Reaction Mechanisms



The Multicomponent Hantzsch Reaction: Comprehensive Mass Spectrometry Monitoring Using Charge-Tagged Reagents

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Abstract: A novel strategy for the ESI-MS monitoring of reaction solutions involving the alternate use of permanently charge-tagged reagents has been used for comprehensive mass spectrometry monitoring of the multicomponent Hantzsch 1,4-dihydropyridine reaction. By placing a charge tag on either, or both, of the two key reactants, ion suppres-

prehensive detection of charge-tagged intermediates was achieved. The strategy allowed the trapping and characterization of the important intermediates in the mechanism for 1,4-dihydropyridine formation.

sion effects for ESI were eliminated or minimized, and com-

Introduction

The Hantzsch reaction^[1] is one of the oldest and most effective multicomponent reactions.^[2] Despite the multitude of alternative reaction routes, it still proceeds very selectively by the dehydrative coupling of ammonia, two equivalents of a 1,3-dicarbonyl compound and an aldehyde (Scheme 1) forming 1,4-dihydro-2,3,5,6-substituted pyridines (1,4-DHP) in an "all roads leads to Rome" fashion. Depending upon the reagents and or reaction conditions, low yields or unexpected products can be obtained,^[3] including isomeric 1,2-DHP,^[4] hence the need to fully understand its intricate mechanism. The 1,4-DHP have been found to posses many pharmacological activities, such as:^[5] antitumorals for multidrug resistant (MDR) tumours,^[6] bronchodilating,^[7] antidiabetic,^[8] neurotropic,^[9] HIV protease inhibitors;^[10] although they are perhaps best known as calcium channel blockers,^[11] for example: aranidipine,^[12] lercanidipine,^[13] nifedipine^[14] and the multibillion dollar drug amlodipine.^[15]

Additionally, the 1,4-DHP have great potential as hydride (or hydrogen) transfer reagents due to their similarity with the natural product enzyme co-factors NAD(P)H and the oxidized form NAD(P).^[16] In addition to the reduction of aldehydes and ketones,^[17] progress has also been made on the reductive ami-

nation of aldehydes and some ketones, as well as the reduction of preformed imines, in the presence of Lewis acids^[18] or Brønstead acids,^[19] and more recently by using asymmetric organocatalytic procedures giving moderate to excellent levels of enantioselectivity.^[20] Electron-deficient alkenes are also readily reduced with an equivalent of 1,4-DHP.^[21] Transition metals and their organometallic complexes can be used in conjunction with 1,4-DHP to reduce functional groups by transfer hydrogenations.^[22]

The classical Hantzsch reaction was modified by Beyer,^[23] and later by Knoevenagel and co-workers to prepare unsymmetrically substituted 1,4-DHP by using (alkyl-) aryl-idene-1,3-dicarbonyls or β -aminocrotonates, and these modifications have been applied by others.^[24] Rabe and co-workers have also replaced the acetoacetate by 1,5-diketones.^[25] These modifications have extended the scope and shed light on the intricate mechanism of the Hantzsch reaction, for which at least five major different pathways (A–E) have been proposed (Scheme 2).

In the aminocrotonate/aldehyde path A, the major key player is the aminocrotonate 5, which condenses with 2 to form 14 via 6. In the aminocrotonate/Knoevenagel path B, 5 is again a key player but reacts with the Knoevenagel intermediate 10 to form 7. Via path C, 14 is also formed as in path A, but via an alternative route. For the diketo/ NH_3 path D, 10 reacts with a second molecule of 1 to form 11, which also con-



Scheme 1. The classical Hantzsch reaction and the synthesis of 1,4-dihydro-pyridines.

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Scheme 2. Possible mechanistic paths (A–F) for the Hantzsch reaction. For a definition of the reactions a, b, c, and d to which the substituent information applies see Scheme 4.

verges to 7. In the aminobiscrotonate path E, 5 is again invoked, but it now reacts with 1 and later with 2 to form 4. Path F is suggested in this study, but seems to be a dead-end route that equilibrates with the reactants.

