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Organic Reactions of Ionic Intermediates Promoted by Atmospheric-Pressure Thermal Activation**

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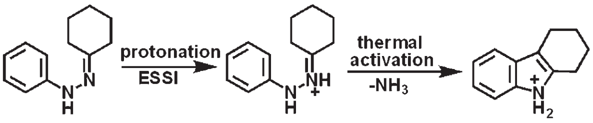
Interest in "green chemistry" has made the development of environmentally benign alternatives to organic solvents and conventional acid catalysts an active area of investigation. The replacement of organic solvents with recyclable ionic liquids[1,2] and supercritical carbon dioxide,[3] as well as the replacement of acid catalysts by supercritical water (400 °C, 200 bar) and near-critical water (275 °C, 60 bar),[4–6] has already been demonstrated in organic synthesis. These developments, and accompanying studies of reaction mechanisms under unusual conditions, have increased the interest in nontraditional ways of carrying out reactions and exploring their mechanisms. Several such approaches are based on mass spectrometry, the best established of which is the use of chemical ionization and gas-phase Brønsted acid/base reactions to generate the ions of interest.[7–15]

Mass spectrometry can be employed to study the reactivity of organic reactants by using electrospray ionization (ESI)[16,17] to generate ionic reagents under ambient pressure.[18–22] ESI has been widely used to ionize organic and biological samples, thus allowing compounds to be protonated at their basic sites or deprotonated at their acidic sites. The protonation process with ESI is known to occur even when the analyte is dissolved in pure protic solvents, such as water or methanol, without any added acids or bases. The dissociation equilibrium $H_2O \rightleftarrows H^+ + OH^-$ and the electrochemical reaction $2H_2O \rightleftarrows 4H^+ + O_2 + 4e^-$[23] are proton sources. This phenomenon prompted us to use ESI as a mild alternative to acid catalysis for generating ionic intermediates in organic reactions. As the protonated analyte ions (potential reaction intermediates in solution-phase reactions) generated by ESI are thermalized by numerous collisions with third body gaseous molecules at atmospheric pressure, they must be activated to undergo reaction. We recently developed an atmospheric-pressure thermal activation method based on a heated coiled tube,[24] which can be used, among other things, for protein/peptide ion dissociation and hence as an aid in sequencing. Herein we have employed this atmospheric-pressure activation method to promote reactions of organic ions generated by electrosonic spray ionization (ESSI),[25] a variant form of ESI. By using this strategy, several organic reactions, including the Fischer indole synthesis, the Borsche–Drechsel cyclization, and the pinacol rearrangement, have been successfully performed under mild conditions (Scheme 1 and Figure 1 a).



Scheme 1. Borsche–Drechsel cyclization promoted by thermal activation and using ESSI to form the ionic intermediate (protonated hydrazone).

The Fischer indole synthesis, which involves formation of the ubiquitous indole ring system by reaction of an aryl hydrazine and a ketone or aldehyde, has remained a useful synthetic method for over 100 years.[26] Various catalysts have been used to effect the cyclization of aryl hydrazones derived from ketones, including Brønsted acids (H_2SO_4, HCl, PPA, AcOH, Brønsted acidic ionic liquids),[27,28] Lewis acids ($ZnCl_2$, $TiCl_4$, PCl_3),[29] and solid acids (zeolite, montmorillonite clay).[30] The Borsche–Drechsel cyclization[31] is similar to the Fischer indole synthesis in that the reactant ketone is a cyclohexanone, although the product is a tetrahydrocarbazole. A solution of the two reactants, phenylhydrazine ($PhNHNH_2$; 2 μL) and cyclohexanone (2 μL), in methanol (1 mL) was analyzed by using ESSI. As directly observed by ESSI mass spectrometry (Figure 1 b), the protonated form of the condensation product, cyclohexanone phenylhydrazone, at m/z 189, is generated. However, the protonated tetrahydrocarazole product ion (m/z 172) was not detected, thus indicating no observable cyclization had occurred.

