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## Nucleophilic aromatic *cine*-substitution of hydrogen: the ionic liquid-promoted von Richter reaction

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Conversion of 4-R-nitrobenzenes into 3-R-benzoic acids under the action of KCN in the  $EtOH-H_2O$  mixture (the von Richter reaction) is significantly accelerated by ionic liquids thus allowing to extend the scope of the reaction. The finding is pioneering ionic liquid-promoted nucleophilic aromatic *cine*-substitution of hydrogen.

The nucleophilic aromatic substitution of hydrogen in electrondeficient arenes (S<sub>N</sub>H) is of great practical importance. Addition of nucleophiles to electron-deficient arenes such as nitroarenes would proceed faster in the positions occupied by hydrogen giving  $\sigma^{H}$ -adducts relative to those, equally activated, occupied by halogens or other nucleofugal groups.<sup>1,2</sup> Since a spontaneous departure of the hydride ion from  $\sigma^{H}$ -adducts is impossible, their conversion to products of the hydrogen nucleophilic substitution should be accomplished by special means. The oxidation of  $\sigma^{H_{-}}$ adducts by external oxidants leads to products of the oxidative nucleophilic aromatic substitution of hydrogen.<sup>3</sup> When nucleophiles contain leaving groups X at the nucleophilic center, e.g.  $\alpha$ -halocarbanions,  $\sigma^{H}$ -adducts undergo a fast base-induced  $\beta$ -elimination of HX giving products of the vicarious nucleophilic substitution.<sup>4</sup> Other less common ways of converting  $\sigma^{H}$ -adducts to stable products are *cine-5* and *tele-substitution*,<sup>6</sup> the intramolecular redox processes leading to nitrosoarenes 5(d),7 and the ANRORC<sup>8</sup> substitution. In the course of *cine*-substitution the nucleophile takes up a position adjacent to that occupied by the leaving group. Conversion of substituted nitrobenzenes into benzoic acids under the action of KCN excess in aqueous EtOH (the von Richter reaction)<sup>5(a)-(c)</sup> is an example of *cine*-substitution when carboxylic group acquires ortho-position to the leaving nitro group.

This reaction was discovered by V. von Richter<sup>5(a),(b)</sup> in 1871 and received relatively little attention until J. F. Burnett *et al.* confirmed many of von Richter's findings and attempted studying the reaction mechanism.<sup>9</sup> This transformation occurs on heating different substituted nitrobenzenes in the presence of the KCN excess in refluxing 48% aqueous ethanol for 48–50 h or in a sealed tube at 150–180 °C for 1–2 h. The expected benzoic acids were usually produced in low yields or were not generated at all. In addition, the reaction is accompanied by a large amount of acidic tar, apparently polymeric by nature. The von Richter reaction mechanism has not been proved so far. The accepted mechanism<sup>10</sup> is given in Scheme 1.

Here we present our results on the ionic liquid-promoted von Richter reaction within the range of electron-deficient 4-R-nitroarenes giving rise to the corresponding 3-R-benzoic acids.

Ionic liquids (ILs) are extensively used as reaction media or catalysts to promote various reactions, especially heterolytic ones, owing to their useful physicochemical properties (non-flammability, low vapor pressure, feasible recovery, *etc.*).<sup>11</sup> Our research team has successfully experienced in the performance of various reactions in ILs.<sup>12</sup> ILs that are comprised of non-



coordinated ions create an ideal environment for polar intermediates produced by the reaction, which may lead to acceleration of the process rate and increase in its selectivity. As evident from Scheme 1, different polar intermediates are formed during the von Richter reaction, which is a good challenge to use ILs as reaction media or catalysts for this purpose. Nitrobenzene **1a** and its *para*-substituted derivatives **1b–f** were selected as substrates.

To optimize the reaction conditions we employed 1-butyl-3methylimidazolium tetrafluoroborate ( $[bmim]BF_4$ ) and 4-chloronitrobenzene **1b** as models. Potassium cyanide was taken in a large excess (5, 10 or 20 mol per 1 mol of **1b**). All reactions were

Table 1Screening of the conditions for the synthesis of 3-chlorobenzoicacid 2bfrom 4-chloronitrobenzene 1b (4 mmol) by the von Richter reactionin the presence of ILs.

Table 1	2 Synthes	is of benzo	ic acids 2	<b>a,c–f</b> fror	n nitrobeze	enes 1a,c–f	by the
von Ric	hter react	ion in the p	resence o	f 175 mol	% of [bmi	m]BF <sub>4</sub> at 8	5°C.

