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PAPER

Lack of correlation between catalytic efficiency and basicity of amines during the reaction of aryl methyl ketones with DMF-DMA: an unprecedented supramolecular domino catalysis†

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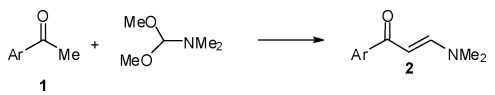
1-Methylimidazole exhibits an unusually high efficiency in promoting the reaction of aryl methyl ketones with DMF-DMA to form (2*E*)-1-aryl-3-dimethylamino-2-propenones which lacks correlation between the catalytic efficiency and the basicity of 1-methylimidazole in comparison to other amines. An unprecedented supramolecular domino catalysis rationalises the lack of correlation between the catalytic efficiency and basicity of the amines. The supramolecular assemblies have been characterized by mass-spectrometric ion fishing. The time-dependent increase/decrease in the concentration (ion current) of the supramolecular species consolidated the mechanism.

Introduction

1-Aryl-3-dimethylamino-2-propenones are versatile synthons which are obtained by the reaction of DMF-DMA with aryl methyl ketones (Scheme 1).[1]



Scheme 1 Synthetic route to 1-aryl-3-dimethylamino-2-propenones.

In our efforts to use enaminones with a substituted aryl moiety as building blocks to synthesise potential therapeutic agents[2] we realised the need of catalytic assistance for the reaction of 2,4-dimethoxyacetophenone **1a** with DMF-DMA in order to form 1-[2,4-dimethoxyphenyl]-(2*E*)-3-dimethylamino-2-propen-1-one **2a**. Different amines were used (Table 1) as the base, anticipating that the formation of the anion of **1a** would facilitate a nucleophilic attack on DMF-DMA. Surprisingly, 1-methylimidazole (MeIm) afforded the best result (entry 13, Table 1) although it is not the strongest base out of those selected to promote the condensation. The advantage of using MeIm is evident from the fact that **2a** is formed in poor yield when performing the reaction in its absence (entry 19, Table 1).

To further exemplify the special catalytic action of MeIm, a few representative aryl/heteroaryl methyl ketones were treated with DMF-DMA in the presence of MeIm and the results were compared with those of the corresponding reactions performed in the presence of other organic bases, such as DBU, TEA, DABCO, and pyridine in place of MeIm (Table 2). For all of these substrates the MeIm promoted reactions afforded superior results and highlighted the specific catalytic role of MeIm.

The lack of correlation between the catalytic efficiency and the p*K*a[3] of these bases prompted us to find out the specific/additional effect, beyond its function as a base, that MeIm might be

Table 1 Reactions of **1a** with DMF-DMA to form **2a**[a]

Entry	Amines	p*K*a[3]	Yield (%)[b]
1	DBU	12	40
2	*N*,*N*-Diisopropylamine	11.5l	30
3	Quinuclidine	11.3	10
4	*N*,*N*-Dicyclohexylamine	11.25	Trace
5	TEA	10.72	20
6	DIPEA	10.5	10
7	DMAP	9.7	20
8	DABCO	8.7	30
9	*N*,*N*-Dimethylpiperazine	8.53	30
10	1,2-Dimethylimidazole (di-MeIm)	8.0	40
11	2-Methylimidazole (2-MeIm)	7.85	40
12	*N*-Methylmorpholine	7.13	40
13	1-Methylimidazole (MeIm)	7.06	70[c,d]
14	Imidazole (Im)	6.99	45
15	TMEDA	6.35	10
16	Pyridine	5.2	20
17	*N*,*N*-Dimethylaniline	5.1	45
18	*N*-Methylaniline	4.85	50
19	None	—	15

[a] **1a** (2.5 mmol) was treated with DMF-DMA (3 mmol, 1.2 equiv.) in the presence of the base (2.5 mmol, 1 equiv.) at 100 °C (oil bath) for 3 h. [b] Yield of **2a** based on GC–MS (except for entry 10). [c] Yield of purified **2a**. [d] Use of PhMe, EtOH, MeCN, DMF, THF, 1,4-dioxane, and H_2O as the solvent afforded **2a** in 5, 30, 10, 5, 0, 0 and 0% yields, respectively.

