Tetrahedron Letters 50 (2009) 7358–7361

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rapid amidic hydrolysis: a competitive reaction pathway under basic conditions for *N*-(hydroxymethyl)benzamide derivatives bearing electron-donating groups

John L. Murphy, William J. Tenn III, Joseph J. Labuda, Richard W. Nagorski *

Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA

ARTICLE INFO

Article history:
Received 10 September 2009
Revised 9 October 2009
Accepted 15 October 2009
Available online 21 October 2009

ABSTRACT

Studies of *N*-(hydroxymethyl)benzamide derivatives have concluded that the hydroxide-dependent reaction occurs via a specific-base catalyzed deprotonation of the hydroxyl group followed by rate-determining loss of the benzamidate and generation of the aldehyde. The 3-methyl, 4-methyl, and 4-methoxy-*N*-(hydroxymethyl)benzamide reaction mechanism deviates at higher [HO^-] with amidic hydrolysis becoming competitive and having reaction half-lives of ~17 s, in 1 M KOH, I = 1.0 M (KCl), 25 °C. An intramolecular general-base catalyzed mechanism has been suggested for the amidic hydrolysis reaction.

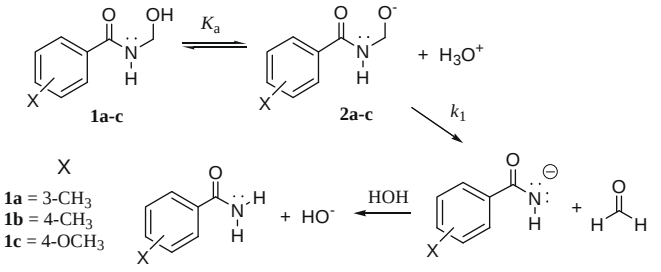
Carbinolamides are the seemingly simple combination of an amide and aldehyde, however, the functionality has a surprisingly diverse range of roles. They are constituents in a number of molecules of medicinal importance[1,2] and have been found as intermediates in biological processes with outcomes that are both positive[3,4] and negative[5] to those systems. Relatively few studies have focused on the mechanisms by which this functionality reacts but, all studies of the hydroxide-dependent breakdown of carbinolamides, in water, agree that the reaction occurs via a specific-base catalyzed deprotonation of the hydroxyl group, followed by rate-determining breakdown to form the aldehyde and amidate (see Scheme 1).[6–8] This conclusion was supported by a lack of buffer catalysis and hydroxide dependence changing from first order to zero order on moving from lower to higher [hydroxide].[6,7] Also, the studies of the effect of substituents with increasing electron demand, on the aromatic ring of *N*-(hydroxymethyl)benzamide, resulted in increasing apparent second-order rates (k_1', see Eqs. 1 and 2) and increased maximal rate constants at high hydroxide (k_1).[7a,c] Reported here are the rates of the hydroxide-dependent aqueous reaction of *N*-(hydroxymethyl)benzamide derivatives bearing electron-donating groups (**1a–c**), where the maximal rates appear to be independent of the aromatic substituent. The kinetic results coupled with the preliminary product analysis indicate that a relatively fast amidic hydrolysis reaction (half-life of ~40 s) has become competitive with carbinolamide breakdown at high [HO^-], in H_2O, I = 1.0 M (KCl) at 25 °C:

$$k_{obsd} = k_1 \frac{K_a[HO^-]}{K_w + K_a[HO^-]} \quad (1)$$

$$k_{obsd} = k_1 \frac{K_a[HO^-]}{K_w} = k_1'[HO^-] \quad (2)$$

In previous studies, the fit of k_{obsd} to the rate expression for the mechanism shown in Scheme 1 (see Eq. 1) yielded both k_1 and K_a of the hydroxyl group of the carbinolamide.[7a,c] These studies found that the aromatic substituents had only a small effect on the K_a of the hydroxyl group (ρ = 0.07), but k_1 was more strongly affected (ρ = 0.67).[7a,c,8] The only detectable product of these reactions was the amide of the carbinolamide starting material.[7a,c] Therefore, it could be predicted that electron-donating groups would continue to progressively reduce the maximal rate constant and have only small effects on the K_a of the hydroxyl group of the carbinolamide.

