NEW CATALYTIC SYSTEM FOR PREPARATION OF METHYL 2-(3-HYDROXY-2-OXO-2,3-DIHYDRO-1*H*-3-INDOLYL)ACRYLATES

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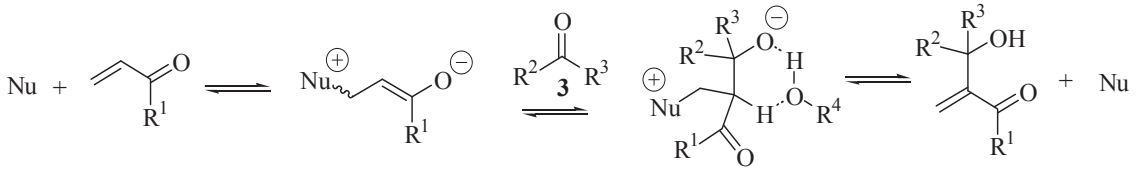
Abstract: A novel catalyst derived from the nitrile functionalized ionic liquids and DMAP promoted the Morita-Baylis-Hillman reaction of N-substituted isatines and the methyl acrylate with moderate up to high yields.

Keywords: catalyst, cocatalyst, functionalized ionic liquids, DMAP, 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indolyl) acrylates, Morita-Baylis-Hillman reaction.

1. Introduction

Considerable attention has recently been focused on the conversion of the simple starting materials into highly functionalized products such as α-hydroxy- or α-amino-alkyl activated olefins [1-6]. The 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indolyl)acrylates sequence plays a very important part in organic as well as medicinal chemistry [7-10]. The method for preparing such substances consists in the condensation of acrylic ester with isatine or its derivatives using the Morita-Baylis-Hillman (MBH) reaction [11]. The reaction is mediated by tertiary amines or phosphines, however DABCO is the most common catalyst employed. Reversible Michael addition of the nucleophilic base to the activated alkene **1** gives zwitterionic enolate **2**. It is well documented that the rate determining the step of the MBH reaction is not the 1,2-addition of the reactive carbonyls **3**, as was previously reported, but rather the proton abstraction followed by the elimination of the catalyst from intermediate **4** [12-21]. This fact points to the proton-donor ability of the catalyst and has a major consequence in the catalyst design.



1 **2** **4** **5**

Scheme 1

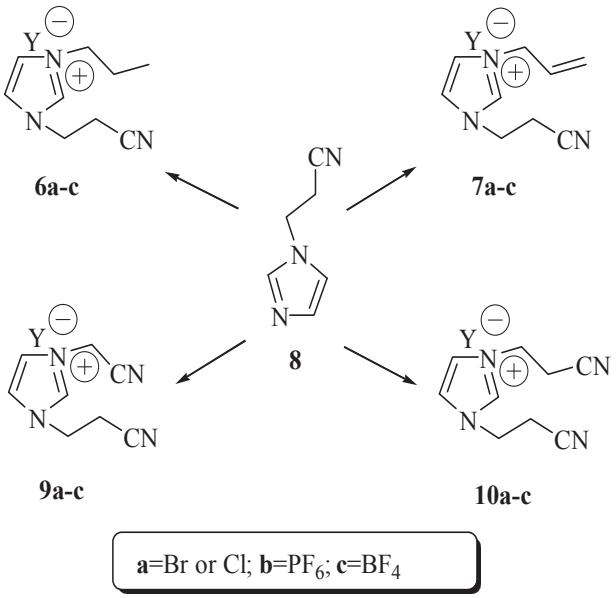
Lin reported the use of ionic liquids as catalysts of the MBH reaction [22-24]. Earlier we also reported the synthesis of new ionic liquids as new generation of solvents/catalysts for "green chemistry" [25]. For example, we published a one step procedure to effect the selective Biginelli, Kondakov, Prince reactions catalyzed by new mono-nitrile (carboxy) functionalized ionic liquids [26-28]. Moreover, there has been proposed a new approach for particularly attractive liquid/liquid metal ion extraction processes by using a carboxy-functionalized imidazolinium salt [29].

2.1. Design and Development of the nitrile functionalized ionic liquids

It was reported earlier that in the key step of the MBH reaction, the addition of the N,N-(dimethylamino)pyridine-activated enone to aldehyde forming the C-C bond, both the aldehyde and enolate are bound and are activated by bis-thiourea cocatalyst [30,31]. It should be noted that DMAP itself may promote the self-aldol reaction of reactive carbonyls. In order to avoid this secondary reaction, we considered that may be use the nitriles group in this case will help to form the complex DMAP-imidazolium ionic liquid. This substance will promote conjugate addition by binding to the zwitterionic enolate and stabilizing these intermediates. Moreover, it remains hydrogen-bonded to the resulting enolate in the enolate-addition step to reactive carbonyls, and finally efficient proton transfer in the rate determining proton abstraction step [19, 32]. Such a model explains the autocatalytic effect of the product **5,** as well.