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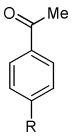
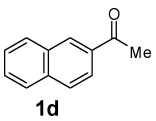
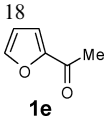
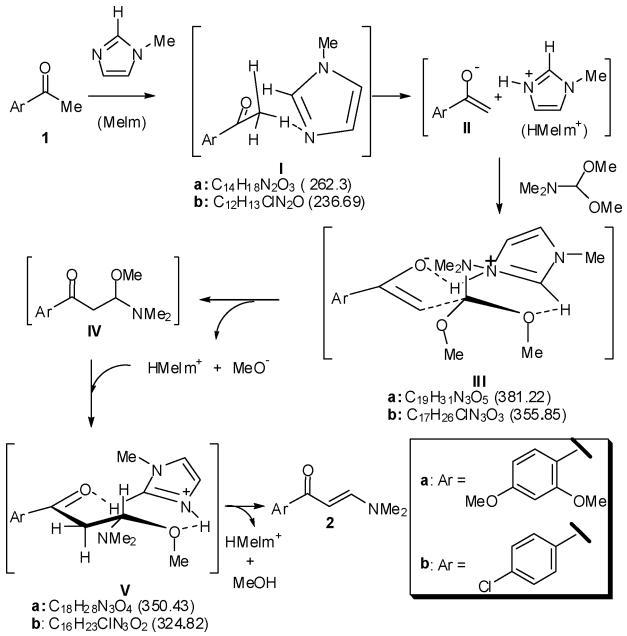
Table 2 The reactions of representative aryl/heteroaryl methyl ketones with DMF-DMA in the presence of MeIM and other organic bases[a]

Entry	Substrate	Base	Time (h)	Yield (%)[b,c]
				
1	**1b**: R = Cl	MeIm	1	70
2		DBU	1	32
3		TEA	1	20
4		DABCO	1	28
5		Pyridine	1	22
6		None	1	20
7	**1c**: R = H	MeIm	2	72
8		DBU	2	38
9		TEA	2	25
10		DABCO	2	28
11		Pyridine	2	22
12		None	2	18
	 **1d**			
13		MeIm	5	90
14		DBU	5	30
15		TEA	5	28
16		DABCO	5	32
17		Pyridine	5	25
18		None	5	12
	 **1e**			
19		MeIm	1	88
20		DBU	1	34
21		TEA	1	20
22		DABCO	1	32
23		Pyridine	1	24
24		None	1	14

[a] The substrate (2.5 mmol) was treated with DMF-DMA (3 mmol, 1.2 equiv.) in the presence of the base (2.5 mmol, 1 equiv.) at 100 °C (oil bath) for the indicated time period (TLC). [b] Isolated yield of the corresponding (2*E*)-1-aryl/heteroaryl-3-dimethylamino-2-propenone after purification. [c] The starting material remained unchanged when the yields were poor.

executing during the progress of the reaction. Since the initial proton abstraction from **1a** by MeIm would generate $HMeIm^+$, we took into consideration the fact that the C-2 hydrogen of the imidazolium cation has an acidic character,[4] contributing to its hydrogen bond donor (H-BD) ability[5] which plays a crucial role in the catalytic activity of 1-butyl-3-methylimidazlium based ionic liquids.[6] Hence the *in situ* formed $HMeIm^+$ may provide catalytic assistance in the subsequent course of the reaction, such as activating DMF-DMA and any intermediate involved during the reaction, as H-bonding additives can act like Lewis acids.[7] The crucial and distinct effect of MeIm on the overall outcome of the reaction can be rationalised through domino catalysis, involving electrophilic activation by $HMeIm^+$ during the: (i) displacement of the OMe group in DMF-DMA by the enolate **IIa** to form the intermediate mixed amino–acetal **IVa** *via* **IIIa** and (ii) elimination of MeOH from **IVa** to produce **2a** *via* **Va** (Scheme 2).



Scheme 2 Supramolecular domino catalysis.