Figure 1 shows the plot of k_{obsd} versus [HO^-] for **1a–c**. The general appearance of these plots is similar to those seen previously



Scheme 1. Accepted mechanism for specific-base catalyzed breakdown of *N*-(hydroxymethyl)benzamide derivatives

* Corresponding author. Tel.: +1 309 438 8978; fax: +1 309 438 5538.
E-mail address: rnagor@ilstu.edu (R.W. Nagorski).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.069

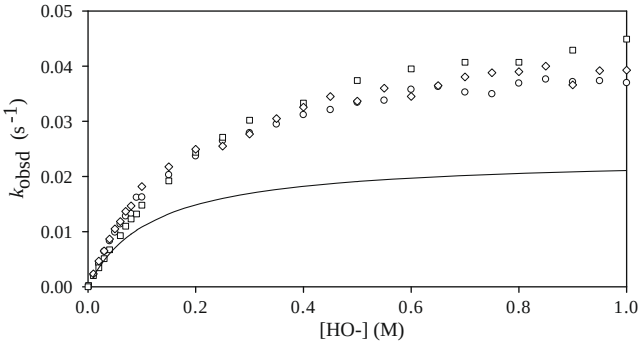


Figure 1. Observed hydroxide dependence of the rate of reaction (k_{obsd}, s^{-1}) for 3-methyl-*N*-(hydroxymethyl)benzamide (**1a**, ◇), 4-methyl-*N*-(hydroxymethyl)benzamide (**1b**, ○), and 4-methoxy-*N*-(hydroxymethyl)-benzamide (**1c**, □) in H_2O, I = 1.0 M (KCl), at 25 °C; solid line represents the predicted rate for the specific-base catalyzed breakdown of **1c** based upon apparent second-order rate of reaction.

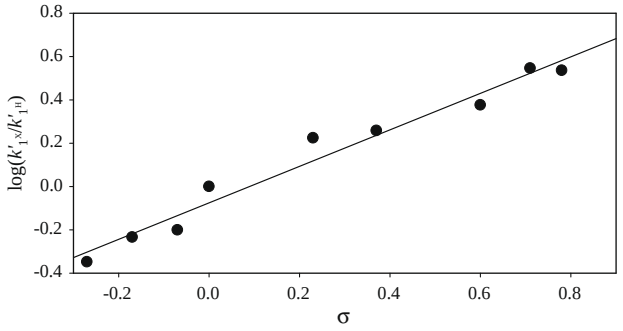


Figure 2. Hammett plot of the apparent second-order rates (k'_1) for the hydroxide-dependent reaction for 3-methyl-*N*-(hydroxymethyl)-benzamide, 4-methyl-*N*-(hydroxymethyl)benzamide, and 4-methoxy-*N*-(hydroxymethyl)benzamide with other apparent second-order rate constants for a series of *N*-(hydroxymethyl)benzamide compounds from Ref. 7c, in H_2O at 25 °C, I = 1.0 M (KCl) versus σ.

for *N*-(hydroxymethyl)benzamide derivatives bearing electron-withdrawing groups.[6,7a,d] However, in contrast to the previous results, there is no strong dependence between the substituent on the amide portion of the carbinolamide and k_1. In fact, the maximal rates observed (k_1) for **1a–c** are similar or larger than that observed for *N*-(hydroxymethyl)benzamide (k_1 = 0.042 s^{-1}),[7a] indicating that electron-donating groups are not extending the previously reported trend.[6,7a,c] Additionally, **1c**, bearing the strongest electron-donating group, has the highest maximal rate of the three compounds reported here (see Fig. 1), and, such a result, would lead to a nonlinear Hammett correlation.[7a,c] This observation indicates that there has been a change in the rate-limiting step of the reaction or a change in the mechanism of the reaction itself.[9] This outcome was unexpected, as it is in contrast to the results reported earlier by Bundgaard et al.[6e]

Previous studies, investigating the apparent second-order rate constants (k'_1) for the hydroxide-dependent reaction of a series of *N*-(hydroxymethyl)benzamide compounds, found that the Hammett correlation was linear (ρ = 1.11, in H_2O, I = 0.5 M (KCl), at 37 °C) for all compounds studied, which included compound **1c**.[6e] Due to the restricted range in pH over which their kinetic experiments were performed, these studies were only able to generate k'_1, but clearly these results indicate that at low [HO^-] all the compounds reported were reacting via a similar mechanism.[6e]

