5152 *J. Org. Chem.* **1999,** *64,* 5152−5155

Acid-Catalyzed Condensations of Ninhydrin with Aromatic Compounds. Preparation of 2,2-Diaryl-1,3-indanediones and 3-(Diarylmethylene)isobenzofuranones[1]

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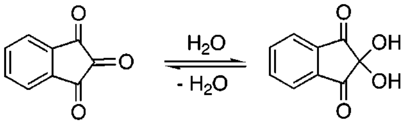
Received February 2, 1999

Ninhydrin (**1**) reacts with aromatic compounds in acid solution to give condensation products. In H_2SO_4, **1** reacts with arenes to give 2,2-diaryl-1,3-indanediones (**2a**−**f**). In superacidic triflic acid (CF_3SO_3H, TfOH), **1** reacts with arenes to give 3-(diarylmethylene)isobenzofuranones (**3a**−**e**). Products **3a**−**e** are proposed to have formed by a condensation and rearrangement involving dicationic intermediates. Benzo[*f*]ninhydrin also reacts with C_6H_6 in H_2SO_4 to give a similar condensation product.

Introduction

Ninhydrin (**1**) is a compound which was first reported in the literature in 1910.[2a] It is the stable, hydrated product of 1,2,3-indanetrione (eq 1). Ninhydrin has been a useful compound in organic chemical, biochemical, analytical, and forensic sciences.[2b] Its varied applications include the qualitative and quantitative assay for α-amino acids in bioanalytical work and the visualization of fingerprints in forensic science.



(1)

Ninhydrin, **1**

The chemistry of ninhydrin has been extensively studied. Much of the work has been directed toward the reaction of amines with ninhydrin.[2] Primary amines and α-amino acids react at the C-2 position of ninhydrin and eventually lead to the formation of a highly colored, condensation product known as Ruhemann's purple. In addition to nitrogen-based nucleophiles, the C-2 position of ninhydrin has also been found to react with sulfur-, oxygen-, and carbon-based nucleophiles.[3] Despite the highly electrophilic character of the C-2 position, little work has been done to examine the electrophilic chemistry of ninhydrin toward aromatic substrates. Ninhydrin was reported to react in high yields with phenols in acetic acid, and more recently, a Friedel−Crafts type reaction of **1** with arenes was described in which 2,2-diaryl-1,3-indanediones were prepared.[4−6]

We have been interested in the chemistry of 1,2-dicarbonyl groups and their electrophilic chemistry in triflic acid (CF_3SO_3H, TfOH). We recently reported the superacid-catalyzed condensations of isatins to 3,3-diaryloxindoles and parabanic acids to 5,5-diarylhydantoins.[7,8] Both of these studies showed that the 1,2-dicarbonyl groups form highly reactive electrophiles in superacidic triflic acid and that these electrophiles could be exploited in synthesis. In a similar respect, Owada and Shudo have studied the chemistry 1,2-diketones in triflic acid and proposed that 1,2-dicarbonyl groups are diprotonated in superacid.[9] These diprotonated intermediates are shown to exhibit superelectrophilic chemistry in electrophilic aromatic substitution reactions.[10] Given the tendency of 1,2-dicarbonyl groups to form reactive electrophiles in superacid, it seemed likely that ninhydrin (**1**) would also exhibit a protolytic activation in strong acid and superacid systems.

We report our studies of the electrophilic chemistry of ninhydrin (**1**) in strongly acidic solutions. In addition to reporting a general synthetic conversion involving **1** and an improved procedure for the preparation of 2,2-diaryl-1,3-indanediones, we also propose a mechanism for the novel, superacid-promoted rearrangement of the condensation products from **1**.

Results and Discussion

Reaction of ninhydrin (**1**) in H_2SO_4 with arenes gives products of electrophilic aromatic substitution. For ex-

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(1) Considered to be Chemistry in Superacids, Part 46. For Part 45, see Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.*, submitted.

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(6) In the earlier study (ref 5) reaction time was limited to 1 h, and only 2.2 equivalents of H_2SO_4 was used in the conversion. Under the more acidic conditions and longer reaction times used in the our study, the condensation reaction goes to completion to give **2a** and no monoarylated product.

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(8) Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1998**, 918.