The enolate **IIa** forms H-Bs with the NH proton of $HMeIm^+$. Concomitant co-operative H-B[8] formation between the C-2 hydrogen of $HMeIm^+$ and one of the OMe groups of DMF-DMA leads to **IIIa** which goes on to facilitate the nucleophilic displacement of the OMe group to form **IVa**. The charge–charge interaction between the $HMeIm^+$ quaternary nitrogen and the electron lone pair of NMe_2 may provide additional stability/rigidity to the supramolecular[9] structure **IIIa**. The formation/involvement of the catalytic species **IIIa** exemplifies an 'electrophile–nucleophile' dual activation process.[6,10] The catalytic domino process continues through co-operative H-B formation between $HMeIm^+$ (involving the NH and C-2 hydrogens) and **IVa**, which generates the non-covalent adduct **Va** to provide assistance for the elimination of MeOH in the final step. Rate enhancement may take place in the initial proton abstraction *via* the hydrogen-bonded structure **Ia**.[11] The lack of feasibility of formation of intermediate structures akin to **I**, **III** and **V** with the other bases accounts for the inferior results obtained with these, although some of these bases are stronger base than MeIm (Table 1). The inferior catalytic efficiency of imidazole (Im) compared to that of MeIm may be due to the lower H-BD ability of HIm^+ compared to that of $HMeIm^+$, as the C-2 hydrogen in HIm^+ is less acidic.[12] In the ^1H NMR, the C-2 hydrogen of Im and MeIm appeared at δ 7.71 and 7.54, respectively, but for HIm^+Br^- and $HMeIm^+Br^-$ it appeared at δ 9.17 and 9.20, respectively. The increase in the δ value ($\Delta\delta$) in converting Im and MeIm to the corresponding protonated species was found to be 1.46 and 1.66, respectively, indicating that the C-2 hydrogen in $HMeIm^+$ should be a better H-BD than the corresponding hydrogen in HIm^+.[13] The importance of the C-2 hydrogen of the imidazolium moiety in the overall progress of the reaction through the active involvement in forming the intermediates **I**, **III** and **V** can be further substantiated by the decreased product yields when using di-MeIm and 2-MeIm (Table 1: entries 17, 18), as these imidazole derivatives and the corresponding protonated species are devoid of the C-2 hydrogen.[14]

To support the mechanistic proposal, we planned to identify the non-covalent species **I/III/V**. Electrospray ionization mass spectrometry (ESIMS) has the ability to efficiently generate the ions of non-covalent adducts in the gas phase and is the front-line analytical technique in biochemical research,[15] intercepting ionic intermediates to probe organic reaction mechanisms[16] and characterisation of non-covalent protein/metal ion complexes and hydrogen-bonded aggregates of high molecular weights.[17] However, identification and structural determination of hydrogen-bonded assemblies of small molecules as discrete species to establish organic reaction pathway remain less explored.[6,18]

The ESIMS experiments were performed[13] under positive ion detection (+pESIMS) on aliquots of samples collected after varied time intervals (*e.g.*, 5, 30, 60 and 120 min) from the separate reaction mixtures of **1a** and 4-chloroacetophenone **1b** during treatment with DMF-DMA in the presence of MeIm at 100 °C under N_2. In initial attempts, the MS experiments were performed by changing various instrument parameters, such as the source and capillary voltages, and using different solvents in the sample preparation for MS experiments. No ion peaks corresponding to **I**, **III** or **V** could be detected using any amount of source voltage indicating the instability of these species under an applied source voltage. The ions corresponding to these supramolecular species were detected in the total ion current (TIC) chromatogram without applying source voltage. Hence, TICs were generated using various capillary voltages (10–40 V) putting the source voltage off. In the case of **1a**, the optimum capillary voltage was 37 V and was used to generate the TIC representing most of the ions, which would support the proposed mechanism (Scheme 1). For **1b**, the effective capillary voltage was 20 V.