In order to explore Bundgaard's observation, the apparent second-order rate constants for **1a–c** were determined from the plot of k_{obsd} versus [HO^-] at low [HO^-] (see Table 1). A Hammett plot of the apparent second-order rate constants for **1a–c** with the previously reported rates for compounds bearing electron-withdrawing groups,[7a,c] resulted in a linear correlation with a ρ-value of 0.87 (ρ = 0.86 previously reported, see Fig. 2).[7c,10] As reported by Bundgaard,[6e] at low [HO^-] all *N*-(hydroxymethyl)benzamide derivatives studied react by the same mechanism (see Scheme 1) and it is only at higher [HO^-] that the mechanism by which **1a–c** react, apparently deviates.

Table 1
Apparent second-order rates for *N*-(hydroxymethyl)benzamide derivatives **1a–c** with predicted pK_a's and calculated limiting rates

Compound	k'_1 (M^{-1} s^{-1})[a]	p$K_a^{predicted}$	k_1^{calc} (s^{-1})
1a	0.23	13.05	0.026
1b	0.22	13.06	0.025
1c	0.17	13.06	0.023

[a] Determined in H_2O, 25 °C, I = 1.0 M (KCl).
[b] Predicted based on pK_a data in Ref. 7c having a ρ-value of 0.07.
[c] Calculated using $k'_1 = ((k_1K_a)/K_w)$ where $K_w = 1 \times 10^{-14}$ M^2.

Extending the conclusion that all compounds discussed react via the same specific-base catalyzed mechanism at lower [HO^-]. It follows that the substituents on compounds **1a–c** would lead to the same small effect on the K_a of the hydroxyl group previously observed for other *N*-(hydroxymethyl)benzamide derivatives (ρ = 0.07).[7c] Thus, the pK_a's for **1a–c** can be predicted by a simple extrapolation of the previously reported Hammett correlation (see Table 1).[7c] The limiting rate (k_1^{calc}) for the specific-base catalyzed carbinolamide breakdown of **1a–c** can then be calculated using Eq. 2, the experimentally determined apparent second-order rates (k'_1) and the predicted K_a's of the hydroxyl group (see Table 1). It is apparent that the limiting rates calculated in this manner are much smaller than the k_{obsd} values seen at high [HO^-] in Figure 1. This difference between predicted rates and k_{obsd} is further illustrated by inserting the predicted K_a and k_1^{calc} into Eq. 1 yielding the expected k_{obsd} values for the specific-base catalyzed carbinolamide breakdown. The solid line in Figure 1 is the predicted rates for the specific-base catalyzed breakdown of 4-methoxy-*N*-(hydroxymethyl)-benzamide. At 1 M KOH, k_{obsd} for **1c** is 2.1-fold larger than the predicted rate under the same conditions and the rate differences for **1a** and **1b** are 1.6 and 1.7, respectively. This trend in rate ratios points to stronger electron-donating groups yielding larger deviations from the predicted rates at higher [hydroxide].

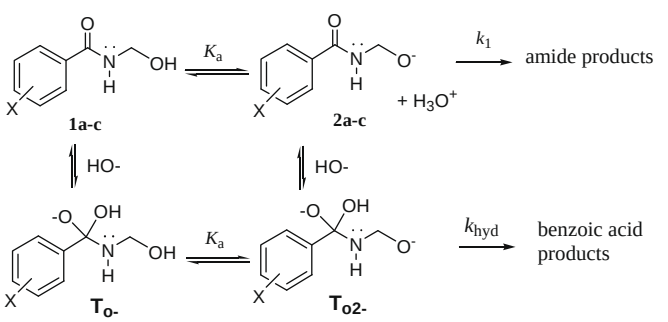
Product analysis studies performed by HPLC, for experiments at p*H*'s below 10 and quenched at ~50% reaction, showed only the starting carbinolamide and the amide of the starting material. However, the same analyses performed at 0.2 M KOH and higher showed the presence of carbinolamide, amide, and carboxylic acid derivative of the starting material. Logically, subsequent hydrolysis of the amide product generated upon breakdown of the carbinolamide might be expected as the source of the carboxylic acid products. However, previous amide hydrolysis studies carried out at 100 °C and 1 M hydroxide were shown to have half-lives of 7.7,[11a] 16,[11a] 7.6,[11a] 100,[11b] and 10^{11b} min for benzamide, *N*-methylbenzamide, *N*,*N*-dimethyl-benzamide, *N*-ethyl-4-toluamide, and *N*,*N*-dimethyl-4-toluamide, respectively. Whereas with a k_{obsd} of ~0.04 s^{-1}, at 1 M KOH (see Fig. 1), in H_2O, at 25 °C, for compounds 1a–**c**, the half-life will be ~17 s. The reactions of **1a–c** occur too quickly for a significant buildup of carboxylic acid due to the subsequent hydrolysis of the amide product of carbinolamide breakdown. Also, parent amide compound, subjected to the same conditions as the product studies detailed above, did not show any detectable amounts of carboxylic acid product when analyzed as described above. The source of the carboxylic acid product must be associated with the increased rate of reaction for **1a–c** versus previously observed trends.[6,7]

