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Two Different Selective Ways in the Deprotonation of β-Bromopropionanilides: β-Lactams or Acrylanilides Formation

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The reactivity of 3-bromo-*N*-(*p*-bromophenyl)propanamide with different bases in an ionic liquid ($BMImBF_4$) and in acetonitrile (ACN) was studied. Two possible deprotonation sites are present in this molecule, leading to different products. When the NH group is deprotonated, a β-lactam is obtained after internal halide displacement; when the CH_2 in alpha to the carbonyl is deprotonated, the corresponding acrylanilide is formed. This study allowed determining the experimental conditions to obtain selectively and in high yields both products starting from the same molecule. In particular, to obtain the acrylanilide Et_3N in ACN is to be used, while to obtain selectively the β-lactam ring the base must be generated by cathodic reduction of a DMF or ACN-Et_4NBF_4 solution. These reactions were extended to other β-bromopropionanilides, allowing to easily synthesize both β-lactams and acrylanilides, molecules having noteworthy biological activities.

Acrylanilides are an important class of molecules, most of which with biological activity. As an example, *p*-bromoacrylanilide is a selective covalent inhibitor of transglutaminase 2 for Huntington's disease,[1] while acrylanilides with different substituents at the aromatic ring are covalent inhibitors of cysteine-containing proteins.[2] Due to the importance of this class of compounds, a multitude of different synthetic approaches have been developed: N-arylation of acrylamide with iodobenzene and a copper catalyst in the presence of *t*-BuONa in DMSO at 100 °C,[3] acylation of anilines with acryloyl chloride in the presence of an amine,[1] base induced β-elimination of *N*-aryl-3-(phenylsulfonyl)propanamides with t-BuOK,[4] etc.

N-Heterocyclic carbenes (NHCs),[5] carbenes obtained by deprotonation in the 2-position of the corresponding imidazolium cation, can behave as nucleophiles but also as bases. As their parents are ionic liquids (ILs), their generation can be obtained using ILs also as solvents, with all the advantages of carrying out reactions in such media (very polar, non-volatile, easily recyclable, etc.).[6] The deprotonation of the imidazolium cation can be carried out using a chemical base (thus generating a stoichiometric amount of BH^+ by-product) or by electrochemical reductive scission of the C–H bond, in which the reagent is the electron (intrinsically non-pollutant and with no reagent derived by-products) and the only other product is hydrogen, which easily escapes the reaction vessel along with the inert gas flow.[7] Recently, the possibility of obtaining NHCs avoiding the use of chemical bases or electrons was advanced, using an ionic liquid whose anion is sufficiently basic to generate at least a small amount of NHC. This is the case of imidazolium acetates.[8]

In continuation of our study on the chemical reactivity of 1-butyl-3-methylimidazolium acetate,[9] we reacted it with 3-bromo-*N*-(*p*-bromophenyl)propanamide **1a**, in order to verify if the base-catalyzed cyclization to β-lactam was possible in the absence of the electrogenerated N-heterocyclic carbene. Surprisingly, we obtained selectively the corresponding acrylanilide **2a** in 92% yield (Table 1, entry 1). In fact, in a previous paper[10] we described the possibility of obtaining selectively the β-lactam structure **3** by electrochemical means, i.e. deprotonation and internal halide displacement of a β-bromopropionanilide **1** by means of tetraethylammonium cyanomethanide. Spurred by these contrasting results and due to the biological importance of some of the acrylanilides **2**, we tried to identify experimental conditions to direct the chemical reactivity selectively towards one of the two possible products. Due to the biological importance of *p*-bromoacrylanilide **2a**, we decided to use 3-bromo-*N*-(*p*-bromophenyl)propanamide **1a** as model compound.

β-Bromopropionanilide **1** can be deprotonated in two different positions: N–H and C–H in alpha to the carbonyl group. If N–H is deprotonated, after internal bromide displacement, a β-lactam ring is obtained; on the other side, if C–H is deprotonated the corresponding acrylanilide is yielded (Figure 1). In order to favour one or the other deprotonation site, many factors can be varied. Yamazaki[11] used pulverized KOH in CH_2Cl_2 (or in a mixture of CH_2Cl_2 and CH_3CN) in the presence of a phase transfer catalyst (Bu_4NBr) and reported that both high concentration (> 0.05 M) and rapid addition of amide to the basic solution resulted in low yields of β-lactams, with substantial formation of acrylamides. The scope of this communication is the determination of simple conditions to obtain selectively and in high yields, either β-lactam **3** or