The MS experiments were also performed using different solvents (*e.g.*, PhMe, dioxane, DCM, and MeOH) in the sample preparation. The requirement of the optimum capillary voltage was dependent on the solvent (*e.g.*, for **1a**, the use of MeOH and DCM required 37 and 20 V, respectively). However, the use of MeOH afforded the most effective TIC, perhaps as it is conducive to form/generate the molecular ions. Hence MeOH was used as the solvent for subsequent MS studies. The TIC (Fig. 1) of the 30 min reaction of **1a** exhibited ion peaks at *m/z* 467 (**Va**$^+$ + MeIm + 2H_2O – H), 437 (**IIIa** + K^+ + H_2O – H), 418 (**IIIa** + H^+ + 2H_2O), 375 (**IIIa** + K^+ – $HNMe_2$), 339 (**IIIa**$^+$ – HNCH═CH), 335 (**Va**$^+$ – Me), 316 (**Va** + Na^+ – OMe – C_2H_2), 304 (**Va** + 2H^+ – Me^+ – OMe), 263 (**Ia** + H^+) which are diagnostic of **Ia**, **IIIa**, and **Va**. Further proof of identity of these species could be derived from the tandem mass spectrometry (MS–MS) studies of selected ions.[13]

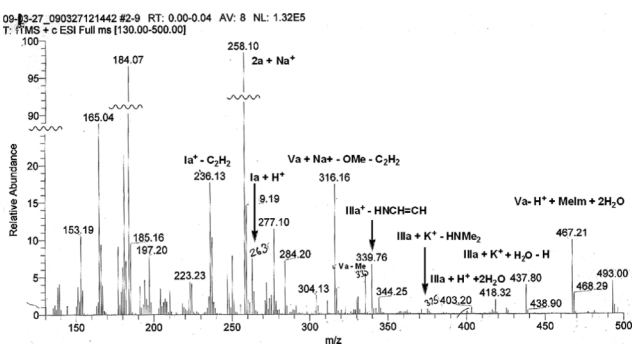


Fig. 1 TIC of the 30 min reaction of **1a** with DMF-DMA, catalysed by MeIm.

A representative MS^2 of the ion at *m/z* 437.80 (m_2) exhibited daughter ions at *m/z* 422.18 (m_2 – Me), 405.16 (m_2 – MeOH), 391.20 (m_2 – $HNMe_2$), 355.17 (m_2 – MeIm) (Fig. 2) that conforms with its structure.

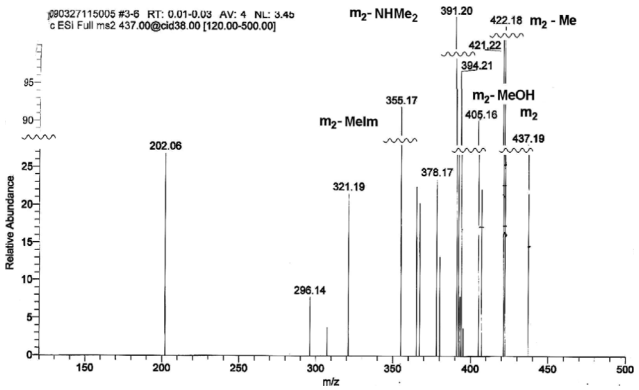


Fig. 2 MS^2 of the ion of *m/z* 437.80 in Fig. 1.

To consolidate the mechanistic proposal, time dependent +pES-IMS studies were performed on aliquots of samples taken from the reaction of **1a** after 5, 30, 60 and 120 min, respectively, to observe the accumulation or disappearance of any of the supramolecular species **Ia**, **IIIa** and **Va** with time. The abundance of the ions (determined through the measurement of ion currents) at *m/z* 263 (represents **Ia**), 437 and 339 (representatives of **IIIa**), 467 and 316 (representatives of **Va**), increased with time but started decreasing after attaining a maxima. The maxima was achieved in 30 min for the ion of *m/z* 263 and in 60 min for other ions (Table 3).[13]