To facilitate Borsche–Drechsel cyclization, atmospheric-pressure thermal activation[24] was used to activate the protonated cyclohexanone phenylhydrazone (m/z 189). When the sprayed droplets from ESSI were directed into a stainless-steel coiled tube heated at 200 °C, the ion corresponding to protonated tetrahydrocarbazole (m/z 172) was generated (Figure 1 c). The details of the activation process of protonated cyclohexanone phenylhydrazone have not been elucidated. As generated by ESSI, this ion is initially solvated and present in the electrosprayed microdroplets. As the ion is

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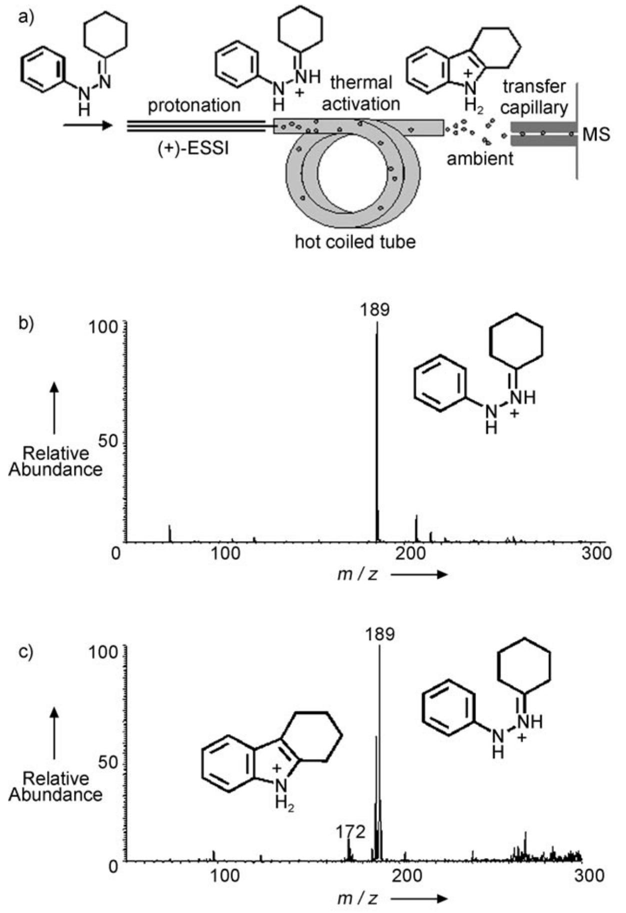


Figure 1. a) Experimental apparatus showing the use of ESSI and thermal activation to promote organic reactions; apparatus includes an ESSI ion source, a coiled stainless-steel tube, and LTQ mass spectrometer as described previously.[24] The pressure of the nebulizer gas (molecular nitrogen) was 175 psi and the sample solution was injected at a rate of 10 $\mu L\,min^{-1}$. b) Mass spectrum showing the protonated cyclohexanone phenylhydrazone generated from the ketone and hydrazine upon ESSI. c) Mass spectrum recorded after the same mixture was passed through a coiled tube heated at 200 °C and showing the occurrence of Borsche–Drechsel cyclization at atmospheric pressure. The protonated tetrahydrocarbazole ion is observed at *m/z* 172.

carried through the heated coiled tube by molecular nitrogen (used as the sheath gas for ESSI), it is thermally activated by numerous collisions with the gas, solvent molecules, or the inside wall of the coiled tube.[24] These processes increase the internal energy of the ion and promote passage over the activation barrier of the reaction, although it is not known whether they occur in the solution (droplet) phase or in the gas phase. Collision-induced dissociation (CID) experiments on the product ion showed loss of CH_3, C_2H_4, C_3H_6, and C_4H_8, namely the same fragmentations seen for the protonated tetrahydrocarbazole generated by ESSI from the authentic compound (see Figure 1S in the Supporting Information). This fragmentation confirms the product structure and the smooth occurrence of Borsche–Drechsel cyclization under ESSI/thermal activation. Although mass spectrometry methods were used here only to generate the ionic reaction intermediate and monitor its conversion into ionic products, it could potentially be used in a preparative fashion through the method of ion soft landing.[32]

