

Insight into the Hard–Soft Acid–Base Properties of Differently Substituted Phenylhydrazines in Reactions with Dimethyl Carbonate[†]

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Following the preliminary studies on the reactivity of the ambident nucleophile phenylhydrazine with dimethyl carbonate, investigations involving *para*-substituted phenylhydrazines were carried out in order to probe differences in the reactivity within this class of nucleophile. Phenylhydrazines substituted by electron withdrawing or donating substituents showed an increase in reactivity of the phenylhydrazine toward dimethyl carbonate. Under the basic conditions used, all phenylhydrazines displayed hard nucleophilicity, signifying that *para*-substitution on the phenyl ring has little effect on the hard–soft behavior of this class of nucleophile. This conclusion fits well within the results previously obtained using other *para*-substituted nucleophiles, i.e., phenols.

Introduction

The hard–soft acid–base (HSAB) theory was introduced by Pearson as a generalization to explain the affinity of both inorganic and organic species toward each other. Simplistically, the theory states that “hard” acids like “hard” bases and the like for “soft” acids for “soft” bases. Lewis acids and bases are categorized using the following: hard acids possess an acceptor atom of high positive charge and small size and do not have easily excited outer electrons; soft acids possess an acceptor atom of low positive charge and large size and have several easily excited outer electrons; hard bases possess a donor atom of low polarizability and high electronegativity and are hard to oxidize; soft bases possess a donor atom of high polarizability and low electronegativity and are easily oxidized. Notably, there are borderline exceptions. In an inorganic sense, this theory is used to describe the complexation of metals and/or metal cations with neutral ligands and/or anions. However, as proposed by Pearson, the theory can also be used in organic chemistry, hence, used to predict/explain organic reactions.¹

In organic chemistry, the theory has been used to explain numerous organic reactions.² Recently, our group has benefited from the HSAB theory, using it to explain organic reactions involving dimethyl carbonate (DMC) as an ambident electrophile (Figure 1).³ The presence of two nonequivalent electrophilic centers, the carbonyl and methyl moieties, make it possible for nucleophiles to undergo methylation or carboxylation (Scheme 1). Discrimination of either reaction is possible due to the difference in hard–soft acid characteristics of the two centers. The central carbon, due to sp² hybridization, results in a greater positive charge of the carbon atom, making it a harder center. The two methyl groups on the other hand are the softer electrophilic centers, owing to the acceptor atom having an sp³ orbital and a saturated carbon atom, which has a weaker positive charge.³ Therefore, in an extension of Pearson's HSAB theory, it is possible to say that harder nucleophiles in a reaction with

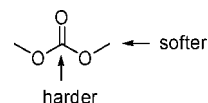


Figure 1. Dimethyl carbonate and its electrophilic centers.

SCHEME 1: (1) Carboxymethylation and (2) Methylation Reactions



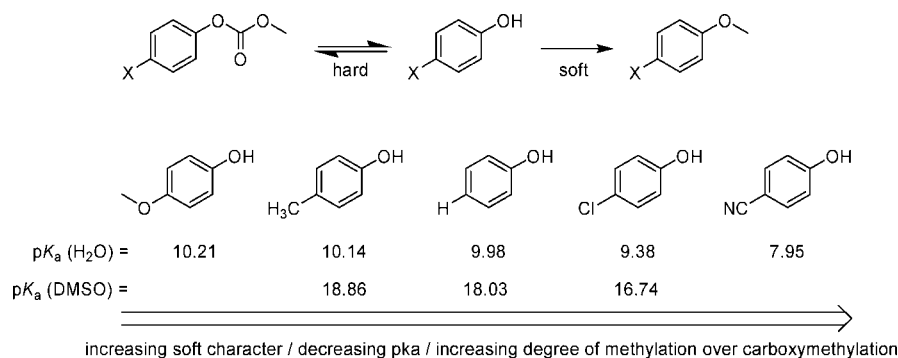
DMC will undergo carboxymethylation (hard reaction, Scheme 1, reaction 1), while softer nucleophiles will undergo methylation (soft reaction, Scheme 1, reaction 2). This concept was supported in a recent report where, within the same class of nucleophiles, the difference in hard–soft nucleophilicity was observed.