Entry	KCN/ mmol	EtOH/ ml	H <sub>2</sub> O/ ml	IL (mmol)	T/°C	t/h	Isolated yield of <b>2b</b> (%)
1	20	0.5	0.5	[bmim]BF <sub>4</sub> (14)	110	20	0
2	20	3	3	[bmim]BF <sub>4</sub> (4)	85	8	40
3	20	5	5	[bmim]BF <sub>4</sub> (7)	85	9	48
4	20	5	5	[bmim]BF <sub>4</sub> (7)	85	13	61
5	20	5	5	[bmim]BF <sub>4</sub> (7)	85	18	70
6	20	5	5	[bmim]BF <sub>4</sub> (7)	85	20	70
7	40	5	5	[bmim]BF <sub>4</sub> (7)	85	20	68
8	80	7	7	[bmim]BF <sub>4</sub> (7)	85	8	58
9	20	5	5	$[bmim]PF_6(7)$	85	40	34
10	20	5	5	$[\text{emim}](C_2F_5)_3PF_3(7)$	85	50	0

performed in 4 mmol scale of reactant **1b** (Table 1).<sup>†</sup> Heating the mixture of nitrobenzene 1b and KCN in [bmim]BF4 in the presence of little EtOH and H<sub>2</sub>O amounts at 110 °C for 20 h gave only tar materials (Table 1, entry 1). Therefore, the temperature was reduced to 85 °C, EtOH and H<sub>2</sub>O were used in larger amounts and the ratio between of 1b, KCN, EtOH, H<sub>2</sub>O and IL was varied. At first, the completion of reaction was monitored by TLC (disappearance of starting nitrobenzene 1b). Prolongation of reaction time promoted raising the yield of **2b** twice (entries 5–7). Since the outcome of the reactions with the KCN: **1b** molar ratio 5:1, 10:1 and 20:1 was comparable (entries 5-8), a fivefold KCN excess was used in the next experiments. The optimum molar ratio [bmim]BF<sub>4</sub>:1b was found to be 1.75:1 (entries 3–8). Optimum EtOH and H<sub>2</sub>O amounts for 4 mmol of 1b proved to be 5 ml of each solvent (entries 3-7). When the KCN: 1b molar ratio was 20:1, EtOH and H<sub>2</sub>O amounts were increased to 7 ml (entry 8). Apart from [bmim]BF<sub>4</sub>, two other ILs – 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF<sub>6</sub>) and 1-ethyl-3-methylimidazolium trifluorotris(pentafluoroethyl)phosphate  $([emim](C_2F_5)_3PF_3)$  – were tested. Ionic liquid [bmim]PF<sub>6</sub> was less effective than [bmim] $BF_4$  (entry 9), whereas in the case of  $[\text{emim}](C_2F_5)_3PF_3$  the reaction did not actually occur (entry 10). Therefore, [bmim]BF<sub>4</sub> was used further on.

Other nitrobenzenes **1a,c-f** (Table 2) were treated similarly under the optimized conditions (see Table 1, entries 5, 6). However, under these conditions, only 4-fluoronitrobenzene **1d** gave the expected 3-fluorobenzoic acid **2d** in 52% yield (Table 2, entry 7). Heating for 90 h was needed to prepare 3-bromobenzoic acid **2c** from 4-bromonitrobenzene **1c** in 40% yield (entry 4). Raising KCN amount to 10 or 20 mol per 1 mol of **1c** rose the yield of **2c** to 67% (60 h, entry 5), or to 52% (12 h, entry 6). Interestingly, 4-fluoronitrobenzene **1d** with 10 and 20-fold molar