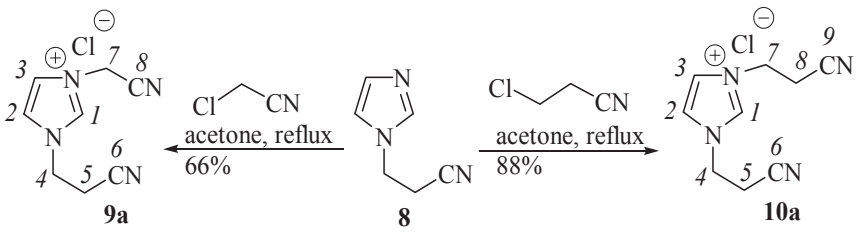
This hypothesis was completely verified and we report in the present paper that the mixture of DMAP with bis-nitrile functionalized ionic liquids catalyzed the MBH reaction under mild conditions.

We began by designing solvents/catalysts which would be prepared from 2-(1*H*-1-Imidazolyl)ethilcarbonitrile **8**. Earlier was published that the quaternization of **8** with alkyl halides to give imidazolium halide salts **6a** (Y=Br)**, 7a** (Y=Br). The next step of the metathesis of **6a, 7a** with the appropriate inorganic salt ($NaBF_4$ or KPF_6) in water or acetone leads to ionic liquids **6b** (Y=PF_6), **6c** (Y=BF_4) as well as to **7b** (Y=PF_6), **7c** (Y=BF_4) [25,26].



Scheme 2

We began with an investigation of the preparation of salts **9a, 10a** from **8** with 2-chloroacetonitrile. As was expected, the reaction of **8** with 2-chloroacetonitrile at room temperature proceeded smoothly (longer than for 48 hours), that is why the synthesis of new imidazole derivatives was realized by refluxing equimolar quantities of imidazole **8** and 2-chloroacetonitrile in acetone solution.



Scheme 3

The reaction product is solid, its composition and structure are confirmed by elemental analysis, IR- and NMR spectra. In the IR spectrum of compound **9a,** the characteristic bands at 620 см$^{-1}$ (C–Cl); 740 cm^{-1} (-CH=CH-); 1170 cm^{-1} (N-Cl); 1565 cm^{-1} (NH_3^+); 1620 cm^{-1} (C=N); 2090 cm^{-1} (C=C); 2250 cm^{-1} ($C\equiv N$) and 2800 cm^{-1} (CH_2) appear. In comparison with ^{1}H NMR spectrum initial **8** [25] the signals of imidazole as well as propylnitrile groups are located in the downfield region (3.33 ppm, 4.58 ppm, 7.99 ppm, 8.04 ppm). Additionally, the signal of the ^{5}C methylene group was observed at 5.75 ppm.

The changing of 2-chloroacetonitrile on 3-chloropropanenitrile has not affected the time of the reaction, whereas the yield of a homologue **10a** has increased up to 88 %.

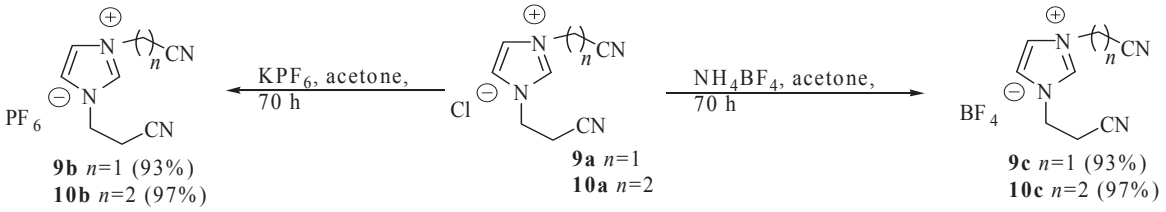
According to the spectral data, the molecule **10a** represents a symmetric product with heterocyclic and alkylnitrile fragments.

The specific feature of ^{1}H NMR spectrum of the investigated compound **10a** in comparison with that of a product **9a**, is the absence of a singlet two-proton signal at 5.75 ppm and the presence of only two triplet signals of methylene group in a combination with singlet signals of the imidazole ring. It is to be mentioned that there are insignificant signals of the mentioned group in a stronger region. Worth pointing out these data are supported by the IR-spectrum of **10a** having characteristic bands at 1168 cm^{-1} (Cl), 2249 cm^{-1} (CN), 2945 cm^{-1} (CH_2), 3368 cm^{-1} (-N=), 3393 cm^{-1} (=N^+=). These data in combination with the results of the elemental analysis confirm the structure **10a**. It is necessary to note that the product **10a** is by itself a lower-melting material than **9a**.

The next step of our investigation was the selection of optimal conditions for an exchange of chloride synthesized salts on anions PF6- and BF4-.

Carrying out the reaction with the appropriate salt ($NaBF_4$ or KPF_6) in acetone at room temperature leads to obtaining target compounds with yields up to 97%.

The specific feature of **9b** from its precursor **9a** is the lowering of the melting point from 122-123^{0}C to 84-85^{0}C. In the IR-spectrum of **10b,** characteristic bands at 822 cm^{-1} (P-F) appear. In the spectrum ^{1}H NMR of **9b** there are signals of the ethylene, methylene, nitrile and heterocyclic fragments as well. The change of anion has resulted in an insignificant shift of signals of propylnitrile substances in stronger field with changing of coupling constants from *J*=6.48 Hz up to *J*=6.0 Hz, whereas the signal $^7CH_2$ is observed at 5.75 ppm.