Hinkel and co-workers^[26] have studied substituent effects for 2, whereas Haley and Maitland investigated pH effects.^[27] They made no claim to favor a specific reaction mechanism but cited the work of $\mathsf{Phillips}^{\scriptscriptstyle[28]}$ who had observed that aromatic aldehydes with two equivalents of ethyl acetoacetate and two equivalents of concentrated aqueous ammonia in ethanol followed by heating gave better results than using the aldehyde in combination with two equivalents of aminocrotonate or with one equivalent of both ethyl acetoacetate and the ethyl aminocrotonate, therefore supporting mechanism D. Insights on the Hantzsch DHP reaction mechanism can therefore be obtained by changing the addition order of reagents or by using preformed intermediates. In a similar strategy, Zhou and co-workers^[29] (Scheme 3) observed no reaction upon treating preformed **5** with α -cyanobenzocinnamate (analogous to **10**), which was taken as evidence against path B, but the one-pot reaction formed the desired pyridine supporting either C or D (Scheme 2). Path C is an interesting deviation from A, where the formation of **5** is unimportant for 1,4-DHP synthesis.



Scheme 3. One-pot Hantzsch reaction studied by Zhou and co-workers.^[29]

Katritzky and co-workers^[30] using ¹³C and ¹⁵N NMR spectroscopy observed that **10** and **5** were always formed, which was taken as evidence for B. They also observed the formation of **18**, but assigned it to a metastable side product. Since **13** from D was not observed, B was assumed to be the most likely path.

Electrospray ionization mass spectrometry (ESI-MS) has become a major tool for investigating reaction mechanisms serving as a bridge between gas phase and solution chemis-

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Scheme 4. The Hantzsch reaction performed with neutral (a) as well as reactions with charge-tagged reagents (b-d).

tries.^[31] ESI "fishes"^[32] intermediates directly to the gas phase in which MS and MS/MS characterization are performed, providing therefore continuous snapshots of the dynamic ionic composition of reaction solutions.^[33] ESI-MS is, however, blind to neutral species and the detection of such species is dependent upon adventitious equilibria with either protons or metal ions. To overcome this ESI-MS limitation, an elegant strategy based on charge tags^[34] added to reagents or catalysts has therefore been developed.^[35]

In this study, we have investigated the mechanism of the Hantzsch reaction with ESI-MS monitoring using a strategy involving alternate reactions with charge-tagged reagents (Scheme 4). Since a multitude of reaction intermediates formed by various but convergent reaction paths (Scheme 2) have been proposed, the Hantzsch DHP reaction provides a challenging test for the charge-tag approach to ESI-MS as a reaction monitoring tool. Specifically, charge tagging was used for none, either one or both of the two key reactants 1 and 2 (Scheme 4).

Alternate tagging of the reagents in different reactions should facilitate detection of any intermediate formed by reaction of the specifically tagged reactant, and therefore ion suppression effects should be minimized or eliminated, thus providing comprehensive monitoring of intermediates. For the neutral untagged reaction, ESI "fishing" is normally effective but relies on the adventitious occurrence of favorable equilibria for (de)protonation or ion association.^[33]

Results and Discussion

Our investigation began with the monitoring of the neutral reaction **a** (Scheme 4) in ethanol at 60 $^{\circ}$ C. Aliquots of the reaction medium (1.0 μ L) were taken, diluted in acidified acetonitrile and subjected to direct infusion ESI in the positive-ion mode. Spectra were collected at different time intervals but those at 10 and 120 min as well as 48 h were the most relevant.

