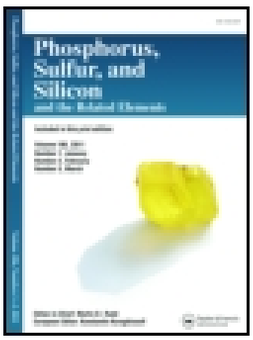

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Mechanistic insight into the thermal 1,3-chlorine migrations of *N*-chloroacetanilides under neutral conditions

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ABSTRACT

The mechanistic insight of the thermal 1,3-chlorine migration reactions of *N*-chloroacetanilides under neutral conditions has been investigated. The results indicate that the 1,3-chorine migration reaction is initiated by the radical reaction of the homocleavage of the Cl-N bond and subsequent radical combination of the Cl-C bond on the aromatic rings. The radical mechanism was verified by the thermal rearrangement of *N*-chloro-*N*-(4-methylphenyl)acetamide in cumene. After generation of hydrochloric acid in the radical mechanism, the migrations occurred through the acid-catalyzed rearrangement as well as the acid-catalyzed Orton reaction. The current results provide a comprehensive understanding on the mechanistic insights in the Orton reaction under different conditions.

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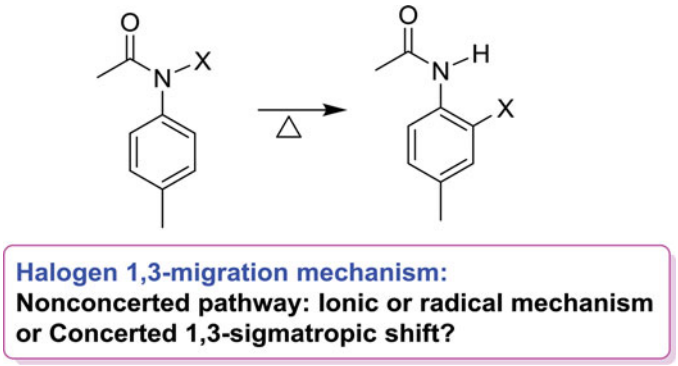
Acetamide; chloro shift; mechanism; Orton reaction; thermal rearrangement

GRAPHICAL ABSTRACT



Introduction

The 1,3-migration, also called 1,3-rearrangement, reactions are very common reactions in organic chemistry.[1–3] Recently we have been interested in heteroatom 1,3-rearrangements. We discovered the N[1,3] sigmatropic shift rearrangements in the *ortho*/*para*-semidine rearrangements and diphenyline rearrangements of *N*,*N*'-diarylhydrazines,[4–6] and the O[1,3] sigmatropic shift rearrangements in the abnormal aromatic Claisen rearrangement.[7] 1,3-Allylic sulfonyl migrations which proceed as *C*- to *C*-transfers have been found to occur by intimate ion pairs,[8,9] free radical chain addition-elimination,[10–12] and even [1,3]-sigmatropic shift mechanism.[13] The 1,3-sulfonyl migrations involving N- to C-migrations have been described in both intra- and intermolecular manners,[14–18] non-concerted processes by a crossover experiment,[19] via a four-membered sulfurane oxide intermediate.[20] The 1,3- and 1,5-sulfonyl shifts of *N*-sulfonylcarbazoles, *N*-arenesulfonylphenothiazines, and *N*-arenesulfonylphenoxazines occurred through radical mechanism under both photo and thermal conditions.[21–23]

In our continuous interest on mechanisms of 1,3-heteroatom migration reactions, we turned our attention to 1,3-halogen migrations. Several 1,3-halogen rearrangements have been observed and investigated.[24,25] The Orton reaction is a typical 1,3-halogen migration in organic chemistry.[26–28] Generally, 1,3-halogen migrations in Orton reactions occur through an ionic mechanism under acidic conditions.[29,30] However, it is still unclear how the 1,3-halohgen migration works under neutral and thermal conditions, ionic, radical, or concerted process (halo[1,3] sigmatropic shift). To get a thorough understanding on the 1,3-halogen migration in the Orton reaction under