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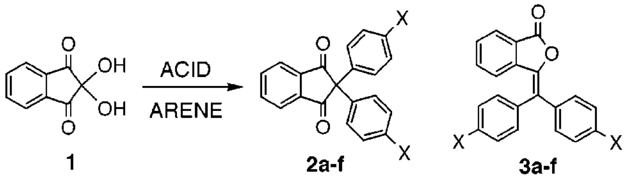
Table 1. Products from the Reaction of Ninhydrin (1) with Arenes in H_2SO_4 or CF_3SO_3H

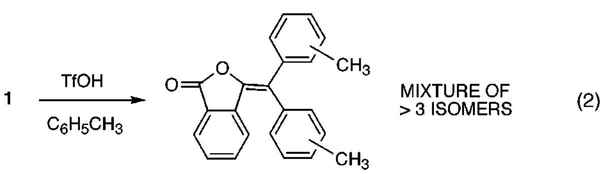


acid	arene	product	% yield[a]
H_2SO_4	C_6H_6	**2a**, X = H	96
	C_6H_5F	**2b**, X = F	94
	C_6H_5Cl	**2c**, X = Cl	97
	C_6H_5Br	**2d**, X = Br	97
	C_6H_5I	**2e**, X = I	86
	$C_6H_5CH_3$	**2f**, X = CH_3	91
CF_3SO_3H	C_6H_6	**3a**, X = H	98
	C_6H_5F	**3b**, X = F	77
	C_6H_5Cl	**3c**, X = Cl	81
	C_6H_5Br	**3d**, X = Br	91
	C_6H_5I	**3e**, X = I	91
	$C_6H_5CH_3$	**3f**, X = CH_3	94[b]

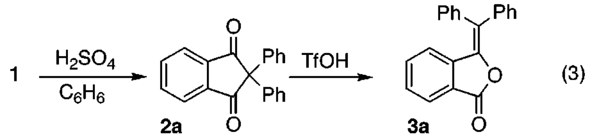
[a] Isolated yields. [b] Prepared from the reaction **2f** and TfOH (eq 5).

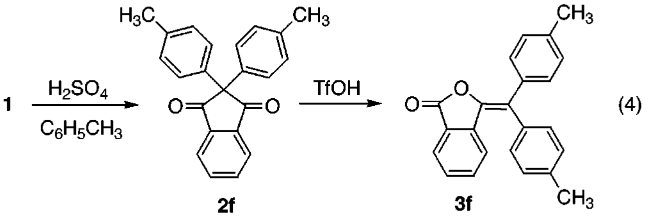
ample, **1** reacts with benzene in H_2SO_4 to provide 2,2-diphenyl-1,3-indanedione (**2a**) in high yield (Table 1). In an earlier report,[5] a significant quantity of the monoarylated product was formed; however, no monoarylated product was detected in our study.[6] The product **2a** is formed as the results of a hydroxyalkylation reaction involving the hydrated carbonyl group at the C-2 position.[11] Like the chemistry involving amines, the C-2 position of ninhydrin is the most reactive position in these electrophilic aromatic substitution reactions. With substituted arenes, the condensation products **2b**−**f** are produced regioselectively from **1** in H_2SO_4. Chorobenzene is a moderately deactivated arene due to the electron-withdrawing effect of the chlorine substituent, and because of this deactivation, weak electrophiles do not react with chlorobenzene in substitution reactions.[12] Nevertheless, **1** reacts with chlorobenzene in high yield. These results indicate that in strongly acidic solution, **1** forms a reactive electrophilic species.

When **1** is reacted with C_6H_6 in the superacidic triflic acid (TfOH), a different product is obtained in high yield. The product from **1**, C_6H_6, and TfOH was determined on the basis of mass spectrum and NMR data to be the isobenzofuranone derivative **3a** (Table 1). The identity of the product was further confirmed by an X-ray crystal structure. If substituted arenes are reacted with **1** in TfOH, similar products are formed. Thus, reaction of **1** with C_6H_5F, C_6H_5Cl, C_6H_5Br, or C_6H_5I produces **3b**, **3c**, **3d**, and **3e**, respectively (Table 1). In all cases, **3b**−**e** are produced regioselectively. Like the conversions in H_2SO_4, ^1H NMR analysis of the crude product mixtures revealed that electrophilic attack occurred exclusively at the *para* position of the halogen-substituted benzenes. Reaction of **1** with toluene results in similar condensation; however, several regioisomers are formed (eq 2).