Figure 1, spectra A and B, show illustrative ESI(+)-MS after 10 and 120 min, respectively. The spectra reveal several of the key players proposed for the Hantzsch reaction (Scheme 2). The same set of intermediates with varying proportions and fading abundances were detected as the reaction progressed to completion. Protonated **1a** of m/z 131 could be detected as an abundant ion after 10 min of reaction (Figure 1A) but after 120 min it had been nearly completely transformed into **5a** or consumed. The ion of m/z 218 (**14a**) was intercepted as one of the most abundant intermediates, which became even more predominant after 120 min of reaction (Figure 1B). Note that **14a** is clearly detected with no signs of **15a** or **16a**.

In Figure 1 (reaction **a**) the ion of m/z 324 (**21 a**) was also abundant, particularly after 10 min (Figure 1A), but it started to fade after about 120 min (Figure 1B), as was also the case for 14a. Since most of the reactants are transformed into the final 1,4-DHP 4, and since it is hard to rationalize a path from 21 a to 4, we assume that 21 a is a "dead-end" intermediate (path F) that reverts to reactants. Another key intermediate in Figure 1 A is that of m/z 348 (7 a). Interestingly, if 7 a is indeed detected, its isomerization to 8a could be monitored. Hence, the ESI(+)-MS/MS of this ion was acquired periodically (Figure 2). Note the drastic change in dissociation chemistry from the early stages of the reaction (30 min, Figure 2A) to that after 48 h (Figure 2B), which is indicative of the $7a \rightarrow 8a$ isomerization (Scheme 2). Additionally, Figures S1-S3 in the Supporting Information show the ESI-MS/MS for the intercepted species, in which the observed dissociation could be properly correlated with the proposed structures.

The final product 4a in its protonated form of m/z 330 was also detected, even at the early stages of reaction (10 min), but always as a minor ion, accompanied by the ion of m/z 328 corresponding to an aromatic pyridine Hantzsch product 23 a or 23 a', which at the end of the reaction became nearly the exclusive ESI(+)-MS detectable ion (Figure 1C). Given this seemingly anomalous finding, the Hantzsch reaction a was repeated with stoichiometric quantities of reagents that were stirred at room temperature in a septum-sealed flask. The reaction was periodically analyzed by GC-MS and the analyses revealed the formation of the principal product 4a as well as very minor quantities of the 1,2-DHP isomer (4a') and its oxidation product (23 a'); for more details see the Supporting Information. But when the Hantzsch reaction a was repeated using an excess of NH₄OAc (4 equiv), substantial quantities of the 1,2-DHP isomer and its oxidation product were readily formed. The oxidation of 4a' to 23a' occurs notably more easily than the respective oxidation of **4a** (Scheme 5).^[4a]

Therefore, the seemingly anomalous result that a pyridine derivative is the only detectable product, can be readily understood by consideration of the enhanced basicity of the pyridines **23a** and **23a'** relative to **4a** and/or **4a'** whereby the former are readily detected by ESI(+)-MS due to more favorable protonation. The suppression of **4a/4a'** demonstrates a lim-





Figure 1. ESI(+)-MS of the reaction solutions for reaction "a" after: A) 10 min, B) 120 min, and C) 48 h; and reaction "b" after: D) 10 min, E) 120 min, and F) 48 h.



Figure 2. ESI(+)-MS/MS of: A) **7** a (m/z 348) after 30 min of reaction, and B) **8** a (m/z 348) after 48 h of reaction. The contrasting spectra corroborate the **7** a \rightarrow **8** a isomerization. Other mesomeric structures can also be proposed for the intermediate structures.

itation of the use of ESI-MS for reaction monitoring when using untagged reactants.

