishimaru, R. Ikeda, H. Ishida, Chem. Phys. Lett. 1997, 275, 485.
- [67] V. N. Emel'yanenko, S. P. Verevkin, A. Heintz, K. Voss, A. Schulz, J. Phys. Chem. B 2009, 113, 9871.
- [68] P. Attri, P. M. Reddy, P. Venkatesu, A. Kumar, T. Hofman, J. Phys. Chem. B 2010, 114, 6126.
- [69] G. L. Burrell, I. M. Burgar, F. Separovic, N. F. Dunlop, *Phys. Chem. Chem. Phys.* 2010, 12, 1571.
- [70] E. Nagy, E. St. Germain, P. Cosme, P. Maity, A. C. Terentis,
  S. D. Lepore, *Chem. Commun.* 2016, *52*, 2311.