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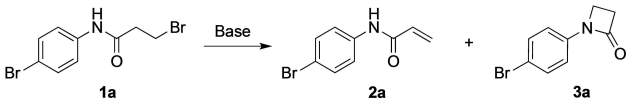
Table 1. Deprotonation of 3-bromo-*N*-(*p*-bromophenyl)propanamide **1 a** to *p*-bromoacrylanilide **2 a** and/or *N*-(*p*-bromophenyl)-β-lactam **3 a**. Optimization of reaction conditions.[a]



Entry	Solvent	Base	pK_a (ACN)[b]	**2 a**[c]	**3 a**[c]	**1 a**[c]
1	-	BMImOAc	22.3	92%	-	-
2	$BMImBF_4$	BMImOAc	22.3	93%	-	-
3	$BMImBF_4$	Bu_4NOAc	22.3	>95%	-	-
4	$BMImBF_4$	H_4NOAc	22.3	73%	-	23%
5	$BMImBF_4$	NaOAc	22.3	55%	-	44%
6	$BMImBF_4$	Et_3N	18.8	>95%	-	-
7	$BMImBF_4$	Cs_2CO_3	24[16]	28%	33%	22%
8	$BMImBF_4$	e^-	22 (DMSO)	33%	25%	36%
9	CH_3CN	BMImOAc	22.3	93%	-	-
10[d]	CH_3CN	Bu_4NOAc	22.3	86%	-	-
11	CH_3CN	NH_4OAc	22.3	29%	-	66%
12	CH_3CN	NaOAc	22.3	28%	-	64%
13	CH_3CN	Me_3Py	14-16	27%	-	64%
14	CH_3CN	Et_3N	18.8	>95%	-	-
15	CH_3CN	DBU	24.3	54%	-	43%
16	CH_3CN	Cs_2CO_3	24[16]	33%	67%	-
17	CH_3CN	K_2CO_3	12-14[16]	50%	23%	26%
18	CH_3CN	Na_2CO_3		4%	7%	83%
19	CH_3CN	$(NH_4)_2CO_3$		19%	-	79%
20	CH_3CN	e^-	31.3 (DMSO)	29%	69%	-
21	EtCN	e^-	32.5 (DMSO)	34%	32%	54%
22[e]	CH_3NO_2	e^-	17.2 (DMSO)	-	48%	-
23	DMSO	e^-	35 (DMSO)	2%	15%	80%
24	DMF	e^-	27 (DMF)	-	>95%	-

[a] Experimental conditions for chemical reaction: **1 a** (0.2 mmol), base (0.4 mmol) and solvent (0.5 mL) were kept at 60 °C for 2 h, then analyzed. Experimental conditions for electrochemical reaction: galvanostatic reduction of 5 mL of solvent-0.1 M Et_4NBF_4 on Pt electrodes in a divided cell till 40 C (2F/mol **1 a**). Then the current was stopped and **1 a** (0.2 mmol) was added to the catholyte, kept at r.t. for 3 h, then analyzed. [b] pK_a in acetonitrile of the conjugate acid of base.[13] In parentheses the solvent if the data in acetonitrile were not known. [c] By NMR of crude reaction. [d] 12% of substitution product was obtained. [e] 52% of substitution product was obtained, in line with what reported in ref. 10.

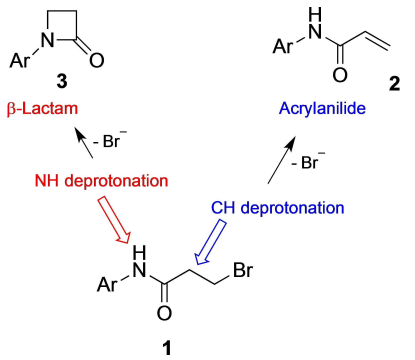


Figure 1. Possible deprotonation sites and corresponding products.

acrylanilide **2** using the same starting material **1**, by chemical or electrochemical means.

Table 1 reports the results obtained using chemical bases in two different solvents, acetonitrile (ACN) and the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$). These two solvents were chosen as our preliminary results were obtained using an ionic liquid (IL) with the same cation, yielding selectively the acrylanilide (entry 1), and ACN by electrochemical means (entry 20, data from our previous paper[10]), yielding selectively the β-lactam. Along with the data from the chemical methodology, the use of electrogenerated bases (EGBs) in different solvents is also reported (entries 8 and 20–24).