Given the apparent limitations of monitoring the neutral reagent reaction **a**, reaction **b** (Scheme 4) employing the chargetagged 2^+ was then monitored without the addition of ESI admediates with varying abundances was detected along the 48 h period. Among these intermediates, as Figure 1 (spectrum E) illustrates for the reaction after 120 min, three major and sequential ions of m/z 294 (**9b**⁺), m/z 276 (**10b**⁺) and m/z 405 (**7b**⁺) were detected, as well as the tagged reactant **2**⁺ of m/z 164 (see Figures S4–S6

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Reaction **b** apparently

proceeded faster than the neu-

tral reaction a as seen from the

abundant product ion 4b⁺ of

m/z 387 detected after 120 min

(Figure 1, spectrum E). However,

this apparent difference can be

attributed to either the en-

hanced reactivity of 2⁺ (an elec-

tron deficient benzaldehyde derivative) or to the fact that the

presence of the charge tag in $\mathbf{4b}^+$ overcomes the problems as-

sociated with monitoring reac-

tion a in which the Hantzsch

product 4a is nonbasic and not

readily detectable, or to both of

the effects. Additionally, Figure 1

(spectrum F) reveals that the

final charged-tagged 1,4-DHP ion $\mathbf{4b}^+$ of m/z 387 was detect-

ed almost as the exclusive ion

after 48 h. Again for reaction **b**, essentially the same set of inter-

ditives.



Scheme 5. Formation of 1,4-DHP (4a) and 1,2-DHP (4a') products and their respective pyridine structures due to oxidative aromatization.

in the Supporting Information for the ESI-MS/MS characterization). If we reasonably assume that ion discrimination is eliminated or substantially reduced by the preloaded charge, and that reaction **b** should facilitate the detection of intermediates involving **2**⁺, the detection of **9b**⁺, **10b**⁺ and **7b**⁺ and the dominance of **10b**⁺ points to the participation of the Knoevenagel intermediate **10** in the rate-limiting step, as also proposed by Katritzky and co-workers from NMR measurements,^[30] and that **10** is transformed into **7**. The ion of *m/z* 220 (Figure 1, spectra D and E) seems again to be the dead-end intermediate **21b**²⁺ of path F. Expansion of spectrum E (Figure 1) at 120 min along the *m/z* 395–430 range (Figure 3) shows that ESI(+)-MS was also able to intercept two intermediates from path D, that is, **11b**⁺ of *m/z* 406 and **12b**⁺ (likely in equilibrium with **13b**⁺) of *m/z* 423.

The periodic analysis of reaction **b** allowed the observation of a large number of intermediates consistent with path **D**. The reaction with the charge-tagged aldehyde 2^+ was therefore also monitored by Venturi easy ambient sonic-spray ionization (V-EASI; Figure 4).^[36] The experiment revealed the rapid consumption of 2^+ to form the Knoevenagel intermediate $10b^+$ and the concomitant consumption of $10b^+$ with the formation of the 1,4-DHP ion $4b^+$. A low steady-state concentration of the ions of m/z 405 ($7b^+$), 406 ($11b^+$) and 423 ($12b^+$) was observed over the timescale in which the reaction was monitored. The low steady-state concentrations of $11b^+$ and $12b^+$ support path D for the formation of 7. Unlike in the study of Singh,^[3]] in which 13 was isolated as the reaction product, due to the presence of the highly electron-withdrawing CF₃ substituents that stabilize the bishemiaminal prod-





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Figure 4. V-EASI monitoring of reaction **b**. Relative intensities of ions as a function of time. A color version of the Figure is provided in the Supporting Information.

uct—as also seen in a number of analogues of **8**^[3f, 3k, 37]—**13** is most likely in the present case to be the product of a deadend equilibrium and is therefore consumed by the transformation of **12** into **7** and the latter isomerizing into **8** (Figure 2).