Various *para*-substituted phenols were reacted with DMC under basic conditions.³ It was observed that phenols with an electron withdrawing group (EWG) produced higher ratios of methylated product (soft reaction) compared to carboxymethylated product (hard reaction) than did phenols with electron donating groups (EDG), as shown in Scheme 2. This follows the description of Pearson for soft and hard bases, as an EWG would make the phenolic oxygen more polarizable, making it a softer donor atom. Contrarily, an EDG would decrease the polarizability of the donor atom, making the phenolic oxygen a harder donor atom. In this case, pK_a can be used directly to validate this trend because it is a direct measure related to the polarizability of the phenolic oxygen (Scheme 2).

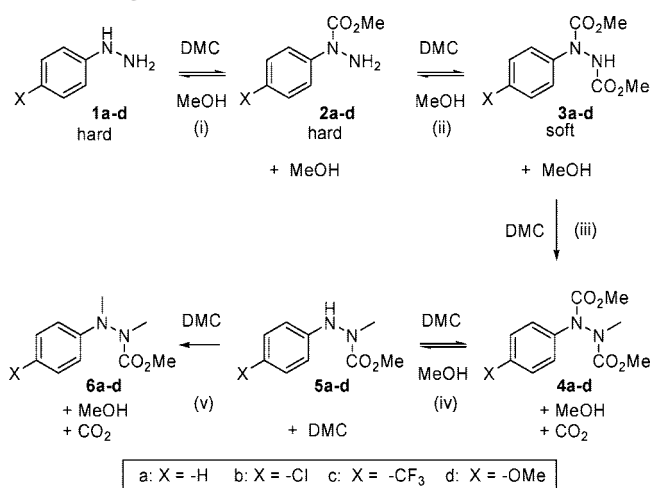
As was investigated for substituted phenols, we wished to similarly investigate another class of molecules whose Brønsted acidity could be affected by *para*-substitution. Recently, we reported the reaction of the ambident nucleophile phenylhydrazine (**1a**) with DMC.⁵ In the presence of a strong base at reflux temperature, the phenylhydrazine moiety underwent many transformations, as shown in Scheme 3 (X = H).⁵ On the basis of the pK_a values of the acid (phenylhydrazine) and the conjugate acid (protonated alkoxide base), the first reaction that

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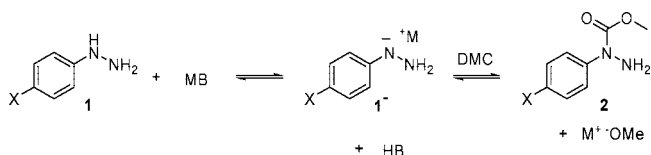
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SCHEME 2: Difference in HSAB Activity of Various Substituted Phenols⁴

SCHEME 3: Reaction of Phenyl Hydrazine Moiety with DMC Using Base



SCHEME 4: Deprotonation of Phenyl Hydrazine with a Base and Carboxymethylation



occurs is the deprotonation of the more acidic phenyl substituted nitrogen (Scheme 4).⁶ The resulting anion, a hard nucleophile, then attacks the hard center of DMC, to produce carbazate **2a** (overall reaction, Scheme 3, step i). The substitution of **N-1** with an EWG is important for the activation of **N-2** in the successive carboxymethylation, as it reduces the pK_a of **N-2** (Scheme 3, step ii). Both **1a** and **2a** are hard nucleophiles. This is because the relevant donor atoms are not readily polarizable, and thus require a strong base in order to activate them.

On the contrary, **N-2** of carbazate **3** is a soft nucleophilic center. The carboxymethyl group is able to stabilize a negative charge on the nitrogen donor, significantly lowering its pK_a and making **N-2** highly polarizable and therefore a soft base. Consequently, the anion formed *via* deprotonation attacks the soft center of DMC, leading to **4**, by the nonreversible methylation reaction (Scheme 3, step iii). The last of the more prominent reactions is the decarboxymethylation reaction, or methanolysis, at **N-1** (Scheme 3, step iv). Methanol produced in the reaction attacks the carbonyl center at **N-1** of **4**, resulting in the formation of carbazate **5** and a molecule of DMC. The anion of carbazate **5** is the leaving group in the methanolysis reaction and is stabilized by both the phenyl ring and the carboxymethyl group on the adjacent **N-2**.