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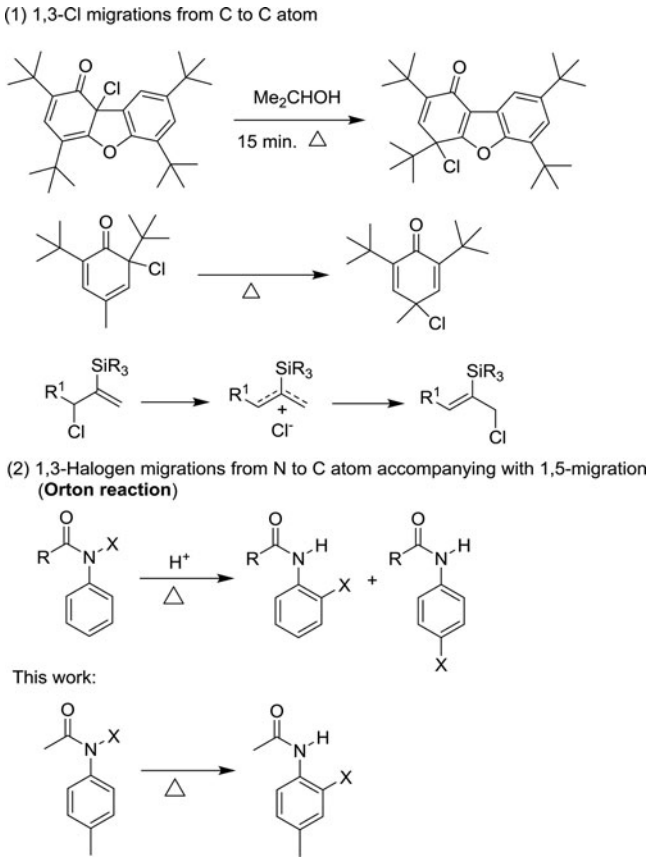


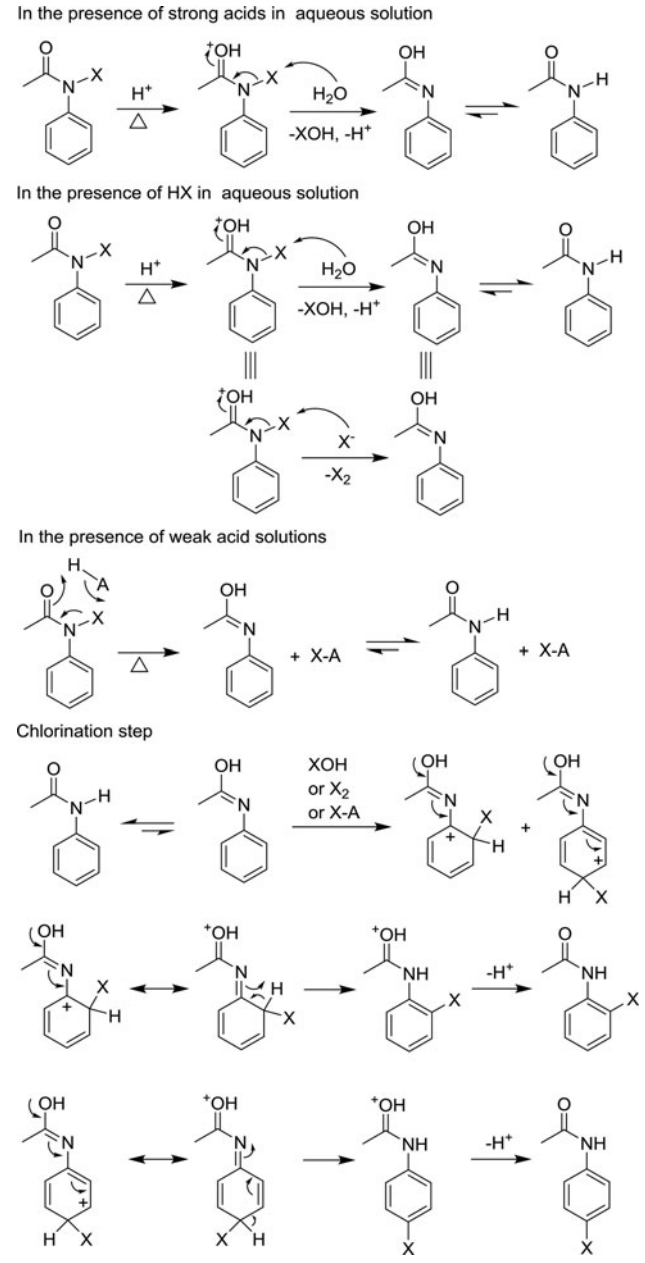
Scheme 1. 1,3-Halogen migrations.

neutral and thermal conditions, we investigated the migrations under thermal and neutral conditions (Scheme 1). Herein, we present our results on the mechanistic insight of the Orton reaction.