As stated before, the two possible products derive from the deprotonation of two different groups, NH and CH, of different acidity and character (harder and softer, respectively[12]). Although we are not able to give accurate pK_a values for these two acid sites, we think that a good estimation would be 21–22 for the NH group and 25–26 for the CH one (by comparison with similar compounds in DMSO[13a]), which means that it would be easier to deprotonate the NH than the CH group. Nonetheless, this is perhaps an over-simplification, as most acid-base reactions are under equilibrium and the subsequent irreversible halide displacement moves towards right both proton abstraction reactions. As a confirmation, triethylamine (which has pK_a 18.8 in ACN) is able to induce the complete conversion of starting **1 a** into **2 a** by exhaustive deprotonation of the CH group in alpha position to the carbonyl, despite the non-favourable value of the pK_a (Table 1, entry 14).

Nonetheless, in Table 1 the base strengths are reported as pK_as in ACN (when possible), in order to understand if this factor influences the outcome of this specific reaction. When using an ionic base (e.g., an acetate or a carbonate), many factors should be taken into account on the effectiveness of the deprotonation step besides base strength (Brønsted-Lowry). In particular, the dielectric constant of the solvent obviously influences the presence and kind of an ion pair, as well as the base solubility.

From this derives that, although in the Table the pK_a of acetate in ACN is always indicated as 22.3, the real strength of acetate as a base strongly depends on its counter-ion. This is well exemplified by the comparison of entries 3 and 5 of Table 1 (in IL), in which the same anionic base has different counter-ions, namely tetrabutylammonium and sodium, with increasing charge density and therefore increasing ion-pairing ability. Using Bu_4NOAc in IL a nearly quantitative yield of **2 a** was obtained, while using NaOAc **2 a** was obtained in lower yield (55%). When the same couple of bases were used in a molecular solvent (ACN), the difference in **2 a** yield was more pronounced: 86% with Bu_4NOAc (Table 1, entry 10) and only 28% with NaOAc (entry 12). This noteworthy different behaviour of NaOAc in the two solvents seems to be strictly related to both solubility and ion-pairing effects. In fact, the literature reports that solvents with a dielectric constant <40 show extensive ion-pair formation,[14] and this is surely the case of ACN ($\varepsilon = 37.5$) in which NaOAc is thus less reactive. The behaviour of NaOAc in $BMImBF_4$ deserves a different discussion. In fact, the dielectric constant of this IL is $\varepsilon = 11.7$,[15] inducing to think that NaOAc could exist mainly ion-paired, but entry 5 shows that this base has a higher reactivity in IL than in ACN. This is probably due to the fact that $BMImBF_4$ is constituted

solely of ions and thus can more efficiently disrupt ion-pairing than ACN, despite the values of ε.

Inspection of the results from the experiments carried out in IL, it should be underlined that only in two cases the β-lactam ring was obtained, *i.e.* with cesium carbonate (entry 7) and with NHC (entry 8). Passing to consider ACN as solvent, again molecular bases and acetate yielded exclusively the acrylamide (entries 13–15), while carbonates promoted also the formation of the lactam ring (entries 16–18). These results are quite difficult to explain. In fact, molecular bases with lower pK_a values should deprotonate the more acidic NH site, while the stronger bases could in principle deprotonate both acidic groups, and this is not the case (as stated before, the subsequent irreversible reaction is important).

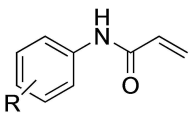
On the other hand, the hard carbonate base should prefer the hard NH acid (yielding the β-lactam), while the soft molecular bases should prefer the soft CH acid (yielding the acrylanilide),[12] and our results are in line with these considerations.

As regards the electrochemically induced reactions, in all cases the electrolyses were carried out on the solvent-supporting electrolyte solution (thus not containing the substrate, which was added after the current was switched off). In all electrolyses, the cathodic electroactive species is the cation ($BMIm^+$ in the case of IL, Et_4N^+ in the case of molecular solvents): the cathodic reduction of $BMIm^+$ yields the corresponding NHC (a neutral base), while the cathodic reduction of Et_4N^+ yields a very strong base which deprotonates the solvent,[17] which in turn should act as base with the β-bromopropionanilide. The use of such electrogenerated bases (whose counter-ion is the tetraethylammonium cation, non-coordinated) seems to favour the NH deprotonation, inducing the formation of the lactam ring. Among the EGBs, the one obtained in DMF is the most effective, giving selectively a very high yield of β-lactam (Table 1, entry 24).