Scheme 4

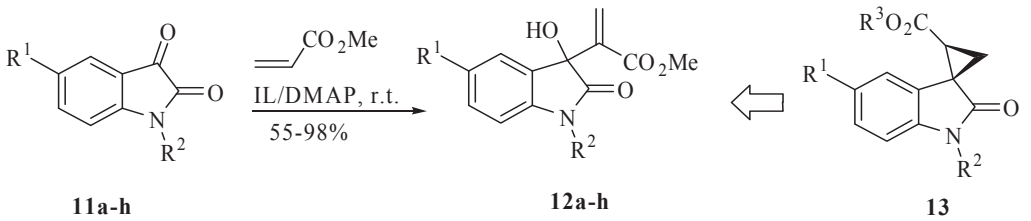
The composition and chemical structure of the product **9c** is confirmed by the data of the elemental analysis, IR - and ^{1}H NMR spectroscopy. The comparative analysis of the ^{1}H NMR spectrum of **9c** from its analogues **9a,b** specifies a shift of the position of aliphatic groups and imidazole ring.

It is necessary to point out, that substances **9c,b** are low temperature crystalline products and so is even the initial **9a**. Changing the methylenenitrile for a propylenenitrile fragment did not essentially influence the yields of products **10b,c**. ^{1}H NMR-spectra of structurally simple salts **10b,10c** were not considerably different from those of **10a**, either (see experimental part). A small difference position of carbonitrile group in IR-spectrum was observed: for **10a** at 2249 cm^{-1}, for **10b** at 2259 cm^{-1} and for **10c** at 2258cm^{-1}. These data in the combination with maximums at 1168 (Cl), 822 (P-F), 1037 (B-F) confirmed the structures of products. The discussed data are supplemented by the results of the elemental analysis.

2.2. Catalytic reaction of N-substituted isatine with methyl acrylate

We therefore focused our attention on preparing a novel catalytic system. We believed that we could increase the activity of DMAP by the application of nitrile-functionalized imidazolinum ionic liquid. Consideration of the transition state suggests that any cocatalyst must be capable of simultaneous associating, and hence, stabilizing both the enolate oxygen arising from the adduct formed between methyl acrylate and DMAP and the partial δ^- charge located on the carbonyl oxygen atom. The nitrile-functionalized imidazolinum ionic liquid has anion-cation aggregates due to the electron-withdrawing effect of the CN group, which makes the aliphatic hydrogen atoms more acidic so that hydrogen bonding between the cation and anion is enhanced, and/or head-to-tail interaction of the CN group with the target atoms is increased.

That is why a new cocatalyst design was generated by placing two CN groups at the locations required to recognize the two oxygen atoms in the intermediate, like **4** (see scheme 1).



11a-h **12a-h** **13**

Ionic Liquids = **9a, 9b, 9c, 10a, 10b, 10c**

a) R^1=H, R^2=-Et; **b**) R^1=H, R^2=-C_3H_7; **c**) R^1=H, R^2=-CH_2CH=CCl-Me;
d) R^1=H, R^2=-CH_2-CH=CH_2; **e**) R^1=-Me, R^2=-CH_2-CH=CH_2;
f) R^1=H, R^2=-CH_2-CCH; **g**) R^1=H, R^2=CH_2-C_6H_5; **h**) R^1=H, R^2=-C_4H_9

Scheme 5

The ability of the six catalysts **9a,b,c** and **10a,b,c** to accelerate the reaction between the methyl acrylate and isatine **11a** was assessed using a standard set of reaction conditions - in the absence of solvent. However, in all cases it resulted in near-quantitative recovery of starting materials. After that a number of mixtures from our ionic liquids and DMAP have been prepared. For each of the six cocatalysts **9a,b,c** and **10a,b,c**, five different cocatalyst loadings were investigated – 2 mol %, 4 mol %, 6 mol %, 8 mol % or 10 mol %. The ratio of isatines to DMAP was held constant and was always 1.0: 0.5. The reaction mixture contained 1.5 equiv of methyl acrylate and 1.0 equiv **11a**.

The progress of the reaction was monitored by TLC over a period of several days, during which the formation of a polar, colorless product and the solubilisation of isatin were observed.

We found that the highest selectivity was obtained at room temperature via mixing isatin **11a**, methyl acrylate, DMAP and salt **10a** in molar ratios of 1: 1.56: 0.5: 0.06. The alcohol **12a** (yield 84 %) appeared as the main product. As expected the reactions proceed smoothly to give target product, indicating that the self-aldol reaction of isatine was avoided. Its IR-spectrum contains absorption bands characteristic of a carbonyl bond at 1700 cm^{-1} and hydroxy group at 1040, 3340 cm^{-1}. In the ^{1}H NMR spectrum of this compound three-proton signals of both methyl groups are presented at 1.16 ppm and 3.46 ppm., two-proton signals of the methylene group at 3.63-3.73 ppm and vinylic protons at 6.46 ppm. In the highest and medium fields of its ^{13}C NMR spectrum, the signals of eleven carbon atoms (see experiment) are supplemented by three signals in the lowest field at 172.30, 164.25 and 144.85 ppm. These data, in combination with the data of elemental analysis specify the structure **12a**. If the condensation is carried out by using chloride **9a**, the reaction product is also the allylic alcohol **12a**, however the yield decreases to 7 %.