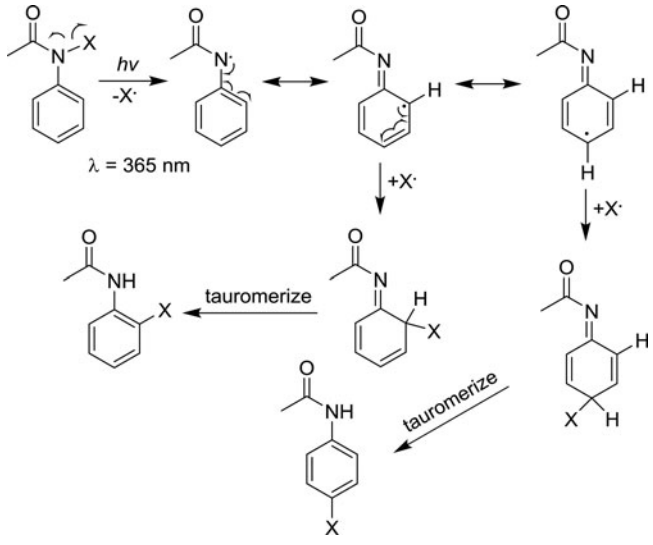
Results and discussion

The acid-catalyzed Orton reactions (Orton rearrangement) and their mechanisms have been well studied and the mechanism is suggested as an ionic mechanism.[29–31] After summarizing and reviewing the previous reported results,[29–33] we proposed different rearrangement processes in the presence of various acids (Scheme 2) and the photoinduced Orton rearrangement radical mechanism in solution phase (Scheme 3). Naumov and co-workers observed an *N*-acetyl-*N*-phenylaminyl radical and proposed a radical mechanism in the solid phase for the photoinduced Orton rearrangement.[33] However, thermal Orton rearrangement reactions under neutral conditions were previously assumed as an ionic or radical mechanism, even a concerted process,[30] but have not been carefully investigated. Because nitrogen, oxygen, and sulfur atoms can undergo concerted 1,3-sigmatropic shifts under thermal conditions,[4,5,7] we are curious whether the thermal Orton rearrangement occurs through halo[1,3] sigmatropic shift under neutral conditions (Scheme 4). After investigations on the N and O[1,3] sigmatropic shifts,[4,5,7] we hoped to verify whether the reaction mechanism in the thermal Orton rearrangement is halo[1,3] sigmatropic shift under neutral conditions.

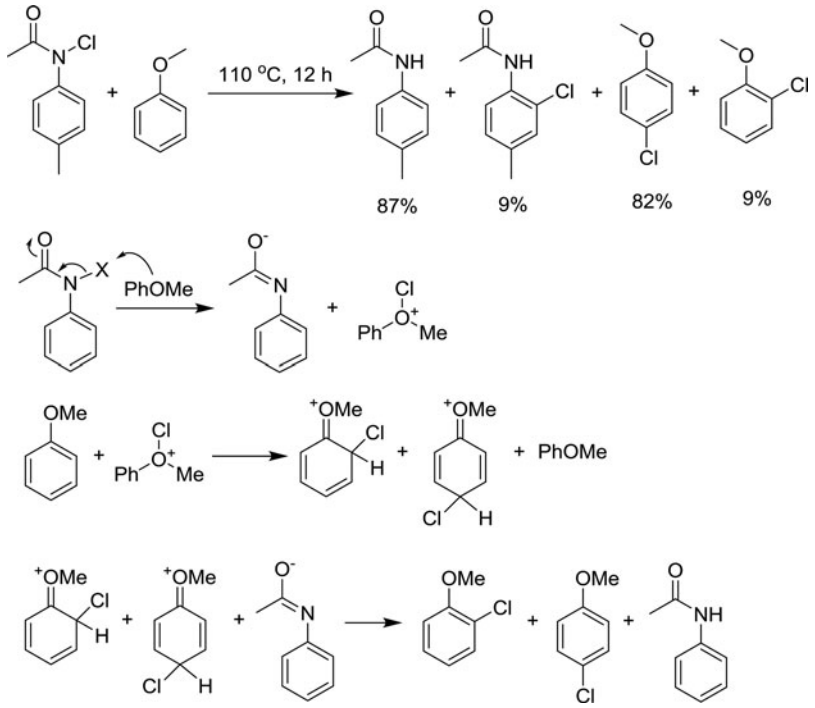
To illustrate the rearrangement mechanism of the thermal Orton reaction under neutral conditions, we designed two competitive experiments to verify whether ionic and radical mechanisms occur. (1) The thermal Orton reaction



Scheme 2. Acid-catalyzed Orton rearrangements.



Scheme 3. Photoinduced Orton rearrangement.