To perform the Fischer indole synthesis, a solution of the two reactants, phenylhydrazine (2 μL) and acetone (5 μL), in methanol/water (1:1 by volume, 1 mL) was analyzed by using ESSI. The acetone phenylhydrazone generated by condensation between phenylhydrazine and acetone appears as the protonated ion (*m/z* 149, Figure 2a). Another signal was observed at *m/z* 189 (Figure 2a); this corresponds to the protonated form of PhNHN=C(Me)CH=CMe$_2$ generated from the decomposition of the unstable acetone phenylhydrazone[33] through a previously unreported pathway (namely the self-addition of acetone phenylhydrazone (PhNHN=CMe$_2$) followed by loss of PhNHNH$_2$ to yield the product PhNHN=C(Me)CH=CMe$_2$; see the detailed discussion in the Supporting Information). Again in this case, thermal activation under ambient conditions drove the reaction of interest, and yielded protonated 2-methylindole (*m/z* 132, Figure 2b). This product was identified through tandem mass spectrometry, which showed the ion to fragment by the loss of CH_3 and HCN, just like the protonated molecule generated by ionization of authentic 2-methylindole (see Figure 3S-d, e in the Supporting Information). The main product ion at *m/z* 133 (Figure 2b) corresponds to protonated 2-aminoindole and is generated through thermal dissociation of the protonated ion of PhNHN=C(Me)CH=CMe$_2$ (*m/z* 189), as demonstrated by tandem MS experiments (see the detailed discussion in the Supporting Information). 2-Methylindole (*m/z* 132) was generated, as expected, by collision-

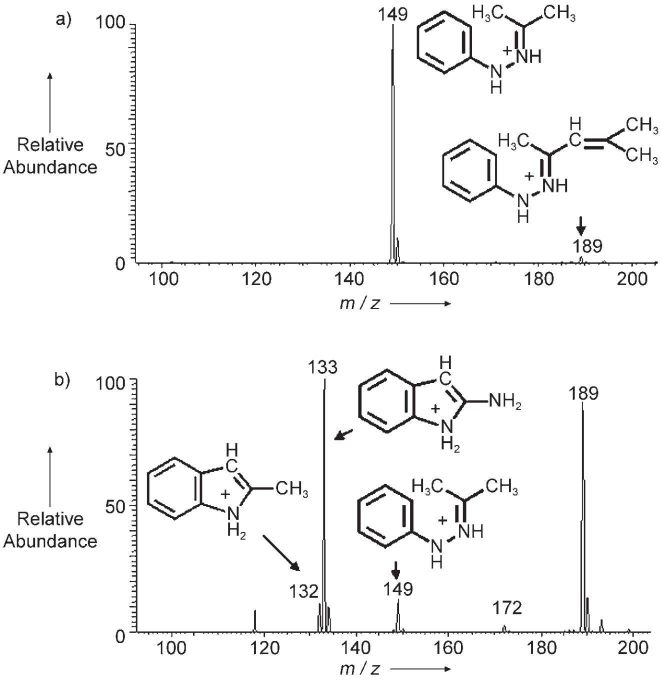


Figure 2. Mass spectra showing the ionic products formed from a methanol/water solution of phenylhydrazine and acetone: a) by ESSI alone, and b) after thermal activation at 300 °C.

induced dissociation of the ion with *m*/*z* 149, which undergoes deamination to yield this indole product (see the Supporting Information). Interestingly, protonated indole is also generated by CID of protonated PhNHN=C(Me)CH=CMe$_2$ (*m*/*z* 189), which suggests the contribution of a second reaction pathway involving this ionic intermediate (again, through thermal dissociation) to the Fisher indole reaction product (Figure 2b).

The pinacol rearrangement is the acid-catalyzed elimination of water from pinacol to yield *tert*-butyl methyl ketone. Typically the reaction involves the formation of a carbenium ion intermediate from protonated pinacol which loses water and rearranges.[34] When a solution of pinacol in methanol (0.4 mg mL^{-1}) was analyzed by using ESSI, the sodiated pinacol ion (*m*/*z* 141) was the predominant species generated (Figure 3a). Ambient-pressure thermal activation at moderate temperature (170 °C) yielded the sodiated pinacolone ion (*m*/*z* 123, Figure 3b). (The absence of the protonated ions can be accounted for by the ubiquitous nature of the sodium ion and by the fact that diols have relatively low proton affinities with relatively high sodium ion affinities.) Evidence supporting the structure of the sodiated pinacolone ion (*m*/*z* 123) is presented in Figure 2S of the Supporting Information, which shows that its dissociation behavior matches that of the sodium adduct of authentic pinacolone. Also, the fragment ion of *m*/*z* 123 generated by CID of the sodiated pinacol ion (*m*/*z* 141) has the same fragmentation pattern (see the MS^3 data in Figure 5S of the Supporting Information) as that shown in Figure 2S of the Supporting Information, thereby supporting the origin and the assignment of sodiated pinacolone (*m*/*z* 123).