We also examined the catalytic activity of hexafluorophosphates **9b** and **10b**. In the reaction catalyzed by **10b**, the highest yield of **12a** (up to 89 %) was achieved. Then, we have tested the influence of **9c, 10c** on the interaction between **11a** and methyl acrylate. The highest yield 77 % was registered in the case of using **10c**.

The relationship between the nature of anion/cation and optimal yield of the allylic alcohols **12a-h** is depicted in table 1.

These results suggests that small changes in structure of the cocatalyst cause a drastic change in the yield of 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indolyl)acrylates. The difference in activity between **9a,9b,9c** or **10a,10b,10c** is intriguing. Despite their structural similarities, in most experiments, cocatalysts **10a,10b,10c** outperforms cocatalysts **9a,9b,9c** significantly. The difference in activity can be found by the examination of the sizes of the side chain to each cocatalyst. This change in size imposed by the cocatalyst in order to satisfy the steric and electronic requirements of binding results in an increase stabilizing both the enolate oxygen arising from the adduct formed between methyl acrylate and DMAP resulting in the highest activity. It should be mentioned that there was no relation between the nature of alkyl substitution of isatine on yield as well as time reaction. As shown in table, hindered substituted isatines are effective generating of 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indolyl)acrylate.

The reason for positive effects of the mixture DMAP-imidazolium ionic liquid is not yet clear. Nevertheless, introduction of imidazolium ionic liquid suppresses undesired direction of reaction. It is necessary to point out, that in the absence of at least one of the components reactions do not take place. We believed that use the nitrile-functionalized imidazolinum ionic liquid helped to form the complex DMAP-ionic liquid. This substance promoted conjugate addition by binding to the zwitterionic enolate and stabilizing these intermediates as well. This chemical phenomenon was brought to our attention by the following observation: although an excess of imidazolium ionic liquid up to 10 mol % is in general required for efficient reactions, in all case 6 mol % of ionic liquid is sufficient. Additionally, the observed experimental results suggest that hexafluorophosphates **9b,10b** were more active in most reactions. However, the undesired cocatalyst exchange clearly becomes uncompetitive and is therefore avoided. For example, even using unmodified **9a** gives high selectivity for **12g**.

3. Conclusion

In conclusion, we have developed a concise and efficient protocol for the preparation of methyl 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-3-indolyl)acrylates from various isatines with methyl acrylate catalyzed by mixture DMAP-nitrile-functionalized imidazolinum ionic liquid. As discussed above, mechanistic studies of DMAP-nitrile-functionalized imidazolinum ionic liquid-catalyzed the Morita-Baylis-Hillman reaction, have revealed that catalytic system promoted the addition of the activated enone to isatine and, at the same time, shows capable of stabilizing both the enolate oxygen arising from the adduct and the partial δ^- charge located on the C-3 carbonyl atom of isatine, and finally proton transferring in the rate determining step. The catalytic system discovered so far are applicable only to reactions that proceed in the presence of nitrile-functionalized imidazolinum ionic liquid.

This catalytic methodology is height attractive and provides a valuable choice for the organic synthesis. Is it possible to develop asymmetric complexes that promote a variety of reactions in highly enantioselective manner? Such reactions might include, for example, the asymmetric addition of the catalyst-activated enone to carbonyl followed proton transfer by use the chiral hydroxy-functionalized imidazolinum ionic liquid according scheme 1.

The research of the enantiospecific variant of the MBH reaction is being carried out in our laboratory.

Table 1

Morita-Baylis-Hillman reactions of N-substituted isatines with the methyl acrylate

Product	Co-Catalist	Time, min	Yield, %
12a	**9a**	90	85
	9b	75	84
	9c	75	70
	10a	60	84
	10b	30	89
	10c	30	77
12b	**9a**	90	48
	9b	150	55
	9c	150	61
	10a	75	86
	10b	75	82
	10c	75	83
12c	**9a**	270	82
	9b	255	87
	9c	240	82
	10a	120	84
	10b	90	98
	10c	60	86
12d	**9a**	60	81
	9b	120	87
	9c	120	80
	10a	50	80
	10b	40	84
	10c	40	75
12e	**9a**	210	79
	9b	210	81
	9c	210	78
	10a	120	80
	10b	120	81
	10c	120	82
12f	**9a**	260	87
	9b	290	86
	9c	260	84
	10a	90	95
	10b	90	88
	10c	90	93
12g	**9a**	90	96
	9b	90	85
	9c	90	78
	10a	90	86
	10b	90	82
	10c	90	77
12h	**9a**	120	86
	9b	240	93
	9c	240	89
	10a	240	63
	10b	240	75
	10c	120	79

4. Experimental methods

All used solvents were of reagent quality, and all commercial reagents were used without additional purification. Removal of all solvents was carried out under reduced pressure. Analytical TLC plates were Silufol® UV-254 (Silpearl on aluminium foil, Czecho-Slovakia). IR spectra were recorded on a Spectrum 100 FT-IR spectrophotometer (Perkin –Elmer) using the universal ATR sampling accessory. ^{1}H and ^{13}C NMR spectra have been recorded for $(CD_3)_2SO$ 2-% solution on a "Bruker -Avance III" (400.13 and 100.61 MHz) and "Bruker AC-80" (80 and 20 MHz).