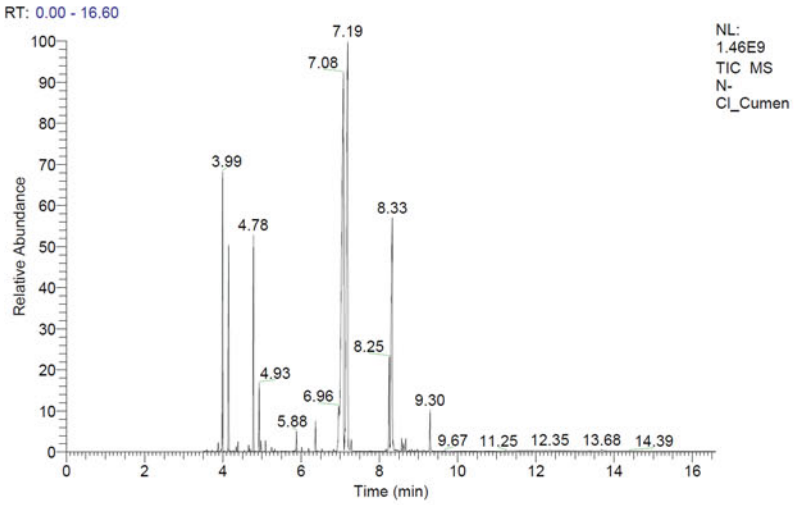
Scheme 4. Thermal Orton rearrangements under neutral conditions in nucleophilic solvent.

of *N*-chloro-*N*-(4-methylphenyl)acetamide in an electron-rich solvent anisole. If the reaction is an ionic reaction, we will observe *ortho*- and *para*-chloroanisoles and *N*-(4-methylphenyl)acetamide as major products because anisole is more electron-rich than *N*-(4-methylphenyl)acetamide. While if the reaction is a concerted Cl[1,3] sigmatropic shift, only *N*-(2-chloro-4-methylphenyl)acetamide would be observed. (2) In the thermal Orton reaction of *N*-chloro-*N*-(4-methylphenyl)acetamide in cumene as solvent, if the reaction undergoes a radical mechanism, the competitive product (1-chloro-1-methyl)ethylbenzene or its derivatives, such as (1-methyl)vinylbenzene or (1-chloromethyl)vinylbenzene, and *N*-(4-methylphenyl)acetamide would be observed. However, if the reaction is the Cl[1,3] sigmatropic shift, only *N*-(2-chloro-4-methylphenyl)acetamide would be generated.

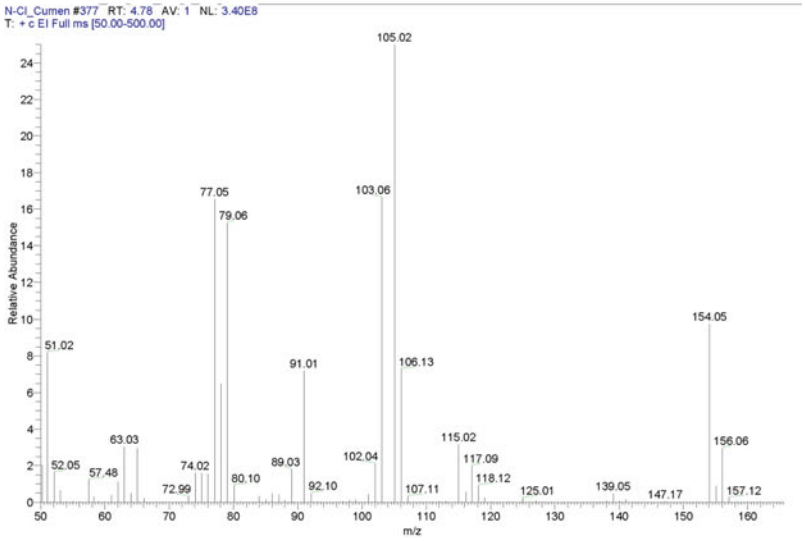
First, we conducted the thermal Orton reaction of *N*-chloro-*N*-(4-methylphenyl)acetamide in anisole and determined the reaction mixture by GC-MS. *N*-Chloro-*N*-(4-methylphenyl)acetamide disappeared during the reaction. The results indicate that *ortho*- and *para*-chloroanisoles and *N*-(4-methylphenyl)acetamide were observed as major products. 2,4- and 2,6-dichloroanisoles were also generated in small amounts, illustrating the reaction occurred through the ionic mechanism as the major process. Underwood and Dietze studied the reactions of triethylamine and *N*-chloroacetanilides and observed that triethylamine underwent nucleophilic substitution at the chlorine atom of *N*-chloroacetanilides.[34] The reported results promoted us to reconsider the function of the solvent and competitive substrate anisole. The anisole has two lone pairs of electrons on the oxygen atom. Thus, anisole serves as a nucleophile, similar to triethylamine, and occurs the nucleophilic substitution at the chlorine atom of *N*-chloro-*N*-(4-methylphenyl)acetamide to generate *O*-chloroanisolium, which is a chlorinating reagent. *O*-Chloroanisolium underwent aromatic electrophilic substitution with other anisole to give rise to the chlorinated anisole derivatives (Scheme 4). The formation mechanism of 2- and 4-chloroanisoles is also shown in Scheme 4. This is the reason why the thermal Orton rearrangement underwent the ionic mechanism in anisole as the solvent. The reaction occurred under basic conditions, or in the presence of nucleophiles, rather than neutral conditions. The results cannot rule out the concerted Cl[1,3] sigmatropic shift under thermal neutral conditions.