Although the reaction of phenylhydrazine (**1a**) with DMC is well understood, we thought it ideal to treat it similarly to those of the phenols, so as to investigate substituted phenylhydrazines. With substitution in the *para*-substitution, we would be able to not only investigate its effect on the first reaction but also the subsequent reactions, i.e., to gauge if there is any change in hard–soft basicity of the two nitrogens. In this paper, we report the effects that various substituents have on the phenylhydrazine moiety, throughout the reaction pathway, and we provide further information toward a more comprehensive understanding of the HSAB theory and also support the mechanism of the reaction with phenylhydrazine.

Experimental Section

Procedure for a Typical Reaction of 1b–d with DMC and Base at Ambient Temperature. To a round-bottom flask containing a stirring solution of 1 equiv of the phenylhydrazine and 1 equiv of *n*-decane (as internal standard) in 40 equiv of dimethyl carbonate was added 1 equiv of either NaOMe or KO-*t*-Bu. The reaction was analyzed periodically by taking a sample of 0.2 mL of the reaction mixture (suspension) and diluting with 1 mL of diethyl ether, with a wash using 1 mL of distilled water. The organic layer was submitted for GC/MS analysis.

Procedure for a Typical Reaction of 1b–d with DMC and NaOMe at Reflux Temperature. A round-bottom flask containing a stirring solution of 1 equiv of the phenylhydrazine and 1 equiv of *n*-decane (as internal standard) in 40 equiv of dimethyl carbonate (or as stated otherwise) was heated to reflux using a water jacketed condenser. Once the reaction reached reflux temperatures, a base, either NaOMe or KO-*t*-Bu, was added. The reaction was analyzed periodically by taking a sample of 0.2 mL of the reaction mixture (suspension) and diluting with 1 mL of diethyl ether, with a wash using 1 mL of distilled water. The organic layer was submitted for GC/MS analysis.

Results and Discussion

In this paper, we document the reaction of different *para*-substituted phenylhydrazines in DMC under basic conditions. The aim of the present work is to determine the effect that different *para*-substituents have on the reactivity and the hard–soft basicity of the phenylhydrazine moiety, using the pK_a of the substituted phenyl hydrazine as a measure of polarizability.

The phenylhydrazines selected for this investigation were *para*-trifluoromethyl, chloro and methoxy.⁷ Initially, the commercially available phenylhydrazine hydrochloride salts were used with an extra equivalent of base. However, due to uneven neutralization of the salts, there was undiscernible starting times,

TABLE 1: Reaction of Substituted Phenylhydrazines 1b–d in DMC at Room Temperature with Base

entry	X =	base	time (min)	conversion to 2 (%)	other products (%)
1	–CF ₃	NaOMe	15	0	0
2	–CF ₃		40	68	0
3	–CF ₃		70	70	0
4	–CF ₃		110	79	0
5	–CF ₃		19 h	84	0
6	–CF ₃	KO– <i>t</i> -Bu	2	78	0
7	–CF ₃		15	80	0
8	–CF ₃		40	83	0
9	–Cl	NaOMe	15	0	0
10	–Cl		40	18	0
11	–Cl		70	78	3 (3b)
12	–Cl		110	88	5 (3b)
13	–Cl		160	92	6 (3b)
14	–Cl	KO– <i>t</i> -Bu	2	>99	0
15	–Cl		15	>99	0
16	–OMe	NaOMe	15	0	0
17	–OMe		40	26	0
18	–OMe		70	85	5 (3d)
19	–OMe		110	89	10 (3d)
20	–OMe		160	84	11 (3d), 4 (4d)
21	–OMe	KO– <i>t</i> -Bu	2	66	0
22	–OMe		15	>99	0

especially for the reactions at room temperature. Ultimately, the free base hydrazines, obtained by neutralization, were used in the monitored reactions.

Reactions at Ambient Temperature. The carboxymethylation of phenylhydrazine (**1a**), with 1 equiv of KO–*t*-Bu and 40 equiv of DMC, occurred exclusively at **N-1**, at room temperature.⁵ The reaction with NaOMe did not proceed. It was proposed that the reaction occurred solely at **N-1** due to its relatively low pK_a ; i.e., deprotonation occurs, and the resulting anion **1[–]** attacks DMC to produce the carboxymethylated species **2** (Scheme 4). The conjugate acids for both [–]O–*t*-Bu and [–]OMe have pK_a 's of 32.2 and 29.0, respectively, while phenylhydrazine has a pK_a of 28.8 (all in DMSO).⁶ Both are capable of deprotonating phenylhydrazine; however, under the reaction conditions, only KO–*t*-Bu promoted the carboxymethylation reaction. With KO–*t*-Bu, carboxymethylation occurred after 2 min, while, with NaOMe, no reaction occurred within 2 h. Conceivably, the stronger base produces more of the phenylhydrazine anion **1[–]**, increasing the reactivity of the substrate with DMC (Scheme 4). Therefore, a sufficiently more acidic **N-1** moiety, i.e., a phenylhydrazine substituted with an EWG on the aryl ring, should be activated by a weaker base such as NaOMe. Similarly, deactivation should occur with a less acidic **N-1** moiety, i.e., when an EDG is present.