From the results described above, two types of general acid-catalyzed reactions of ninhydrin (**1**) with arenes have become apparent: condensation of **1** in H_2SO_4 produces 2,2-diaryl-1,3-indanediones **2a**−**f** and condensation of **1** in TfOH produces the isobenzofuranone derivatives **3a**−**e**. In considering the mechanisms for these two reaction pathways for ninhydrin, the condensation products **2a**−**f** are clearly the result of an acid-catalyzed hydroxyalkylation reaction involving the hydrated carbonyl group at the C-2 position of **1**.[11] The mechanism of product formation is less obvious for the products **3a**−**e** in the superacidic reactions. When **2a** was isolated from the H_2SO_4-induced conversion and then reacted with TfOH, product **3a** is formed (eq 3). This result is in contrast to an earlier report that **2a** decomposes to benzophenone and other indentified products in TfOH.[5] Product **2f** is formed regioselectively from **1** and toluene in H_2SO_4. Similarly, the reaction of **2f** in TfOH generates **3f** through a rearrangement which occurs with complete retention of the regiochemistry at the *p*-tolyl groups (eq 4). Given these observations, the mechanism proposed for the conversion of **1** to **3a** is described in Scheme 1.





Protonation of **1** is followed by elimination of water to produce the oxonium ion **4**. In superacidic media, cation **4** may be in equilibrium with dication **5**. Given that **1** reacts regioselectively with toluene in H_2SO_4 (eq 2) but with poor regioselectivity with toluene in the superacid (eq 3), this suggests that TfOH generates a more reactive electrophile from **1** than does H_2SO_4. TfOH ($H_o = -14.1$) is 100 times more acidic than H_2SO_4 (anhydrous, $H_o = -12$) and thus may be capable of forming the dication **5** as a superelectrophilic intermediate.[13] Condensation reaction steps lead to **6**, which yields **2a** as the product of the H_2SO_4 induced reactions, but which gives the rearrangement product **3a** in TfOH. Dication **7** is formed by protonation of **6**, and this dication undergoes ring-opening, bond rotation, and ring-closure to give **3a**.

There may be several contributing factors which cause the protosolvated dication **7** to undergo the proposed rearrangement. Diprotonation of the carbonyl group gives an accumulation of positive charge, and ring-opening would serve to spread out the positive charge between

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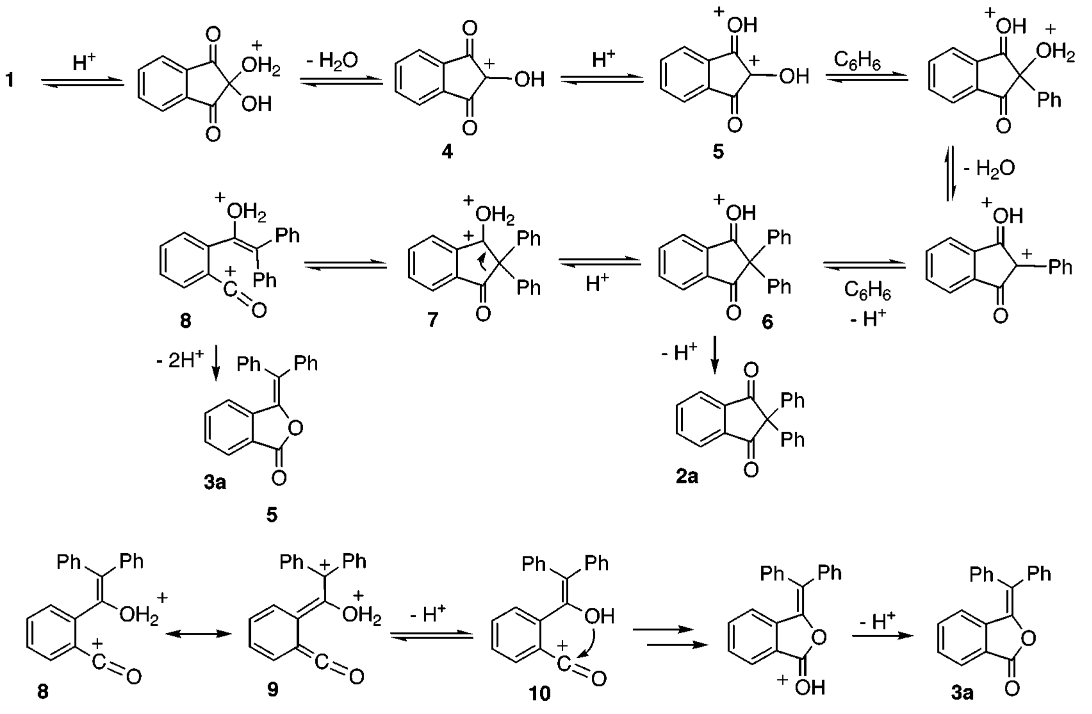
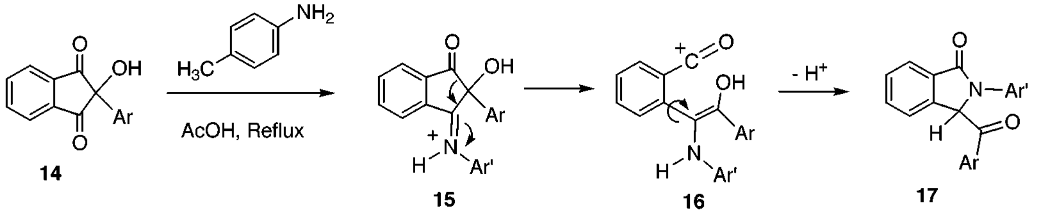
(11) Olah, G. A. *Friedel−Crafts and Related Reactions*; Wiley: New York, 1964; Vol 2, pp 597−640.