Considering our model compound **1a**, it is thus possible to obtain selectively and in very high yields acrylanilide **2a** using triethylamine in ACN (Table 1, entry 14) or β-lactam **3a** using the EGB in DMF (Table 1, entry 24).

These two methodologies were extended to β-bromopropionanilides with different substituents on the aromatic ring. The substrate scope is exemplified in Figure 2, showing high yields and selective conversions for a number of substrates. In the synthesis of acrylanilides no difference in terms of yields was observed both with electron-withdrawing and electron-releasing groups on the aniline ring. Instead, in the formation of β-lactams lower yields were obtained with chlorine substituent (but not with iodine) in *para*- and *ortho*- positions on the aniline ring (59% and 54%, respectively). Finally, starting from a β-bromopropionanilide with steric hindrance, like the 3-bromo-*N*-mesitylpropanamide **1g**, 83% of acrylanilide (compound **2g**) and 57% of β-lactam (compound **3g**) were obtained, demonstrating again that mainly the ring formation is influenced by substituents on aniline ring.

It should be noted that these methodologies can be applied also to other substrates. As an example, when *N*-benzyl-β-bromopropionamide was considered, the corresponding *N*-benzyl-β-lactam was obtained by electrochemical means in 91% yield (in ACN), while *N*-benzylacrylamide was isolated in 94% after chemical reaction (Et_3N in ACN).



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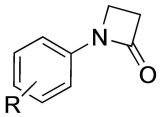

3

R = 4-Br	**2a** (>95%, A)	**3a** (>95%, B)
R = H	**2b** (>95%, A)	**3b** (98%, C*)
R = 2-CH_3	**2c** (91%, A)	**3c** (98%, C*)
R = 3-CH_3	**2d** (>95%, A)	**3d** (>95%, C)
R = 4-CH_3	**2e** (>95%, A)	**3e** (98%, C*)
R = 4-*i*Pr	**2f** (>95%, A)	**3f** (>95%, C)
R = 2,4,6-Me_3	**2g** (83 %, A)	**3g** (57%, B)
R = 4-OCH_3	**2h** (>95%, A)	**3h** (98%, C*)
R = 2-Cl	**2i** (>95%, A)	**3i** (54%, B)
R = 3-Cl	**2j** (>95%, A)	**3j** (86%, C)
R = 4-Cl	**2k** (>95%, A)	**3k** (59%, C*)
R = 4-I	**2l** (>95%, A)	**3l** (90%, C)

Figure 2. Synthesis of acrylanilides **2** and β-lactams **3** from the corresponding β-bromopropionanilide **1** (Figure 1). In parentheses: isolated yields and experimental conditions (A, chemical (Et_3N in ACN): entry 14 of Table 1; B, electrochemical (in DMF): entry 24 of Table 1; C, electrochemical (in ACN). *Data from ref. 10).

In conclusion, we were able to selectively direct the deprotonation of β-bromopropionanilides towards one of the two possible acid sites (NH and CH), simply changing the nature of the base. In particular, if Et_3N is used the corresponding acrylanilides can be obtained in very high yields, while using electrochemical conditions the reaction forms the β-lactam in good to high yields.

Experimental Section

Chemical reactions: **1** (0.2 mmol) and base (0.4 mmol) in 0.5 mL of solvent were kept at 60 °C for 2 h, then the solvent was eliminated under reduced pressure and the crude reaction analyzed by NMR. When $BMImBF_4$ was used as solvent, after the reaction the mixture was extracted thrice with diethyl ether, the solvent eliminated under reduced pressure and the crude reaction analyzed by NMR.

Electrochemical reactions: (the electrochemical cell was described elsewhere[18]) galvanostatic reduction ($I=$ 20 mA cm^{-2}) of 5 mL of solvent-0.1 M Et_4NBF_4 on Pt electrodes in a divided cell till 40 C (2F/mol **1**). Then the current was stopped and **1** (0.2 mmol) was added to the catholyte and kept at r.t. for 3 h. The solvent was eliminated under reduced pressure and the crude reaction analyzed by NMR.

All the products were then purified by flash column chromatography (eluent: petroleum ether/ethyl acetate 7/3). In all cases, their spectral data (reported in S.I.) were in accordance with those reported in the literature.

Supporting Information Summary

All spectroscopic data are provided in the Supporting Information.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: β-bromopropionanilide · β-lactam · acrylanilide · regioselective deprotonation · base

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