To exclude both acidic and basic (nucleophilic) conditions, we conducted the thermal Orton reaction of *N*-chloro-*N*-(4-methylphenyl)acetamide in cumene as the solvent and competitive substrate for the chlorination. In the reaction, both radical and ionic reactions would be observed if they exist. The GC-MS analysis results reveal that the radical substituted product (1-chloro-1-methyl)ethylbenzene and its derivative (1-chloromethyl)vinylbenzene produced from radical substitution, elimination, and further radical substitution, and *N*-(4-methylphenyl)acetamide and its chlorinated derivative *N*-(2-chloro-4-methylphenyl)acetamide were observed (Figure 1). In addition, 2- and 4-chlorocumenes were also observed in small amounts (Scheme 5) on the basis of molecular weights, isotopic peaks, and mass spectral fragments. The results indicate that the thermal Orton rearrangement undergoes the radical reaction under non-nucleophilic neutral conditions accompanying certain ionic process. After carefully considering the radical mechanism, especially radical substitution with cumene, we can rationalize the reason why the ionic chlorination, namely, aromatic electrophilic substitution, occurred as well under neutral conditions. Even under neutral conditions, after initiating the radical reaction, the competitive radical substitution occurred. In the radical substitution, acidic HCl generated. Thus, the acid (HCl)-catalyzed Orton rearrangement followed. The mechanism of the thermal rearrangement was proposed and is shown in Scheme 5. Finally, we can conclude that the thermal Orton rearrangement can be realized

(a) GC profile



(b) (1-Chloro-1-methyl)ethylbenzene



(c) (1-Chloromethyl)vinylbenzene

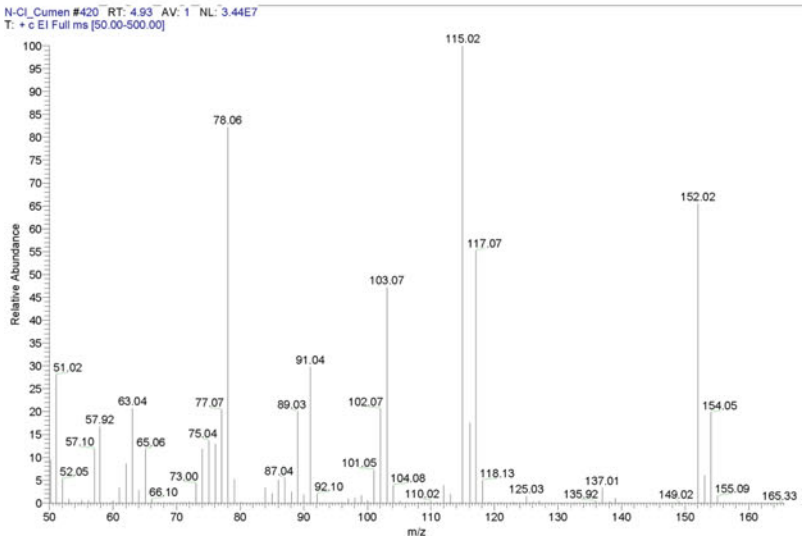
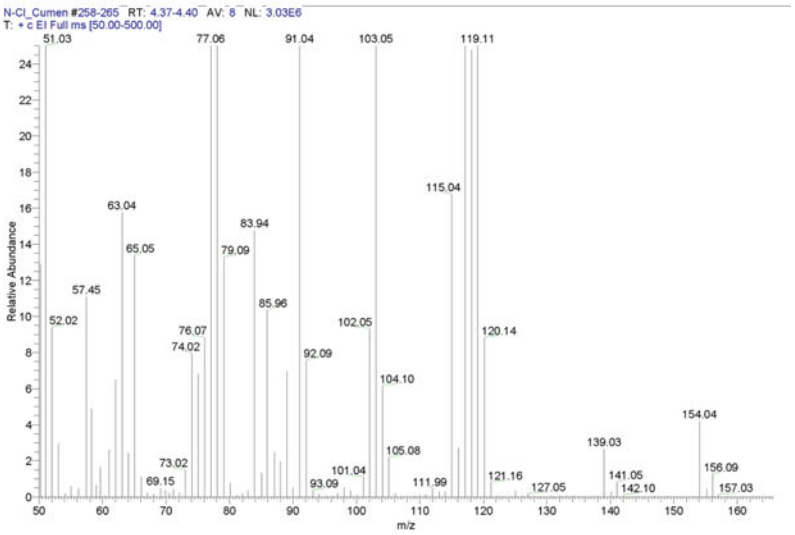
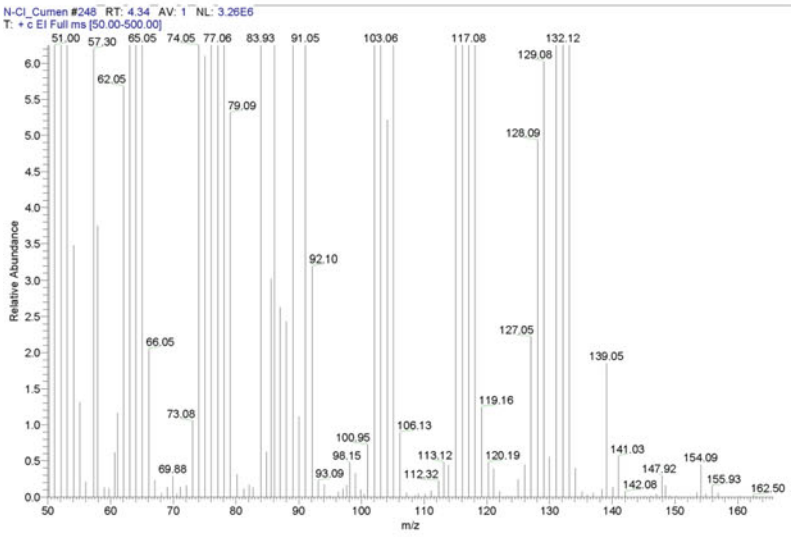