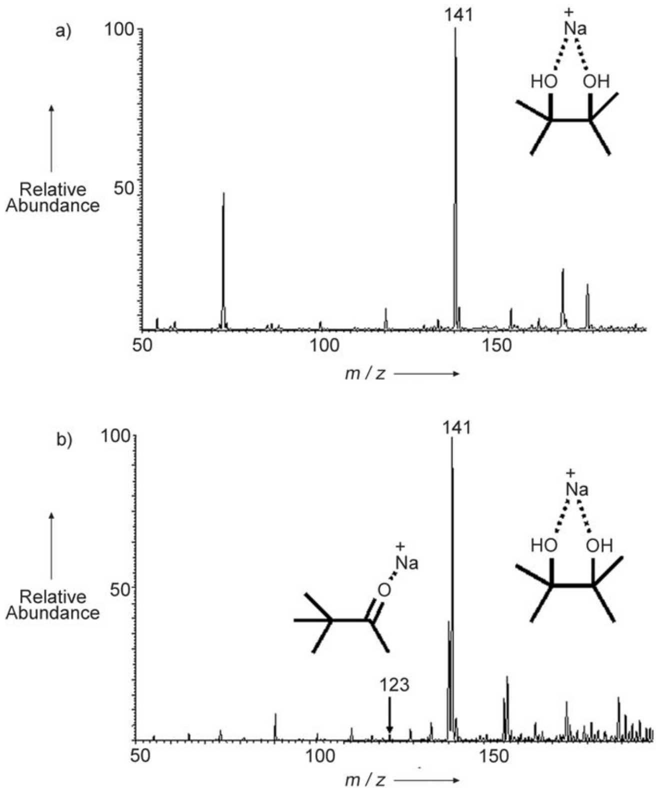
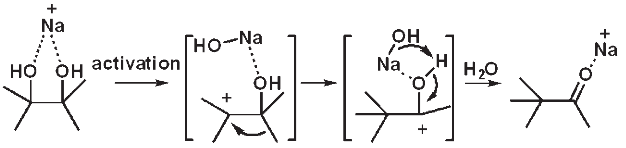


Figure 3. Mass spectra shows the ionic products formed from a solution of pinacol in methanol: a) by ESSI alone, and b) after thermal activation at 170 °C.

Mechanistically, the conversion of pinacol into pinacolone mediated by sodium is both unprecedented and intriguing, and suggests the potential of inorganic ion catalysts for this reaction. A possible mechanism for the sodium ion mediated pinacol rearrangement is proposed in Scheme 2 . Again, it is proposed that the carbenium intermediate is formed first, followed by subsequent transfer of the methyl group and loss of water to give the sodiated pinacolone.



Scheme 2. A possible mechanism for the sodium ion mediated pinacol rearrangement.

In conclusion, we have presented a novel methodology using electrosonic spray ionization as a proton source coupled with atmospheric-pressure thermal activation to promote organic reactions. A new pathway for the Fischer indole synthesis (through the protonated ion of PhNHN=C(Me)CH=CMe$_2$, *m*/*z* 189) and a novel sodium ion mediated pinacol rearrangement were revealed. The generality of the protonation/deprotonation capability of ESSI and the simplicity of the thermal activation methodology mean that this approach could find unique applications in the development of “green chemistry” pathways. Also, the conversion of ionic reaction intermediates into products by atmospheric-pressure thermal activation should be a useful adjunct to the study of ion/molecule reactions under more conventional conditions. The examples of parallel behavior between thermal activation at atmospheric pressure and collision-induced dissociation in a vacuum under conventional tandem MS conditions encourages a search for further examples that link conventional mass spectrometry with thermal processing of ionic reaction intermediates.

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