As hypothesized, carboxymethylation occurred when NaOMe was used with phenylhydrazines bearing and EWG in the *para*-position, i.e., chloro and trifluoromethyl (Table 1, entries 1–15). The resultant lower pK_a , 27.2 for **1b** and 25.7 for **1c** in DMSO, allows for a more facile deprotonation.⁶ No methylation was observed in either case, although extra stabilization by the EWGs should have softened the nucleophilicity of the phenylhydrazine moiety.

When KO–*t*-Bu was used, the reactions proceeded much more rapidly. The stronger base produces more of the deprotonated hydrazine **1[–]**, allowing a more facile reaction with DMC. In the case of 4-trifluoromethylphenylhydrazine (**1c**), however, the reaction did not go to completion (Table 1, entries 1–8). This occurred to the same degree with both KO–*t*-Bu and NaOMe. Presumably, the equilibrium reaction favors the starting materials more when a greater EWG is used. In fact,

the methanolysis reaction that produces the phenylhydrazine **1**, from carbazate **2** and methanol (produced from the carboxymethylation), would occur more readily with the F₃C substituent. The leaving group, **1c[–]**, would be better stabilized by the electron withdrawing F₃C substituent, therefore promoting the reverse equilibrium reaction (Scheme 4).

On the other hand, the reaction with 4-methoxyphenylhydrazine (**1d**) was quite surprising. It was originally thought that the electron donating effect of the methoxy group would increase the pK_a at **N-1**, therefore making the hydrazine **1d** even less active than the parent phenylhydrazine (**1a**).⁸ However, as observed in the reaction of 4-methoxyphenylhydrazine (**1d**) with NaOMe as the base (Table 1, entries 14–22), carboxymethylation occurred readily, whereas the reaction with phenylhydrazine did not occur. In this case, the anion **1d[–]** is a harder donor than **1a[–]**. The *para*-methoxy group pushes electron density onto **N-1**, therefore making the donor atom less likely to hold a negative charge and thus less polarizable. In other words, anion **1d[–]** is more basic than **1a[–]** and therefore is a harder base. Therefore, when produced, anion **1d[–]** is more reactive toward the carbonyl moiety, the hard center of DMC. Even though the likelihood of producing anion **1d[–]** is lowered in terms of pK_a ,⁸ the chance of a successful attack is increased due to a lower activation energy of the reaction, in terms of hard–hard compatibility. Therefore, when considering the reactivity of a system, it is also important to consider the hardness of the reactive species and not only their concentration.

Reactions at Reflux Temperature. As noted in our preliminary communication,⁵ when reactions were conducted at reflux temperature with excess base, consecutive reactions took place, as shown in Scheme 3. In this paper, we report the analogous reactions that were attempted with the three named phenylhydrazines. The reaction of 4-trifluoromethylphenyl hydrazine (**1c**) was investigated. However, GC/MS evidence suggested that after fluorine substitution occurred carbazate **2c** was produced. The change to the phenylhydrazine backbone meant this phenylhydrazine could no longer be validly investigated. The investigations into electron withdrawing and donating groups were subsequently tested on the 4-chloro and 4-methoxy phenylhydrazines (**1b** and **1d**), respectively.