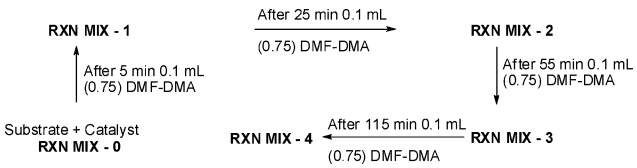
The increase and decrease of the abundance of the ions conforms with the sequence of formation of **Ia**, **IIIa**, and **Va**. The involvement of the co-operatively (doubly) hydrogen-bonded structure **Ia** in the deprotonation step to form the enolate **IIa** could be justified by observations made when the reaction mixtures of (i) DMF-DMA and benzophenone and (ii) DMF-DMA and 4-chlorobenzaldehyde were individually subjected to +pESIMS, as no ion peak corresponding to the H-B adduct of DMF-DMA with benzophenone or 4-chlorobenzaldehyde was detected. Although the carbonyl oxygen of benzophenone and 4-chlorobenzaldehyde has the feasibility to form H-B with the C-2 hydrogen of MeIm, the corresponding adduct was not formed as these are devoid of an enolisable hydrogen which could form the cooperative H-B network. On the other hand, the absence of ionic species relevant to **I**, in the +pESIMS spectra of the mixture of (i) di-MeIm and

Table 3 The abundance of characteristics species during the progress of the reaction of **1a** with DMF-DMA in the presence of MeIm

		Abundance (ion current) after different time intervals			
Entry	Ion at *m/z*	5 min	30 min	60 min	120 min
1	263	8.37×10^7	2.06×10^9	1.53×10^8	2.51×10^6
2	339	1.01×10^5	3.45×10^5	8.95×10^5	8.11×10^5
3	437	3.65×10^5	9.04×10^6	1.11×10^7	4.34×10^6
4	467	5.71×10^5	1.08×10^6	2.00×10^6	1.79×10^6
5	316	2.70×10^5	2.90×10^5	4.59×10^5	1.36×10^5

1a, (i) 2-MeIm and **1a**, (i) di-MeIm and **1b**, and (i) 2-MeIm and **1b**, further highlighted the importance of the ability of the C-2 hydrogen in the imidazole moiety to from the non-covalent adduct **I** and other supramolecular species during the course of the reaction.

The involvement of **I**, **III** and **IV** was further demonstrated by the +pESIMS of the individual components. The aliquot of the mixture **1a** with MeIm only exhibited an ion peak at *m*/*z* 263.51, corresponding to **Ia**. However, no ion peaks corresponding to **Ia**, **IIIa** and **Va** were observed from the mixture obtained after treatment of **1a** with DMF-DMA. For this, a separate experiment was designed where the reagent (DMF-DMA) was added gradually after 5, 30, 60, 120 min (0.75 mmol, each time for the reaction using 2.5 mmol of **1a**) (Scheme 3).



Scheme 3 Gradual addition of DMF-DMA.

For each reaction mixture an aliquot (20 μL) was taken and diluted with 1 mL of MeOH and was then subjected to +pESIMS. At 0 min [**RXN MIX-0**] when the reaction mixture was subjected to +pESIMS, the TIC resembles the TIC of the substrate and catalyst. After gradual addition of DMF-DMA for the first [**5 min**: **RXN MIX-1**], second [**30 min**: **RXN MIX-2**], third [**60 min**: **RXN MIX-3**] and fourth time [**120 min**: **RXN MIX-4**], the TIC looks like the TIC of the model reaction (2,4-di-methoxy acetophenone) at 5, 30, 60, 120 min, respectively.

The aliquots of samples from the MeIm catalysed reactions of **1a** with DMF-DMA performed in MeCN, H_2O, MeOH, PhMe and dioxane did not exhibit any of these supramolecular species in the +pESIMS and justified why there were poor results obtained in these solvents.

The generality of the mechanistic proposal is demonstrated by time dependent (5, 20, 40, and 60 min) +pESIMS studies of the samples from the reaction of 4-chloroacetophenone **1b** with DMF-DMA using an optimum capillary voltage of 20 V. In all cases, the ion peaks relevant to **Ib**, **IIIb**, and **Vb** were observed in the TICs. The most prominent TIC was obtained for the sample from the 40 min reaction (Fig. 3) and showed ions at *m*/*z* 475 (**IIIb** + K^+ + MeIm − H), 459 (**IIIb** + Na^+ + MeIm − H), 432 (**IIIb** + 2K^+ − H^+), 391 (**IIIb**$^+$ + $2H_2O$), 375 (**IIIb** + H^+ + $2H_2O$ − Me), 360 (**Vb**$^+$ − Cl), 338 (**Vb** + K^+ − C_2H_2), 304 (**Ib**$^+$ + MeIm − Me), 292 (**Vb**$^+$ − MeOH), 277 (**Va** + 2H^+ − Me^+ − Cl), and 237 (**Ib**$^+$) which are characteristic of the supramolecular species **Ib**, **IIIb**, and **Vb**. The MS–MS of selected ions provided further structural support.[13]