Figure 1. GC-MS analysis on the reaction mixture of thermal rearrangement of *N*-chloro-*N*-(4-methylphenyl)acetamide in cumene.

(d) 4-Chlorocumene



(e) 2-Chlorocumene



(f) *N*-(4-Methylphenyl)acetamide

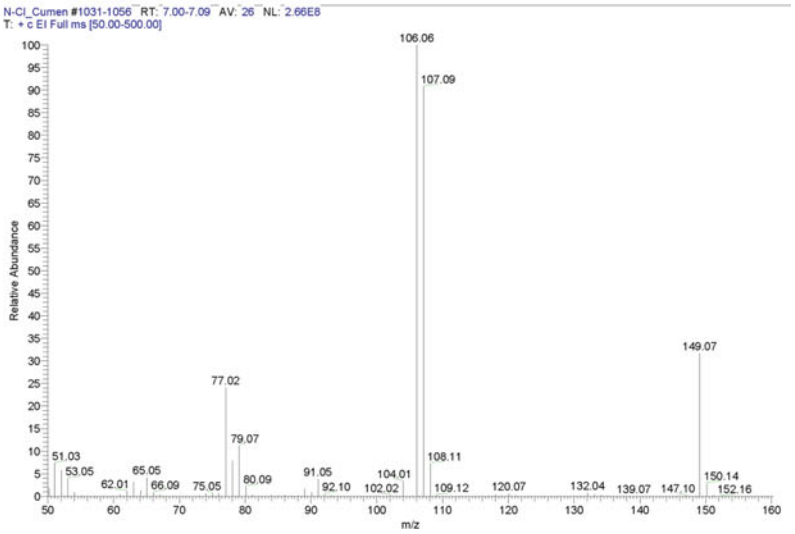


Figure 1. (Continued)