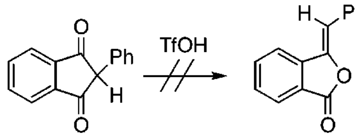
Scheme 1



Scheme 2



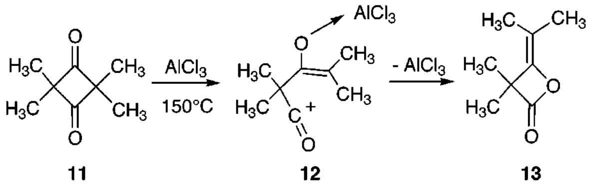
an acyl cation and a protonated enol group (**8**). Moreover, the acyl cation is in conjugation with the diphenylmethylene group as shown by resonance structure **9**. This stabilizing effect of the *gem*-diphenyl group may be an important aspect in the rearrangement,[14] because when 2-phenyl-1,3-indanedione is reacted in TfOH, no rearrangement is observed and the starting material is recovered quantitatively (eq 5).



(5)

Another important factor in this conversion may be the protolytic solvation of rearrangement product itself in the acid. Protolytic product solvation can be an important driving force in acid-catalyzed reactions.[15]

At least two similar conversion have been reported in the literature. When diketone **11** is reacted with an excess of $AlCl_3$, rearrangement occurs to give a high yield of product **13** (eq 6).[16] Presumably, this occurs through a ring-opening step to give an intermediate like **12**. Another similar reaction involves the ninhydrin product **14**.[4] When **14** is reacted with 4-methylaniline in refluxing acetic acid, rearrangement product **17** is produced (Scheme 2). Although no mechanism was proposed for the conversion, it is similar to the formation of **3a** from **1**. For example, **14** could form the iminium ion **15**. Ring-opening could generate the acyl cation which then leads to product **17** from a ring-closure and tautomerization reaction steps.



(6)

In addition to the studies of **1**, the electrophilic chemistry of benzo[*f*]ninhydrin (**18**) was also examined. When **18** is reacted with C_6H_6 in H_2SO_4, the expected condensation product **19** is formed in high yield (eq 7). However when **18** is reacted with C_6H_6 in TfOH, the expected rearrangement product is not formed as the major product, but instead a complex product mixture is produced.

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[12] March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; Chapter 9.

[13] (a) Saito, S.; Saito, S.-i.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39*, 2718. (b) Olah, G. A., Prakash, G. K. S., Sommer, J. In *Superacids*; Wiley: New York, 1985.

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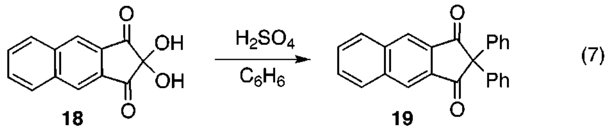
[15] (a) Olah, G. A.; Laali, K.; Farooq, O. *J. Org. Chem.* **1985**, *50*, 1483. (b) Olah, G. A.; Kuhn, S. J. In *Friedel−Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley: New York, 1964; Vol. 3, Chapter 38.