The MS–MS of selected ions provided further structural characterisation.[13] A representative MS^2 [of the ion at *m*/*z* 391.27 (m_2') of Fig. 3] generated daughter ions at *m*/*z* 375.23 (m_2'–Me-H), 365.23 (m_2'–C_2H_2), 347.13 (m_2'–NMe_2), 334.15 (m_2'–OMe–C_2H_2), and 309.15 (m_2'–Im) that are in agreement with the structure (Fig. 4).

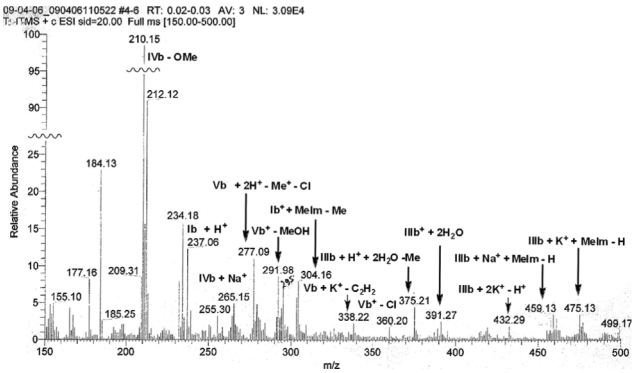


Fig. 3 TIC of the 40 min reaction of **1b** with DMF-DMA catalysed by MeIm.

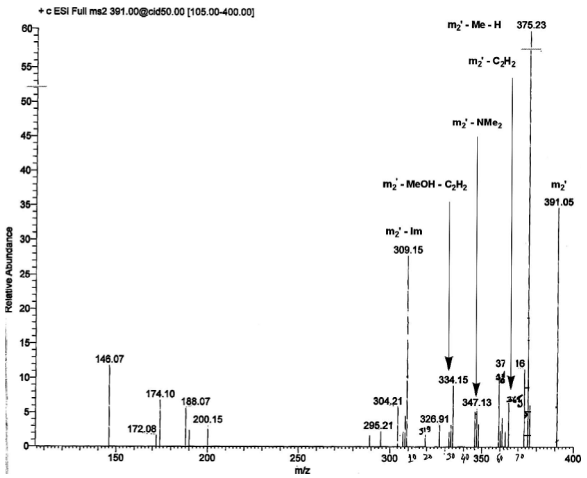


Fig. 4 MS^2 of the ion of *m*/*z* 391.27 in Fig. 3.

Conclusions

In conclusion, an unprecedented supramolecular domino catalysis has been revealed through the mass-spectrometric identification of supramolecular assemblies of small molecules as discrete catalytic intermediates. These intermediates rationalise the lack of correlation between the basicity and catalytic efficiency of amines for the reactions of aryl methyl ketones with DMF-DMA and accounts for the unusual high catalytic power of MeIm compared to other amines with higher basicities. The involvement of the multicomponent organocatalyst–substrate supramolecular assemblies formed by co-operative H-Bs has been demonstrated by the increase/decrease in the concentration of the relevant ions of the supramolecular species with time under ESIMS that has consolidated the mechanistic proposal.

Experimental

General procedure for the synthesis of (*E*)-3-dimethylamino-2-propene-1-ones:

1-(2,4-Dimethoxyphenyl)-3-dimethylamino-2-propene-1-one (2a):