Entry	<b>1</b> (4 mmol)	KCN/ mmol	EtOH/ ml	H <sub>2</sub> O/ ml	t/h	Yield of <b>2</b> (%)	Yield of <b>2</b> (%) (lit. data)	
1	1a	20	5	5	90	<b>2a</b> (0)	100(b) a	
2	1a	40	5	5	90	<b>2a</b> (26)	$10^{9(b)} a$	
3	1a	80	7	7	90	<b>2a</b> (44)	0,000	
4	1c	20	5	5	90	<b>2c</b> (40)		
5	1c	40	5	5	60	<b>2c</b> (67)	$37^{9(b)} c$	
6	1c	80	7	7	12	<b>2c</b> (52)		
7	1d	20	5	5	50	<b>2d</b> (52)		
8	1d	40	5	5	20	$-(42)^d$	$0^{9(b) e}$	
9	1d	80	7	7	8	$-(41)^d$		
10	1e	20	5	5	90	<b>2e</b> (0)		
11	1e	40	5	5	30	<b>2e</b> (61)	$40^{9(b) f}$	
12	1e	80	7	7	20	<b>2e</b> (50)		
13	1f	20	5	5	90	<b>2f</b> (0)	29(a) a	
14	1f	40	5	5	90	<b>2f</b> (12)	$5^{9(d)} g$ $0^{9(d)} h$	
15	1f	80	7	7	40	<b>2f</b> (15)	0	
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<sup>*a*</sup> Sealed tube, 180 °C, 1.5 h. <sup>*b*</sup> Sealed tube, 160 °C, 2 h. <sup>*c*</sup> 48 h reflux in 48% EtOH, 8-fold molar excess of KCN. <sup>*d*</sup> 4-Ethoxynitrobenzene was a product. <sup>*e*</sup> Sealed tube, 150 °C, 1 h, or 5% of 4-ethoxynitrobenzene. <sup>*f*</sup> Sealed tube, 150 °C, 1 h. <sup>*s*</sup> Sealed tube, 170–180 °C, 1 h. <sup>*h*</sup> 72 h reflux in 48% EtOH.

excess of KCN was transformed to 4-ethoxynitrobenzene instead of 3-fluorobenzoic acid 2d (entries 8, 9). Therefore, KCN amount was screened for nitrobenzenes 1a,e,f. The fivefold KCN molar excess was insufficient for these compounds to react even at 90 h heating (see Table 2, entries 1, 10, 13), while the 10-fold and 20-fold KCN molar excess provided positive results. Benzoic acid 2a was prepared in 26% yield with 10-fold and 44% yield with 20-fold molar excess of KCN (entries 2, 3). 3-Iodobenzoic acid 2e was obtained in 61% yield with 10-fold and in 50% yield with 20-fold molar excess of KCN (entries 11, 12). 3-Methoxybenzoic acid 2f was merely yielded in 12% with 10-fold and 15% with 20-fold molar excess of KCN on heating for 90 and 40 h, respectively, on full conversion of initial nitrobenzene 1f (entries 14, 15). Structures of compounds obtained were established by a comparison of their melting points, IR, <sup>1</sup>H, <sup>13</sup>C NMR and mass spectra with published data.

In summary, the von Richter reaction of nitroarenes **1a–f** in the presence of ILs provided results which were inaccessible under previously described conditions (Table 2, the last column). We found that the increase in electron-donating properties of substituents in nitrobenzenes decelerated the reaction. Our results represent the first example of nucleophilic aromatic *cine*-substitution of hydrogen promoted by ionic liquids.

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<sup>&</sup>lt;sup>†</sup> General procedure. A mixture of nitrobenzene **1** (4 mmol), KCN (20, 40 or 80 mmol), EtOH (5 or 7 ml), water (5 or 7 ml) and [bmim]BF<sub>4</sub> (7 mmol, 175 mol%) was heated on the oil bath with stirring at 85 °C (see Tables 1 and 2). Then 10 ml of water was added and the mixture was extracted with  $CH_2Cl_2$  (3×10 ml) and diethyl ether (3×20 ml). The aqueous layer was acidified with HCl to pH 1–2 and extracted with diethyl ether (3×20 ml). Magnesium sulfate (~5 g) and absorbent carbon (~1 g) were added to the ether layer and this was stirred for 5 h. The solid was filtered off, the filtrate was evaporated and the residue was crystallized from the corresponding solvent to give product **2**.

Benzoic acid **2a**: mp 121–122 °C (H<sub>2</sub>O) (lit.,<sup>13</sup> 121–123 °C).

<sup>3-</sup>Chlorobenzoic acid **2b**: mp 154–156 °C (EtOH) (lit.,<sup>14</sup> 154–158 °C).

<sup>3-</sup>Bromobenzoic acid **2c**: mp 156–157 °C (EtOH) (lit.,<sup>15</sup> 156–158 °C).

<sup>3-</sup>Fluorobenzoic acid **2d**: mp 122–123 °C (H<sub>2</sub>O) (lit.,  $^{16}$  122–123 °C).

<sup>3-</sup>Iodobenzoic acid **2e**: mp 184–185 °C (Pr<sup>i</sup>OH) (lit.,<sup>17</sup> 185–186 °C). 3-Methoxybenzoic acid **2f**: mp 106–107 °C (H<sub>2</sub>O) (lit.,<sup>18</sup> 107–108 °C).

<sup>4-</sup>Ethoxynitrobenzene: mp 55–56 °C (light petroleum) (lit.,  $^{19}$  55–56 °C).

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