2-(1*H*-1-Imidazolyl)ethilcarbonitrile 8 has been prepared according to the known procedure [25].

Synthesis of the 1-(2-cyanoethyl)-3-cyanomethyl-1*H*-imidazol-3-ium chloride 9a.

2-chloroacetonitrile (2.20 g, 0.035 mol) was added dropwise to a solution of **8** (4.2 g (0.035 mol) in 15 ml acetone. The reaction mixture was stirred for 6 hours. Solvent was removed in vacuum, followed by crystallization from EtOH to give 4.5 g of **9a**. Yield: 66%. M.p. 122-123^{0}C. IR (ν/cm^{-1}): 620 (Cl), 740, 1455, 1570 (CH=CH), 2250 (CN), 2800 (CH_2). ^{1}H NMR (80 MHz, δ, ppm, *J*/Hz): 3.33 t (2H, $^{5}CH_2$, *J*=6.48), 4.58 t (2H, $^{4}CH_2$, *J*=6.48), 5.75 s (2H, $^{7}CH_2$), 7.99, 8.04, 9.58 s, s, s, (3H, imidazol). ^{13}C NMR (20 MHz, ppm): 132.71 (^{1}C), 120.12 (^{3}C), 118.01 (^{8}C), 117.81 (^{2}C), 116.19 (^{6}C), 43.16 (^{4}C), 42.92 (^{7}C), 20.11 (^{5}C). Found,%: C 48.12, H 4.44, N 29.01. $C_8H_9ClN_4$. Requires, % C 48.87, H 4.61, N 28.49.

Synthesis of the 1-(2-cyanoethyl)-3-cyanomethyl-1*H*-imidazol-3-ium hexafluorophosphate 9b.

KPF_6 (0.74 g, 0.0041 mol) was added to a solution of chloride **9a** (0.8 g, 0.0041 mol) in acetone (10 ml). The reaction mixture was stirred for 70 hours. Solids were filtered, and the solvent was removed to give 1.12 g of **9b**. Yield: 93%. M.p. 84-85^{0}C (EtOH). IR (ν/cm^{-1}): 740, 2090 (CH=CH), 822 (PF_6), 2250 (CN), 2800 (CH_2). ^{1}H NMR (80 MHz, δ, ppm, *J*/Hz): 3.28 t (2H, $^{5}CH_2$, *J*=6.0), 4.56 t (2H, $^{4}CH_2$, *J*=6.0), 5.62 s (2H, $^{7}CH_2$), 7.92, 7.95, 9.37 s, s, s, (3H, imidazol). ^{13}C NMR (20 MHz, ppm): 132.14 (^{1}C), 121.16 (^{3}C), 119.42 (^{8}C), 117.14 (^{2}C), 116.90 (^{6}C), 45.12 (^{4}C), 43.91 (^{7}C), 21.16 (^{5}C). Found, %: C 31.14, H 3.12, N 18.65. $C_8H_9F_6N_4P$. Requires, %: C 31.39, H 2.96, N 18.30.

Synthesis of the 1-(2-cyanoethyl)-3-cyanomethyl-1*H*-imidazol-3-ium tetrafluoroborate 9c.

Chloride **9a** (0.8 g, 0.0041 mol) has reacted with KBF_4 (0.51 g, 0.0041) according to the procedure described for the preparation of **9b** to give **9c** (0.98 g) as a yellow oil. Yield: 97%. IR (ν/cm^{-1}): 740, 2090 (CH=CH), 1037 (BF_4), 2250(CN), 2800 (CH_2). ^{1}H NMR (80 MHz, δ, ppm, *J*/Hz): 3.20 t (2H, $^{5}CH_2$, *J*=6.0), 4.52 t (2H, $^{4}CH_2$, *J*=6.0), 5.53 s (2H, $^{7}CH_2$), 7.75, 7.78, 9.24 s, s, s, (3H, imidazol). ^{13}C NMR (20 MHz, ppm): 133.15 (^{1}C), 121.70 (^{3}C), 118.16 (^{8}C), 116.72 (^{2}C), 116.03 (^{6}C), 44.11 (^{4}C), 43.13 (^{7}C), 20.99 (^{5}C). Found, %: C 38.12, H 3.54, N 23.02. $C_8H_9BF_4N_4$. Requires, %: C 38.75, H 3.66, N 22.59.

Synthesis of the 1,3-di(2-cyanoethyl)-1*H*-imidazol-3-ium chloride 10a.