When 4-methoxyphenylhydrazine (**1d**) was reacted with DMC and 3 equiv of NaOMe, the reaction proceeded similarly to that of phenylhydrazine (**1a**).⁵ Immediately, carboxymethylation occurred at **N-1** of phenylhydrazine **1d**, producing carbazate **2d**. This was followed by a second carboxymethylation at **N-2**, producing **3d**. There was no great difference in reactivity between the two phenylhydrazines, **1a** and **1d**, and their resultant carbazates, **2** and **3**, as both reaction profiles were almost identical with respect to these components over the given time period (Figure 2 and ref 3). The main difference in the two reactions, however, was the relative percentages of carbazates **4** and **5** produced at the completion of the reaction. For the reaction of 4-methoxyphenylhydrazine (**1d**), 80% of **4d** and 15% of **5d** were produced after 550 min (Figure 2), while, for the reaction of phenylhydrazine (**1a**), 40% of **4a** and 55% of **5a** were produced after 650 min.⁵ This result is of importance in supporting the hypothesis that **5** is produced from the methanolysis of **4**, as stated in our preliminary communication.⁵

Methanolysis of carbazate **4** occurs *via* the nucleophilic attack from methanol onto the **N-1** carbonyl. This reaction produces an equivalent of DMC and carbazate **5** (Scheme 3, step iv). When there is a *para*-methoxy substituent present instead of a hydrogen (i.e., **4d** instead of **4a**), the reaction is hindered. This is because the electron donating effect of the methoxy group

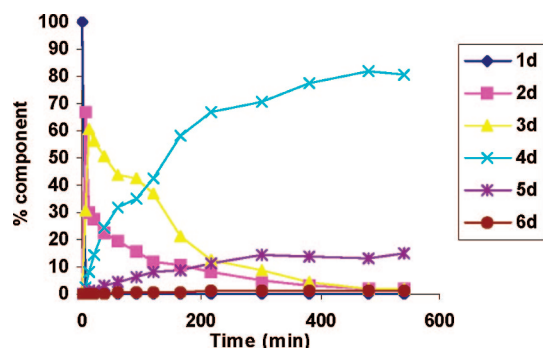


Figure 2. The reaction of 4-MeOPhNHNH₂, 3 equiv of NaOMe, and 40 equiv of DMC at reflux.

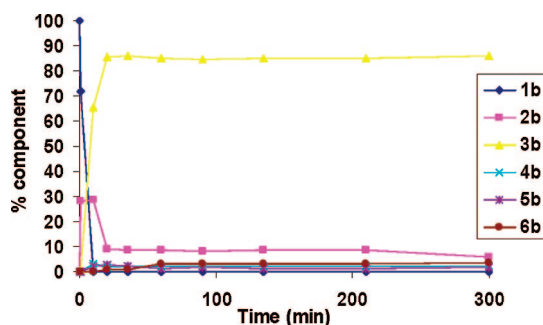


Figure 3. The reaction of 4-ClPhNHNH₂, 3 equiv of NaOMe, and 40 equiv of DMC at reflux.

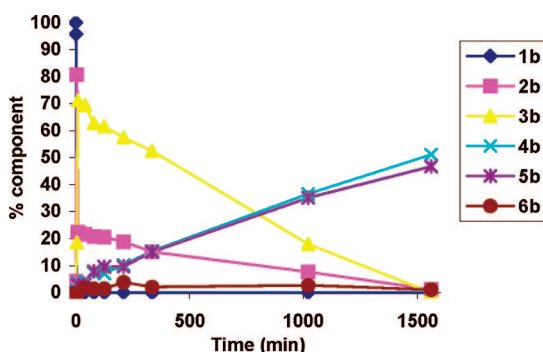


Figure 4. The reaction of 4-ClPhNHNH₂, 3 equiv of NaOMe, and 80 equiv of DMC at reflux.

pushes electron density onto N-1, which makes it less capable of holding a negative charge and therefore less likely to participate as the leaving group in the methanolysis reaction. Therefore, less of carbazate **4d** is produced than carbazate **4a** in their respective reactions.

The importance of the EWG was also investigated, using 4-chlorophenylhydrazine (**1b**) as the model. It is more likely that a switch in hard–soft basicity would occur at reflux temperatures with an EWG, as was observed in the case of the phenols (Scheme 2).³ However, methylation did not occur at N-1; instead, carbazate **2b** readily formed (Figures 3 and 4) (Scheme 3, step i). The second carboxylation, at N-2, to produce carbazate **3b** proceeded relatively quickly, in comparison to carbazates **3a** and **3d**, as the maximum amount of carbazate **2b** in the reaction was only ~30% (Figure 3). The electronegative *para*-chloro substituent reduces electron density on N-1, therefore making it more likely for N-2 to be deprotonated and sustain a negative charge. Subsequently, anion **2b**[−] reacts with DMC to produce **3b** (overall Scheme 3, step ii).