(g) *N*-Chloro-*N*-(4-methylphenyl)acetamide

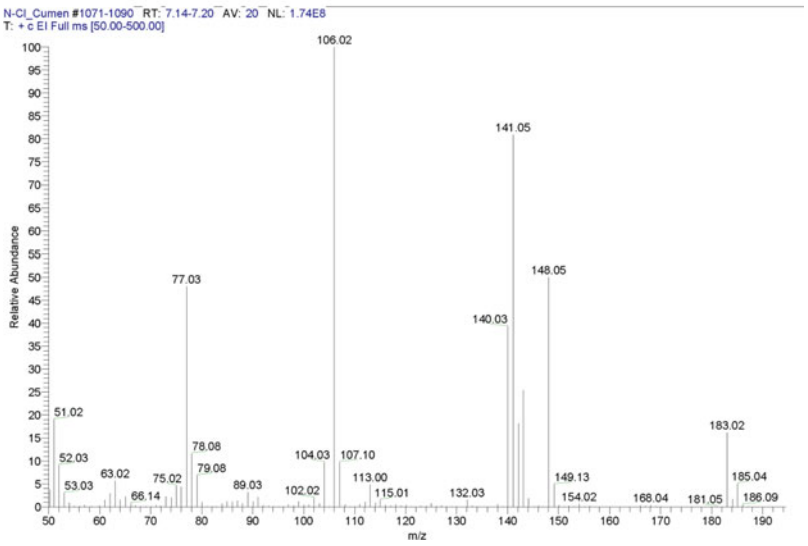
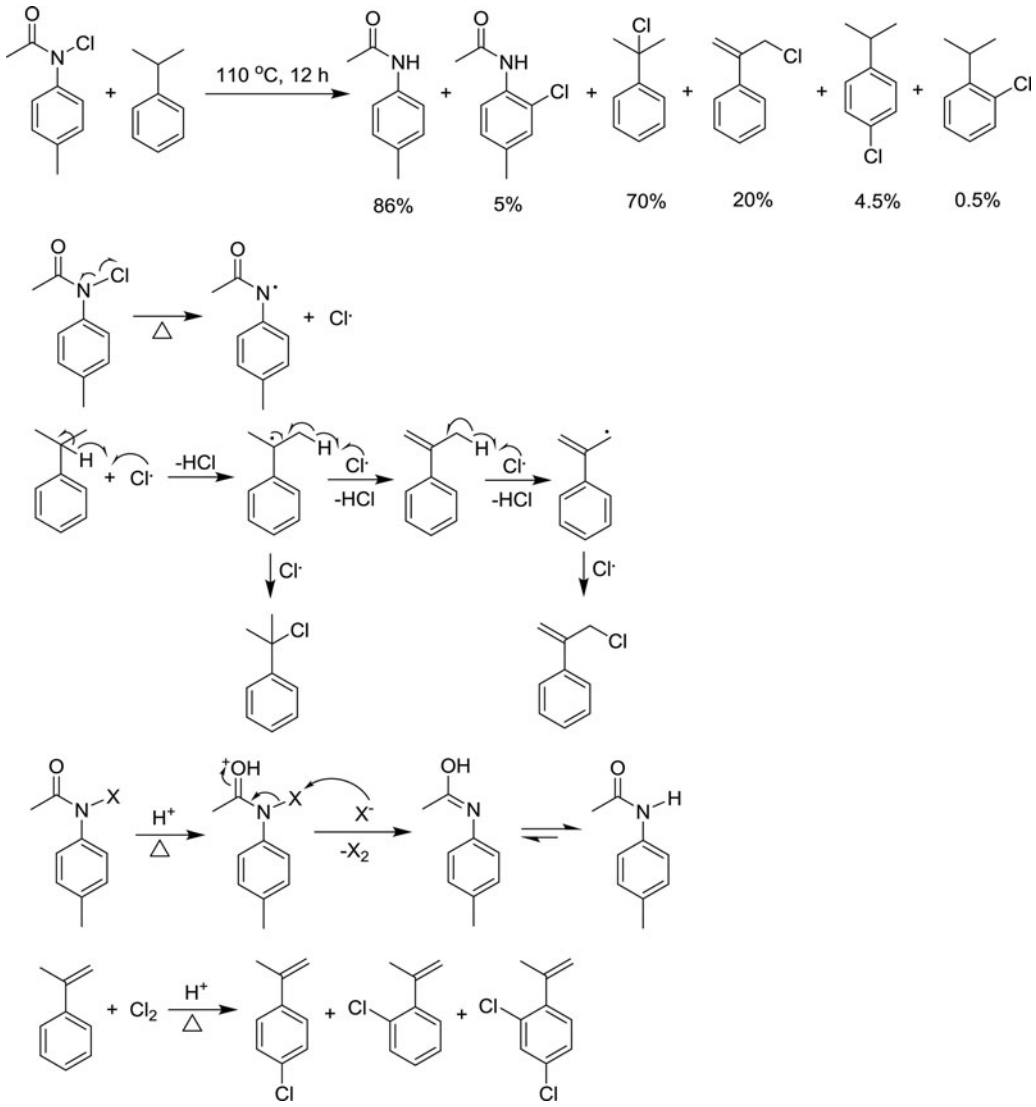


Figure 1. (Continued)



Scheme 5. Thermal Orton rearrangements under neutral conditions.

only at the beginning of the reaction under non-nucleophilic neutral conditions and then it would be accompanied by the acid-catalyzed ionic rearrangement. The current results do not provide any evidence for the concerted Cl[1,3] sigmatropic shift mechanism.