Product **10a** (6.3 g) was prepared from **8** (4.1 g, 0.034 mol) and 3-chloropropanenitrile (2.7 ml, 0.034 mol) by the same procedure as for the preparation of **9a** for 10 hours. Yield: 88%. IR (ν/cm^{-1}): 770 (Cl), 1453, 1571 (CH=CH), 2249 (CN), 2945 (CH_2) 1639, 2469, 2489, 2500 (=N$^+$-). ^{1}H NMR (80 MHz, δ, ppm, *J*/Hz): 3.22 (t, 4H, $^{5}CH_2$, $^{8}CH_2$, J=6.4), 4.56 (t, 4H, $^{4}CH_2$, $^{7}CH_2$, J=6.4), 7.64, 7.85, 9.20 (s, s, s, 3H, imidazol). ^{13}C NMR (20 MHz, ppm): 140.16 (^{1}C), 124.02 (^{3}C), 121.35 (^{2}C), 115.93 (^{9}C), 115.63 (^{6}C), 48.03 (^{4}C), 40.21 (^{7}C), 17.29 (^{5}C), 10.93 (^{8}C). Found, %: C 51.12, H 5.03, N 26.90. $C_9H_{11}ClN_4$. Requires, %: C 51.31, H 5.26, N 26.60.

Synthesis of the 1,3-di(2-cyanoethyl)-1*H*-imidazol-3-ium hexafluorophosphate 10b.

Product **10b** was prepared from **10a** and KPF_6 by the same procedure as for the preparation of **9b**. Yield: 97%. IR (ν/cm^{-1}): 822 (PF_6), 1450, 1561, 3170 (CH=CH), 2259 (CN), 2988 (CH_2), 3336 (-NH=). ^{1}H NMR (80 MHz, δ, ppm, *J*/Hz): 3.14 t (4H, $^{5}CH_2$, $^{8}CH_2$, *J*=6.4), 4.50 t (4H, $^{4}CH_2$, $^{7}CH_2$, *J*=6.4), 7.61, 7.74, 9.07 s, s, s, (3H, imidazol). ^{13}C NMR (20 MHz, ppm): 136.14 (^{1}C), 122.79 (^{3}C), 120.92 (^{2}C), 115.99 (^{9}C), 115.42 (^{6}C), 48.12 (^{4}C), 45.42 (^{7}C), 17.52 (^{5}C), 10.93 (^{8}C). Found, %: C 33.64, H 3.79, N 17.53. $C_9H_{11}FN_4P$. Requires, %: C 33.76, H 3.46, N 17.50.

Synthesis of the 1,3-di(2-cyanoethyl)-1*H*-imidazol-3-ium tetrafluoroborate 10c.

Product **10c** was prepared from **10a** and KBF_4 by the same procedure as for the preparation of **9c**. Yield: 98%. IR (ν/cm^{-1}): 1037 (BF_4), 1453, 1576, 3169 (CH=CH), 2258 (CN), 756, 2988 (CH_2). ^{1}H NMR (80 MHz, δ, ppm, *J*/Hz): 3.14

t (4H, $^{5}CH_2$, $^{8}CH_2$, *J*=6.4), 4.50 t (4H, $^{4}CH_2$, $^{7}CH_2$, *J*=6.4), 7.62, 7.74, 9.08 s, s, s, (3H, imidazol). ^{13}C NMR (20 MHz, ppm): 139.98 (^{1}C), 123.16 (^{3}C), 122.00 (^{2}C), 116.04 (^{9}C), 115.90 (^{6}C), 47.92 (^{4}C), 41.19 (^{7}C), 17.14 (^{5}C), 11.12 (^{8}C). Found, %: C 41.38, H 4.63, N 20.68. $C_9H_{11}BF_4N_4$. Requires, %: C 41.26, H 4.23, N 21.38.

Isatines 11a-h have been prepared according to the known procedure [33].

Preparation of methyl 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-3-indolyl)acrylates. General procedure.

To a mixture of 0.37 g (0.0042 mol) of methyl acrylate, 0.17g (0.0014 mol) of DMAP and (0.0028 mol) of an appropriate N-substituted isatine was added ionic liquid (0.00017 mol). The reaction mixture was stirred at room temperature. On completion of the reaction (TLC moniroring by C_6H_6/acetone : 4/1) the mixture was dispered in 5% HCl, the residue was filtered off and washed with H_2O. A sample was recrystallized for the analysis from appropriate solvent.

The methyl 2-(1-ethyl-3-hydroxy-2-oxo-2,3-dihydro-1*H*-3-indolyl)acrylate 12a.

M.p. 175-176^{0}C (EtOH). IR (ν/cm^{-1}): 730, 745 (CH-Ar), 795 (C_2H_5), 940, 2975 (C=CH_2), 1040, 3340 (OH), 1020, 1715 (CO_2CH_3), 1695 (N-C=O). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 1.16 t (3H, $^{14}CH_3$, *J*=6.8), 3.46 s (3H, $^{11}CH_3$), 3.63-3.73 m (2H, $^{13}CH_2$), 6.46 d (2H, $^{12}CH_2$, *J*=10.4), 6.56 s (1H, OH), 6.92-7.29 m (4H, Ar). ^{13}C NMR (100 MHz, ppm): 172.30 (^{7}C), 164.25 (^{10}C), 144.85 (^{2}C), 144.60 (^{9}C), 126.85 (^{6}C), 123.01 (^{12}C), 120 (^{1}C), 118.03 (^{3}C), 115.92 (^{5}C), 110.73 (^{4}C), 85.32 (^{8}C), 54.23 (^{11}C), 38.16 (^{13}C), 12.63 (^{14}C). Found, %: C 31.14, H 3.12, N 18.65. $C_{14}H_{15}NO_4$. Requires, %: C 64.36, H 5.79, N 5.36.