Reaction **c** (Scheme 4) employing the charge-tagged 1^+ was then monitored (Figure S7a-c in the Supporting Information). The reaction apparently occurred at a similar rate to the neutral reaction a but after 48 h, the ESI(+)-MS was quite noisy showing that intermediates were mainly consumed. Further, the final product $4c^{2+}$ was not detected (Figure S7c) despite being observed at shorter reaction times. The failure to detect the product $4c^{2+}$ at the end of the reaction is perhaps due to the high reactivity or low stability promoted by the presence of multiple permanent charge sites under the reaction or analytical conditions. As Figure 5A illustrates for reaction c after 120 min, two major intermediates were detected: $5c^+$ of m/z234 (the enamine) and $10c^+$ of m/z 323, the Knoevenagel product. Note that the final product $4c^{2+}$ of m/z 270, the reactant 1^+ of m/z 235 and the dead-end intermediate $21 c^+$ of m/z 428 from F were also detected at this time interval. In contrast to the neutral reagent reaction \mathbf{a} , the intermediate $\mathbf{14c}^+$ of m/z 322 is a minor ion at early stages of the reaction but is

one of the principal ions after 48 h (Figure S7c).

Reactions **b** and **c** illustrate how the complimentary charge tagging of the reagents **1** and **2** can allow the detection of important reaction intermediates in the absence of any purposefully incremented ESI additive that could artificially shift equilibria of species in solution. Reaction **c** also reveals, however, a limitation associated with the detection of multiply charged species. The



Figure 5. ESI(+)-MS of: A) reaction solution "c" after 120 min, and B) reaction solution "d" after 120 min.

reasons for this limitation are not clear at present and require further examination.

As $7c^{2+}$ (an intermediate that could be formed through the diverse possibility of mechanisms) could not be detected and due to the difficulty in following the reaction of charge-tagged 1⁺ using the V-EASI technique, an investigation of the reaction of 5a with 10a was conducted. Both of these intermediates were prepared by improvising upon literature methods and subjected to reaction in the presence or absence of a molar equivalent of AcOH in 95% EtOH at room temperature (for further details see the Supporting Information). Unlike the use of 10' (Scheme 3) the enamine 5a and the Knoevenagel product 10a readily reacted with one another to give the Hantzsch ester 4a in reasonable yield. Notably, the reaction in the presence of AcOH readily became yellow colored and precipitated a solid that when isolated was colorless (51% yield), whilst the reaction in the absence of AcOH precipitated a colorless solid (with a slightly better 58% yield) after a few days at room temperature. Additional experiments using the enamine 5a, 1,3-dicarbonyl compounds (1 e or 1 f) and the Knoevenagel product 10a revealed that in the presence of AcOH the enamine 5a readily equilibrates with 1a and the additional 1,3-dicarbonyl compound (1 e or 1 f) forms the respective enamine (Scheme 6). No transamination to give 5 f was observed to occur in the absence of AcOH. The final ratio of the products 4a/4f was found to be 5.6:1 and 1.5:1 for 4a/4e for the reactions conducted in the presence of AcOH.

In the absence of AcOH (Scheme 7), the reaction of **5a** and **10a** in the presence of an equivalent of **1f** resulted almost exclusively in the formation of the 1,4-DHP **4a**. A very minor quantity of 1,4-DHP **4f** was readily detectable by GC-MS towards the end of the reaction. Notably, even at early stages of the reaction it was possible to observe the formation of a small quantity of *tert*-butyl benzylidene acetoacetate (**10f**) due to a transbenzylidination reaction. The reaction of **10f** with **5a** could give rise to the small quantity of **4f** that was formed during the reaction. The final ratio of **4a/4f** was 40:1.

The analogous reaction of 5a and 10a in the presence of an equivalent of 1e resulted in a 6:1 mixture of the 1,4-DHPs 4a and 4e. At early stages during the reaction the formation of 10e was evident and at a later stage the presence of 5e was also detected. The increased acidity of 1e compared with either 1a or 1f may facilitate both the transamination and transbenzylidination reactions even in the absence of AcOH. Both the reactions of 1e and 1f resulted in the formation of considerable quantities of 1 a. Therefore, under neutral or slightly basic conditions (for example,



Scheme 6. Transamination of 5 a and 1(e,f) under acidic conditions and the formation of unsymmetrically substituted 1,4-DHPs 4e and 4f as well as symmetrical 4a.

employing an excess of NH_4OH as the ammonia source) mechanism B is likely to be very important (transamination is relatively unimportant) whilst under slightly acidic conditions (for example, using an excess of NH_4OAc as the ammonia source) the various mechanisms will contribute to product formation.