[16] Hasek, R. H.; Clark, R. D.; Mayberry, G. L. In *Oganic Syntheses*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Coll. Vol. 5, p 456.



(7)

Conclusion

We have found that ninhydrin (**1**) forms highly reactive, electrophilic species from acidic solution. Ninhydrin reacts at the hydrated carbonyl (C-2 position) and condenses with aromatic compounds in high yields. From H_2SO_4, the condensation of **1** provides 2,2-diarylindanediones (**2a**−**f**), and from TfOH, the condensation and subsequent rearrangement gives 3-(diarylmethylene)-isobenzofuranones (**3a**−**e**). The results suggest diprotonated, superelectrophilic species are intermediates in the superacid-catalyzed conversions. In accord with results from 1,2-dicarbonyl compounds, these results indicate that 1,2,3-tricarbonyl groups also generate reactive electrophiles in acidic media and that these electrophilic reactions may be exploited in synthesis.

Experimental Section

^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz. High-resolution mass spectra were recorded at the Southern California Mass Spectrometry Facility, University of California, Riverside. GCMS spectra were recorded from a gas chromatograph fitted with a DB-5 capillary column and electron impact MS detector. Column chromatography was done with Merck silica gel (grade 9385) according to standard procedures.[14] Triflic acid was obtained from 3M and distilled prior to use. Concentrated sulfuric acid was obtained from Aldrich and used as received. Benzene was dried over Na and distilled. Ninhydrin was obtained from Aldrich and used as received. Reactions were done under a dry, N_2 atmosphere.

General Procedure for the Synthesis of 2,2-Diaryl-1,3-indanediones (2a−f) and Product 5. Ninhydrin (1.00 g, 5.6 mmol) is combined with 2 mL of benzene (or other arene) and 10 mL of concentrated H_2SO_4. The mixture is stirred at 25 °C for 8 h and then poured over 10−20 g of ice. The product is extracted into $CHCl_3$, and the organic phase is washed twice with water, twice with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting white solid (1.60 g, 5.4 mmol, 96%) can be further purified by recrystallization from $CHCl_3$ to give **2,2-diphenyl-1,3-indanedione (2a):** colorless crystals, mp 123−125 °C. ^{1}H NMR ($CDCl_3$) δ 7.27−7.34 (m, 10H), 7.91 (m, 2H), 8.1 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 67.6, 124.1, 127.8, 128.6, 128.8, 136.2, 138.1, 141.6, 199.7. IR (NaCl, thin film) 3000 cm^{-1}, 1710, 1480, 1205, 740. HRMS *m*/*e* calcd for $C_{21}H_{14}O_2$ (M^+) 298.0994, found 298.0983.

General Procedure for the Synthesis of 3-(Diarylmethylene)isobenzofuranones (3a−e). Ninhydrin (0.4659 g, 2.62 mmol) is combined with 2 mL of benzene (or other arene), and 5 mL of triflic acid is added. The mixture is stirred at 25 °C for 8 h and then poured over 10−20 g of ice. The product is extracted into $CHCl_3$, and the organic phase is washed twice with water, twice with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting white solid (0.7634 g, 2.56 mmol, 98%) can be further purified by recrystallization from C_6H_6 to give **3-(diphenylmethylene)isobenzofuranone (3a):** colorless crystals, mp 159−162 °C. ^{1}H NMR ($CDCl_3$) δ 6.30 (d, J = 7.8 Hz, 1H), 7.30−7.46 (m, 8H), 7.51−7.58 (m, 4H), 7.91 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 123.6, 124.9, 125.2, 128.1, 128.2, 128.7, 129.3, 129.4, 130.4, 130.5, 133.9, 137.4, 137.6, 139.6, 167.1. IR (NaCl, thin film) 3050 cm^{-1}, 1780, 1095, 1000, 750. HRMS *m*/*e* calcd for $C_{21}H_{14}O_2$ (M^+) 298.0994, found 298.0991.

Acknowledgment. The support of the NIH through an MBRS Grant (D.A.K.; SO6GM53933-0251) and the NSF (G.A.O) and the Loker Hydrocarbon Research Institute is gratefully aknowledged.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2a** and **3a**; experimental procedures and spectroscopic data for compounds **2b**−**f**, **19**, **3b**−**f**; X-ray structure and data for compound **3a** including tables of atomic coordinates, bond lengths, and bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990197H