To the magnetically stirred mixture of 2,4-dimethoxyacetophenone (**1a**) (2.5 mmol, 450 mg) and DMF-DMA (357 mg, 3 mmol, 0.39 mL, 1.2 equiv.) at 100 °C under N_2 was added MeIm (2.5 mmol, 0.19 mL, 1 equiv.) and the mixture was stirred

until **1a** was completely consumed (3 h; TLC: the enaminone is highly polar and is identified/traced at the bottom of the TLC plate after elution). The mixture was subjected to rotary evaporation *in vacuo* to remove the volatile components (excess DMF-DMA and the liberated MeOH). The crude product was passed through a column of silica gel (60–120 mesh: 3 g) and eluted with 30% EtOAc in hexane (500 mL) to remove the unreacted starting materials, if any, and less polar components. Final elution with 80% EtOAc in hexane (700 mL) afforded 1-(2,4-dimethoxyphenyl)-3-dimethylamino-2-propene-1-one (**2a**) as a yellow solid (410 mg, 70%); Mp: 48–50 °C. IR ν_{max} (DCM) = 2932, 1639, 1604, 1436, 1355, 1253, 1210, 1109, 1032, 893, 833, 789 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.97 (bs, 6H), 3.83 (s, 6H), 5.67 (d, J = 12.60 Hz, 1H), 6.46–6.52 (m, 2H), 7.58–7.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9, 56.2, 98.3, 99.2, 105.0, 124.7, 129.3, 131.4, 131.8, 154.1, 159.3, 162.7, 189.5. MS (APCI) m/z 236.3 (M + H$^+$).

The characterisation data of other compounds are given below:

(*E*)-1-(4-Chlorophenyl)-3-(dimethylamino)prop-2-en-1-one (2b)[19]

Brown solid, yield 70%; Mp: 69–71 °C. IR ν_{max} (KBr) = 3417, 2925, 1648, 1580, 1437, 1410, 1353, 1305, 1280, 1119, 1089, 1055, 1012, 981, 901, 838, 788, 742, 678, 526 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.93 (s, 3H), 3.14 (s, 3H), 5.66 (d, J = 12.29 Hz, 1H), 7.38 (s, 2H), 7.79–7.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.2, 37.8, 45.6, 92.2, 128.8, 129.4, 137.4, 139.3, 155.1, 187.6. MS (APCI) m/z 210.2 (M + H$^+$).

(*E*)-3-(Dimethylamino)-1-phenylprop-2-en-1-one (2c)[19]

Yellow solid, yield 72%; Mp: 82–84 °C. IR ν_{max} (KBr) = 3055, 2908, 1640, 1584, 1544, 1482, 1432, 1364, 1311, 1275, 1233, 1204, 1122, 1053, 1025, 899, 755, 741, 697, 659 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3H), 3.08 (s, 3H), 5.69 (d, J = 12.33 Hz, 1H), 7.37–7.46 (m, 3H), 7.78 (d, J = 12.33 Hz, 1H), 7.88 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.1, 37.7, 45.5, 92.6, 127.9, 128.6, 128.9, 130.4, 131.3, 141.0, 154.8, 189.1. MS (APCI) m/z 175.1 (M + H$^+$).

(*E*)-3-(Dimethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one (2d)[19]

Yellow solid, yield 90%; Mp: 107–109 °C. IR ν_{max} (KBr): 2456, 1640, 1577, 1547, 1422, 1366, 1283, 1111, 783 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79–3.14 (m, 6H), 5.87 (d, J = 12.34 Hz, 1H), 7.49–7.53 (m, 2H), 7.84–8.03 (m, 5H), 8.39 (s, 1H). MS (APCI) m/z 226.3 (M + H$^+$).

(*E*)-3-(Dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (2e)[19]

Low melting brown solid, yield 88%; IR ν_{max} (DCM) = 3441, 1638, 1576, 1531, 1469, 1419, 1364, 1266, 1068, 1017, 882, 780 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71–3.14 (m, 6H), 5.68 (d, J = 12.49 Hz, 1H), 6.47–6.48 (m, 1H), 7.06–7.15 (m, 1H), 7.49 (s, 1H), 7.81 (d, J = 12.48, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.8, 45.6, 92.0, 112.3, 113.9, 144.7, 145.2, 154.1, 178.0. MS (APCI) m/z 166.3 (M + H$^+$).