The methyl 2-(3-hydroxy-2-oxo-1-propyl-2,3-dihydro-1*H*-3-indolyl)acrylate 12b.

M.p. 176-177^{0}C (EtOH). IR (ν/cm^{-1}): 750, 760 (CH-Ar), 950 (C=CH_2), 805 (C_3H_7), 1050, 3340 (OH), 1170 (CO_2CH_3), 1695(N-C=O). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 0.93 t (3H, $^{15}CH_3$, *J*=7.2), 1.59-1.64 m (2H, $^{14}CH_2$), 3.46 s (3H, $^{11}CH_3$), 3.56-3.61 m (2H, $^{13}CH_2$), 6.46 d (2H, $^{12}CH_2$, *J*=10.8), 6.55 s (1H, OH), 6.93-7.28 m (4H, Ar). ^{13}C NMR (100 MHz, ppm): 171.53 (^{7}C), 164.25 (^{10}C), 148.15 (^{2}C), 143.20 (^{9}C), 128.40 (^{6}C), 123.80 (^{12}C), 121.95 (^{1}C), 119.12 (^{3}C), 116.45 (^{5}C), 115.02 (^{4}C), 87.36 (^{8}C), 51.32 (^{11}C), 46.42 (^{13}C), 22.05 (^{14}C), 12.05 (^{15}C). Found, %: C 65.38, H 6.29, N 5.12. $C_{15}H_{17}NO_4$. Requires, %: C 65.44, H 6.22, N 5.09.

The methyl 2-[1-(3-chloro-2-butenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-3-indolyl]acrylate 12c.

M.p. 150-151^{0}C (C_6H_6). IR (ν/cm^{-1}): 740 (CH-Ar), 750(Cl), 960 (C=CH_2), 1160 (CO_2CH_3), 1700 (N-C=O), 3350 (OH). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 1.91 s (3H, $^{16}CH_3$), 3.25 s (3H, $^{11}CH_3$), 4.15 d (2H, $^{13}CH_2$, *J*=5.6), 5.41 t (1H, ^{14}CH, *J*=5.6), 6.25 d (2H, $^{12}CH_2$, *J*=10.8), 6.42 s (1H, OH), 6.65-7.07 m (4H, Ar). ^{13}C NMR (100 MHz, ppm): 165.65 (^{7}C), 160.52 (^{10}C), 145.02 (^{2}C), 142.48 (^{9}C), 134.50 (^{15}C), 126.72 (^{6}C), 122.97 (^{12}C), 121.32(^{14}C), 120.92 (^{1}C), 119.03 (^{3}C), 118.93 (^{5}C), 115.64 (^{4}C), 88.17 (^{8}C), 52.4 (^{11}C), 41.07 (^{13}C), 27.09 (^{16}C). Found, %: C 60.10, H 5.17, N 4.19. $C_{16}H_{16}ClNO_4$. Requires, %: C 59.73, H 5.01, N 4.35.

The methyl 2-(1-allyl-3-hydroxy-2-oxo-2,3-dihydro-1*H*-3-indolyl)acrylate 12d.

M.p. 176-177^{0}C (C_6H_6). IR (ν/cm^{-1}): 760 (CH-Ar), 960, 3050 (C=CH_2), 1170, 1200 (CO_2CH_3), 1055, 3320 (OH), 1700 (N-C=O). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 3.46 (s, 3H, $^{11}CH_3$), 4.25-4.29 (m, 2H, $^{13}CH_2$), 5.17-5.39 (m, 2H, $^{15}CH_2$), 5.80-5.84 (m, 1H, ^{14}CH), 6.49(d, 2H, $^{12}CH_2$, J=0.8), 6.63 (s, 1H, OH), 6.89-7.02 (m, 4H, Ar). ^{13}C NMR (100 MHz, ppm): 172.60 (^{7}C), 165.54 (^{10}C), 145.90 (^{2}C), 144.95 (^{9}C), 130.01 (^{14}C), 128.02 (^{6}C), 126.17 (^{12}C), 125.31 (^{15}C), 120.91 (^{1}C), 120.14 (^{3}C), 119.03 (^{5}C), 116.92 (^{4}C), 88.12 (^{8}C), 54.72 (^{11}C), 52.16 (^{13}C). Found, %: C 66.14, H 5.81, N 5.02. $C_{15}H_{15}NO_4$. Requires, %: C 65.93, H 5.53, N 5.13.

The methyl 2-(1-allyl-3-hydroxy-5-methyl-2-oxo-2,3-dihydro-1*H*-3-indolyl)acrylate 12e.