At the time the reaction was mainly composed of carbazate **3b** (ca. 10 min), the physical properties of the mixture changed

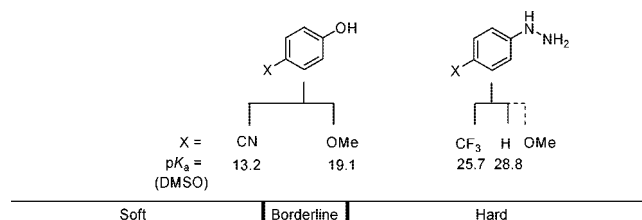


Figure 5. Proposed spectrum of hard–soft basicity of various nucleophiles reacted with DMC.

quite dramatically. Despite the reaction mixture being quite dilute, in terms of starting material to DMC (1–40 molecular equiv), the reaction mixture solidified (or gelled) with refluxing solvent still visible. Present at this time of the reaction was carbazate **3b**, and/or even possibly the sodium salt of, in more than 80%. This surely had an effect on the reaction, as it did not progress much further. Also, beyond this point, stirring became an issue; therefore, double the amount of DMC was used. When the reaction was carried out with double the amount of DMC (1–80 molecular equiv), solidification did occur; however, liquid DMC was still present and the stirring issue was circumvented. In this reaction, there was a slow conversion of the double carboxymethylated product **3b** into **4b** and **5b**.

Despite the reaction possessing double the ratio of DMC to methanol produced, methanolysis at N-1 of **4b** occurred to a much larger extent in comparison to carbazate **4d** (possessing methoxy group). In this case, the EWG removes the electron density away from N-1. The negative charge of the leaving group is therefore more readily tolerated, as it is stabilized with the aid of the *para*-chloro substituent.

In summary, although the reactivity of the phenylhydrazine moiety was altered by varying the *para*-substituent, there was no marked change in hard–soft basicity of either nucleophilic nitrogen, N-1 or N-2. The *para*-substituted phenylhydrazines followed the same pathway as the parent phenylhydrazine **1a** with no switch in methylation/carboxymethylations (Scheme 3).

What can be preliminarily concluded is that the class of phenols may actually rest on and/or around the borderline of the hard–soft basicity, under these conditions. Using a pK_a scale, it may be possible to suggest what soft or hard basicity a nucleophile of particular pK_a possesses (Figure 5). When a strong EWG group is used, the polarizability of the donor oxygen atom is soft in nature, the pK_a suggesting that the charge is well stabilized. When an EDG group is used, the nature of the oxygen donor atom increases in hard character. The pK_a suggests that the oxygen is less polarizable and less capable of carrying a negative charge; therefore, it is a harder nucleophile.

With respect to the *para*-substituted phenylhydrazines, pK_a values suggest polarization of N-1 would change, as the difference in reactivity is observed between the phenylhydrazines. However, although the hard basicity may actually change, it does not switch from hard to soft or borderline basicity (Figure 5). Generally, nitrogen donor atoms are not easily polarizable and therefore do not hold a negative charge well, unless they are connected to strong EWGs.⁹ Therefore, it is not intangible that there be no switch in hard–soft basicity.

Conclusions

When reactions with dimethyl carbonate were used as a measure for hard–soft basicity of the ambident nucleophile phenylhydrazine, it was determined that both N-1 and N-2 are strongly basic donor atoms. The relative hardness of both donor sites was elucidated as substitution of the phenyl ring at the

para-position with either an electron withdrawing or donating group had little effect on the hard–soft basicity of either nitrogen. The electron withdrawing groups, trifluoromethyl- and chloro-, failed to facilitate enough polarization at N-1 to cause a switch from hard to soft basicity.

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Supporting Information Available: Synthesis and characterization of all reference compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) Reactions with nitrophenylhydrazine were also carried out; however, it was found to be unstable under the reaction conditions.

(8) Although pK_a values are not available for all of the substituted phenylhydrazines, the relative effect of the *para*-substituent on the pK_a can be inferred from the relative anilines. The effect on the pK_a follows a similar trend for both substituted anilines and phenylhydrazines. Bordwell, F. G.; Zhang, X.-M.; Cheng, J.-P. *J. Org. Chem.* **1993**, *58*, 6410–6416 and ref 6.

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