Typical procedure for ion-fishing of the supramolecular adducts "Ia–Va" using +pESIMS:

To the magnetically stirred mixture of 2,4-dimethoxyacetophenone (**1a**) (2.5 mmol, 450 mg) and DMF-DMA (357 mg, 3 mmol, 0.39 mL, 1.2 equiv.) at 100 °C under N_2 was added MeIm (2.5 mmol, 0.19 mL, 1 equiv.) and the mixture was stirred, after 30 min, an aliquot (10 μL) of the reaction mixture was taken out using a micro pipette and dissolved in MeOH (1 mL). From the resultant solution an aliquot amount (50 μL) was subjected to +pESIMS (capillary voltage, 37 V) in an ion-trap mass spectrometer.

The sampling (mobile-phase) for the +pESIMS study was performed using a wide range of solvents (PhMe, dioxane, DCM, MeOH, H_2O). The best result was obtained in MeOH due to its ability to help with the formation of ions under MS conditions.

Both, in the case of 2,4-di-methoxyacetophenone **1a** and 4-chloroacetophenone **1b**, the application of an external source voltage had a detrimental effect on the ion formation, suggesting that the hydrogen-bonded intermediates (**I**, **III** and **V**) are transient species. So the +pESIMS study was performed in the absence of a source voltage. Whilst having the source voltage off, the capillary voltage was varied from 10 to 40 V in order to determine the optimum MS experiment conditions which would generate the total ion current (TIC) chromatogram representing most of the ions.

In the case of **1a**, when the +pESIMS study was performed in MeOH (used only during preparation of the sample for the MS injection/experiments but not in performing the reaction) the optimum capillary voltage was 37 V. But for the same reaction when the +pESIMS study was performed in DCM (used for MS sample preparation but not in performing the reaction) the optimum capillary voltage was 20 V.

For the +pESIMS study with **1b** using MeOH (used for MS sample preparation but not in performing the reaction) the optimum capillary voltage was 20 V.

Typical procedure for ion-fishing of the supramolecular adducts "Ib–Vb" using +pESIMS:

To the magnetically stirred mixture of 4-chloroacetophenone (**1b**) (2.5 mmol, 385 mg) and DMF-DMA (357 mg, 3 mmol, 0.39 mL, 1.2 equiv.) at 100 °C under N_2 was added MeIm (2.5 mmol, 0.19 mL, 1 equiv.) and the mixture was stirred, after 40 min, an aliquot (10 μL) of the reaction mixture was taken using a micro pipette and dissolved in MeOH (1 mL). From the resultant solution an aliquot (50 μL) was subjected to +pESIMS (capillary voltage, 20 V) in an ion-trap mass spectrometer.

Typical procedure for ion-fishing of the supramolecular adducts, if any, of the substrate and the catalyst/base:

2,4-Di-methoxyacetophenone **1a** (1 mmol) was mixed with MeIm (1 mmol) and the mixture stirred at 100 °C for 5 min. An aliquot of the resultant reaction mixture (20 μL) was taken, diluted with 1 mL of MeOH and subjected to +pESIMS, the ion peak at m/z 263.51 was detected and reflects the formation of **Ia**. The 5 min TIC: 263 can be assigned as 262 (**Ia**) + H$^+$ (hydrogen-bonded adduct of **1a** with MeIm).

Typical procedure for ion-fishing of supramolecular adducts, if any, of the substrate and the reagent/DMF-DMA:

2,4-Di-methoxyacetophenone **1a** (1 mmol) was mixed with DMF-DMA (1 mmol) and the mixture stirred at 100 °C for 5 min. An aliquot of the resultant reaction mixture (20 μL) was taken, diluted with 1 mL of MeOH and subjected to +pESIMS, however, no ion peaks corresponding to **IIa**, **IIIa** and **Va** were observed/detected.

Typical experimental procedure for the determination of ion current using +pESIMS:

To the magnetically stirred mixture of 2,4-dimethoxy-acetophenone (**1a**) (2.5 mmol, 450 mg) and DMF-DMA (357 mg, 3 mmol, 0.39 mL, 1.2 equiv.) at 100 °C under N_2 was added MeIm (2.5 mmol, 0.19 mL, 1 equiv.) and the mixture was stirred. An aliquot (20 μL) of the reaction mixture was taken at various times by a micro pipette and dissolved in DCM (1 mL). From the resultant solution an aliquot amount (10 μL) was subjected to +pESIMS in an ion-trap mass spectrometer.

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