M.p. 152-153^{0}C (EtOH). IR (ν/cm^{-1}): 750 (CH-Ar), 950, 3050 (C=CH_2), 1160, 1190, 1200, 1370 (CO_2CH_3), 1700(N-C=O), 1050, 3340 (OH). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 2.21 s (3H, CH_3), 3.48 s (3H, $^{11}CH_3$), 4.22-4.26 m (2H, $^{13}CH_2$), 5.17-5.38 m (2H, $^{15}CH_2$), 5.78-5.85 m (1H, ^{14}CH), 6.49 d (2H, $^{12}CH_2$, *J*=0.8), 6.57 s (1H, OH), 6.77-7.06 m (3H, Ar). ^{13}C NMR (100 MHz, ppm): 173.15 (^{7}C), 169.12 (^{10}C), 149.70 (^{2}C), 144.79 (^{9}C), 130.91 (^{14}C), 127.03 (^{3}C), 125.14(^{6}C), 124.01 (^{12}C), 123.11 (^{15}C), 120.73 (^{1}C), 116.18 (^{5}C), 112.3 (^{4}C), 86.32 (^{8}C), 52.10 (^{11}C), 49.15 (^{13}C), 22.71(^{16}C). Found, %: C 66.01, H 5.14, N 5.51. $C_{16}H_{17}NO_4$. Requires, % C 66.89, H 5.96, N 4.88.

The methyl 2-[3-hydroxy-2-oxo-1-(2-propynyl)-2,3-dihydro-1*H*-3-indolyl]acrylate 12f.

M.p. 169-170^{0}C (EtOH). IR (ν/cm^{-1}): 760 (CH-Ar), 970 (C=CH_2), 1170, 1390 (CO_2CH_3), 1700(N-C=O), 2140 (-C≡CH), 1040, 3290 (OH). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 3.28 s (1H, ^{15}CH), 3.46 s (3H, $^{11}CH_3$), 4.49-4.51 m (2H, $^{13}CH_2$), 6.47 d (2H, $^{12}CH_2$, *J*=16), 6.70 s (1H, OH), 6.99-7.35 m (4H, Ar). ^{13}C NMR (100 MHz, ppm): 170.51 (^{7}C), 164.12 (^{10}C), 145.00 (^{2}C), 144.89 (^{9}C), 128.92 (^{6}C), 124.18 (^{12}C), 121.43 (^{1}C), 119.62 (^{3}C), 118.04 (^{5}C), 116.72 (^{4}C), 93.15 (^{8}C), 79.34 (^{14}C), 74.12 (^{15}C), 52.42 (^{11}C), 34.61 (^{13}C). Found, %: C 66.95, H 5.12, N 5.21. $C_{15}H_{13}NO_4$. Requires, %: C 66.42, H 4.83, N 5.16.

The methyl 2-(1-benzyl-3-hydroxy-2-oxo-2,3-dihydro-1*H*-3-indolyl)acrylate 12g.

M.p. 199-200^{0}C (EtOH). IR (ν/cm^{-1}): 750, 1100 (CH-Ar), 960 (C=CH_2), 1175 (CO_2CH_3), 1650 (N-C=O), 1050, 3300 (OH). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 3.51 s (3H, ^{11}CH), 4.90 s (2H, $^{13}CH_2$), 6.59 d (2H, $^{12}CH_2$, *J*=8), 6.66 s (1H, OH), 6.91-7.40 m (9H, Ar). ^{13}C NMR (100 MHz, ppm): 170.72 (^{7}C), 162.83 (^{10}C), 146.08 (^{2}C), 145.00 (^{9}C), 136.17 (^{14}C), 129.98 (^{6}C), 129.63 (^{15}C, ^{18}C), 125.02 (^{17}C), 123.14 (^{12}C), 122.84 (^{16}C, ^{19}C), 122.01 (^{3}C), 120.01 (^{1}C), 119.16 (^{5}C), 116.72 (^{4}C), 80.94 (^{8}C), 54.42 (^{11}C), 50.19(^{13}C). Found, %: C 70.04, H 5.26, N 4.53. $C_{19}H_{17}NO_4$. Requires, %: C 70.58, H 5.30, N 4.33.

The methyl 2-(1-butyl-3-hydroxy-2-oxo-2,3-dihydro-1*H*-3-indolyl)acrylate 12h.

M.p. 124-125^{0}C (C_6H_6). IR (ν/cm^{-1}): 750 (CH-Ar), 950 (C=CH_2), 1050, 3360 (OH), 1170, 1200 (CO_2CH_3), 1370 (C_4H_9), 1700 (N-C=O). ^{1}H NMR (400 MHz, δ, ppm, *J*/Hz): 0.91 t (3H, $^{16}CH_3$, *J*=7.2), 1.34-1.39 m (2H, $^{14}CH_2$), 1.55-1.60 m (2H, $^{15}CH_2$), 3.46 s (3H, ^{11}CH), 3.59-3.64 m (2H, $^{13}CH_2$), 6.46 d (2H, $^{12}CH_2$, *J*=11.6), 6.55 s (1H, OH), 6.93-7.27 m (9H, Ar). ^{13}C NMR (100 MHz, ppm): 175.92 (^{7}C), 168.13 (^{10}C), 148.44 (^{2}C), 146.30 (^{9}C), 130.18 (^{6}C), 128.15 (^{12}C), 123.74 (^{1}C), 120.74 (^{3}C), 117.75 (^{5}C), 15.61 (^{4}C), 88.94 (^{8}C), 55.31 (^{11}C), 50.30 (^{13}C), 35.60 (^{14}C), 24.03 (^{15}C), 14.06 (^{16}C). Found,%: C 65.95, H 6.67, N 4.92. $C_{16}H_{19}NO_4$. Requires, %: C 66.42, H 6.62, N 4.84.

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