Additionally, given that 5a was reportedly inert to the ethyl arylidene cyanoacetate 10' (Scheme 3) the reaction of 5a in



Scheme 7. Formation of unsymmetrically substituted 1,4-DHPs 4e and 4f in the absence of added AcOH.

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Figure 6. ESI(+)-MS for reaction solution **d** in the: A) m/z 196–204 range after 120 min, and B) m/z 202–209 range after 48 h.

the presence of ethyl benzylidene cyanoacetate with and without AcOH was also investigated. However, in both cases no reaction was observed to occur, confirming the inertness of this substrate type under the reaction conditions employed.

In principle, reaction d (Scheme 4) could seem ideal at first in terms of charge tagging as two reactants are tagged, but could be intrinsically challenging since it requires the interaction of two positively charged ions: 2⁺ and 1⁺. The reaction, however, if properly assisted by counter-anions, could favor detection of all intermediates displaying net charges varying from 1⁺ to 3⁺ (Scheme 2). Reaction d was indeed much slower and the reactants 1^+ of m/z 235 and 2^+ of m/z 164 were always detected as the predominant ions (Figure S8a-c in the Supporting Information), but after 120 min (Figure 5, spectrum B) and particularly at 48 h (Figure S8c), two intermediates could be detected: $5d^+$ of m/z 234 and the dead-end intermediate 21 d^{2+} of m/z 181, as well as the final product 4^{3+} of m/z 199. In addition, spectrum expansion around m/z 200 revealed the presence of $9d^{2+}$ of m/z 199.63 at 120 min (Figure 6 A). The key intermediate $7 d^{3+}$ of m/z 205.14 was also detected at 48 h (Figure 6 B).

Conclusion

By using ESI(+)-MS(/MS) monitoring and the alternate chargetagging strategy most, if not all, relevant intermediates for the Hantzsch DHP reaction were intercepted and characterized. Combined with experimental data using preformed intermediates, the evidence supports the overall mechanistic view of Scheme 8. The intermediate **5** was detected by ESI-MS, as has also been the case by NMR spectroscopy,^[30] but the intermediate **6** as well as the sequential intermediates **17–19** were not detected. Therefore, the participation of 5 may be limited to direct reaction with 10 (mechanism B) to give 7 and to act as a reservoir of 1 and 3 (Scheme 2) depending upon the reaction conditions. Evidence for the direct reaction of 5a and 10a was obtained by conducting the reaction in the presence of a second 1,3-dicarbonyl compound in which in the absence of acid, transamination was minimal or did not occur and the principal product was 4a. Aldehyde 2 seems also to be easily converted into 21 in the presence of 1 and 3, but 21 acts as a dead-end intermediate (Scheme 8). Monitoring of the neutral reaction a suggests that 14 and 7 are key intermediates whereas in the charge-tagged reactions b--d, ions 7(8), 9, 10, 11 and 12 were intercepted as the most important intermediates, but there was no sign of 6, 16 or 17. The combined data, therefore, suggest the predominance of three convergent paths B, C and D, and the formation of the final product 4 via cyclization of 7 and dehydration of 8 (Scheme 8). As proposed by Katritzky and co-workers from NMR measurements,^[30] the Knoevenagel intermediate 10 seems indeed to participate in the rate-limiting step of the Hantzsch reaction, being converted into the convergent intermediate 7 by reaction with 5, as well as via 11 and possibly 14.