Attempts to trap the chlorine radical with TEMPO were performed, but failed, possibly due to the existence of the hydrochloric acid generated in the reaction system.

Conclusion

The thermal 1,3-chlorine migration reactions of *N*-chloro-*N*-(4-methylphenyl)acetamide under nucleophilic neutral conditions in anisole as the solvent and under non-nucleophilic neutral conditions in cumene as the solvent have been investigated. The results indicate that the thermal 1,3-chlorine migration occurs through an ionic process under nucleophilic neutral conditions. However, under non-nucleophilic neutral conditions, it is initiated by the radical homolysis of the Cl-N bond and subsequent radical combination of the Cl-C bond on the aromatic rings. After generation of hydrochloric acid in the radical substitution, the migrations occurred through the acid-catalyzed rearrangement, similar to the acid-catalyzed Orton reaction. The current results provide a comprehensive understanding on the mechanistic insights in the Orton reaction under different conditions.

Experimental

Cumene was dried over $CaCl_2$ and refluxed with sodium wire and benzophenoneas an indicator under nitrogen, and freshly distilled prior to use. Anisole was dried over $CaCl_2$ and refluxed over CaH_2 under nitrogen and freshly distilled prior to use. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard and the chemical shifts (δ) are reported in parts per million (ppm). Melting points were obtained on a melting point apparatus and are uncorrected. GC-MS measurements were carried out on GC System with a Mass Selective Detector. TLC analysis was performed on silica gel GF_{254} plates. Spots were visualized with UV light or iodine. Column chromatography was performed on silica gel (200–300 mesh) with a mixture of petroleum ether (PE) (60–90°C) and ethyl acetate (EA) as an eluent.

Synthesis of N-(4-methylphenyl)acetamide

To a solution of 4-methylaniline (5.30 g, 49.46 mmol) in dichloromethane (100 mL) was added anhydrous Na_2CO_3 (5.24 g, 49.46 mmol) under stirring at 0°C. And then acetic anhydride (7.57 g, 74.19 mmol) was added dropwise. After addition, the resulting mixture was stirred for 3 h at room temperature. TLC monitoring indicated that starting materials consumed completely. After filtration and washing solid with acetone, the solid was recrystallized from dichloromethane to afford colorless crystals 6.64 g (90%). M.p.: 153−154°C (CH_2Cl_2) (Lit.[35] 154°C).^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.13$ (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.09 (d, $J = 8.2$ Hz, 2H, ArH), 7.37 (d, $J = 8.3$ Hz, 2H, ArH), 7.60 (br, 1H, NH).

Synthesis of N-chloro-N-(4-methylphenyl)acetamide

N-Chloro-*N*-(4-methylphenyl)acetamide was prepared as colorless crystals in 70% yield by following the reported procedure.[34] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.05$ (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.23−7.28 (m, 4H, ArH).

Thermal rearrangement of N-chloro-N-(4-methylphenyl)acetamide in anisole

N-Chloro-*N*-(4-methylphenyl)acetamide (366 mg, 2 mmol) was dissolved in anisole (5 mL) in a round-bottom flask under nitrogen. After covered the flask with aluminum foil, the solution was heated at 110°C under stirring for 12 h. The reaction mixture was monitored by TLC and GC-MS. Evaporation of the solvent and purification by silica gel column chromatography afforded products *N*-(4-methylphenyl)acetamide 259 mg (87% yield), 4-chloroanisole 234 mg (82%). In addition, GC analysis of the crude reaction mixture indicated that both *N*-(2-chloro-4-methylphenyl)acetamide and 2-chloroanisole generated in 9% yield.

Thermal rearrangement of N-chloro-N-(4-methylphenyl)acetamide in cumene

N-Chloro-*N*-(4-methylphenyl)acetamide (366 mg, 2 mmol) was dissolved in cumene (5 mL) in a round-bottom flask. After covered the flask with aluminum foil, the solution was heated at 110°C under stirring for 12 h. The reaction mixture was monitored by TLC and GC-MS. Evaporation of the solvent and purification by silica gel column chromatography afforded products *N*-(4-methylphenyl)acetamide 256 mg (86% yield), 4-chlorocumene 215 mg (70% yield) and (1-chloromethyl)vinylbenzene 61 mg (20% yield). In addition, GC analysis of the crude reaction mixture indicated that *N*-(2-chloro-4-methylphenyl)acetamide, 4-chlorocumene, and 2-chlorocumene generated in 5%, 4.5%, and 0.5% yields, respectively.

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