Therefore, the novel approach of alternate charge tagging of reagents was successfully applied to investigate an intricate multicomponent reaction mechanism with ESI(+)-MS, facilitating the interception of most if not all major intermediates. There was no need for the addition of acidic or basic additives to promote (de)protonation, and the absence of such additives implies that the true ionic composition of the reaction under its normal reaction conditions can be probed. ESI-MS with charge-tagged reactants potentially offers a comprehensive technique for reaction monitoring.

Experimental Section

ESI-MS(/MS) monitoring of the Hantzsch reaction

In all four experiments studied (a-d) the reactions were performed as follows: in a flask (10 mL) with ethanol (2 mL), 0.1 mmol of each reagent: aldehyde, acetoacetate (in the case of **a** and **b**) or acetoacetamide (in case of c and d) and ammonium acetate were mixed and stirred at 60 °C for 48 h. Aliquots of the reaction medium (5.0 μ L in the case of reaction **a** and 1.0 μ L in the case of the experiments with charged tags b-d) were taken, diluted in acetonitrile (1 mL) with formic acid (0.1%) in experiment a due to the lack of charge in the reagents, or without additive in the case of all other experiments (b-d). The aliquots were directly infused into the ESI source using a syringe pump (Harvard Apparatus) at a flow rate of 10 μ L min⁻¹. In the case of the V-EASI experiments the reaction solution was directly analyzed as the ionization method promotes the self-pumping of the reaction solution by the Venturi effect.^[36] All experiments were performed on a tandem Q-Tof mass spectrometer (Micromass, UK) equipped with an electrospray (ESI) source in positive ion mode. The main ESI conditions were capillary voltage: 3000 eV; cone voltage: 30 eV; source and desolvation temperature: 100 $^\circ\text{C}.$ The spectra were acquired along the 100–500 m/z range. ESI-MS/MS of the cationic species was performed by mass selecting the ion of interest using the first quadrupole Q1. The selected ion was in turn subjected to 4-40 eV collision-induced



Scheme 8. Mechanistic view of the Hantzsch reaction as evidenced by combined experimental data and ESI(+)-MS(/MS) monitoring.

dissociation (CID) experiments in the second rf-only collision quadrupole (Q2) while scanning the orthogonal TOF mass analyzer to acquire its tandem mass spectrum. The collision gas pressure was optimized to produce extensive dissociation with minimal loss of ion current.

The charge-tagged reagents were prepared by N-methylation, using MeI in acetone, of *p*-dimethylaminobenzaldehyde^[38] and *N*-[4-(dimethylamino)phenyl]acetoacetamide.^[39] Spectroscopic data: *N*-[4-(dimethylamino)phenyl]acetoacetamide ¹H NMR (500 MHz, CDCl₃): δ = 8.85 (s, 1 H), 7.37 (d, *J* = 9.0 Hz, 2 H), 6.71 (d, *J* = 9.0 Hz, 2 H), 3.54 (s, 2 H), 2.91 (s, 5 H), 2.30 ppm (s, 3 H); ¹³C NMR (126 MHz, CDCl₃): δ = 205.4, 163.4, 147.9, 127.9, 122.1, 113.4, 50.1, 41.2, 31.3 ppm; spectroscopic data: *N*-[4-(trimethylamino)phenyl] acetoacetamide iodide ¹H NMR (200 MHz, [D₆]DMSO/CDCl₃): δ = 2.20 (s, 3 H), 3.59 (s, 2 H), 3.68 (s, 9 H), 7.78 (s, 4 H), 10.23 ppm (s, 1 H); ¹³C NMR (50 MHz, [D₆]DMSO/CDCl₃): δ = 30.1, 52.1, 57.1, 120.1, 120.2, 140.0, 141.2, 165.2, 202.0 ppm; HRMS calcd: 235.1447; found: 235.1428.

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Keywords: charge tags · electrospray ionization · ionic intermediates · multicomponent reactions · reaction mechanisms

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