At low [HO^-], all substituted *N*-(hydroxymethyl)benzamide compounds react by the same mechanism (see Fig. 2). The rate-

determining step involves breakdown of **2**, yielding benzamidate and formaldehyde. As electron-withdrawing groups are added to the amide portion of the carbinolamide, the reaction rate increases, indicating that the nucleofugality of the benzamidate has increased.[7a,c] From Figure 1, it is only when significant amounts of **2a–c** (based upon K_a's of other *N*-(hydroxymethyl)benzamide derivatives, see Scheme 2) are in solution that k_{obsd} deviates from the previous trends and amidic hydrolysis products are observed. Thus, the addition of electron-donating groups has decreased the leaving group ability of the benzamidate, yielding an intermediate (**2a–c**) with a longer lifetime and with the potential to undergo other forms of reactivity.

It is easy to tie the presence of carboxylic acid product, at higher [HO^-], to the kinetic deviation observed. However, if hydrolysis were becoming competitive with carbinolamide breakdown, why is the carboxylic acid product not observed at lower [HO^-]? We are proposing a mechanism that is second order in hydroxide wherein **2a–c** are attacked at the carbonyl carbon by a second hydroxide molecule to yield $T_{o^{2-}}$ or T_{o^-} which subsequently ionized, leading to $T_{o^{2-}}$. This is followed by breakdown of $T_{o^{2-}}$ to yield the benzoic acid derivative and aminomethanol. While it is difficult to predict an expected rate of hydrolysis due to the unique structure of $T_{o^{2-}}$, this hydrolysis reaction occurs much more quickly than would be anticipated based upon the available data (see half-lives listed above).[11,12] It is generally accepted that amide hydrolysis occurs with rate-limiting loss of the nitrogen leaving group and that nitrogen must be protonated or, in the case of very acidic amines, can depart as an anion.[12] Data concerning the K_a of the nitrogen of aminomethanol are not readily available; however, it could be safely assumed that the aminomethanol acting as a leaving group with a negative charge on both the nitrogen and the oxygen would be energetically unlikely. Alternatively, mechanisms for amide hydrolysis have been investigated wherein the rate is second order in hydroxide and the second hydroxide ion deprotonates the hydroxyl group of the tetrahedral intermediate, leading to product formation.[12,13] The deprotonated hydroxyl group in $T_{o^{2-}}$ could act as an intramolecular general base to deprotonate the OH group in $T_{o^{2-}}$ (see Scheme 2), with subsequent loss of the nitrogen leaving group. Intramolecular catalysis and general catalysis have been observed within a number of systems.[14] It could be further proposed that the anionic nitrogen leaving group could undergo further decomposition with the loss of hydroxide but no direct evidence for such a mechanism has been found.

When differences in structure and reaction conditions are considered,[12,15] the hydrolysis reaction occurs, at least, a 130-fold faster than normal amide hydrolysis. While the exact nature of the reaction is currently under further investigation, the results indicate the discovery of a new mechanism for the breakdown of carbinolamides involving facile amidic hydrolysis whose onset is dependent on the protonation state of the carbinolamide. In the case of 4-methoxy-*N*-(hydroxymethyl)benzamide, amidic hydrolysis occurs at that same rate as 'normal' carbinolamide breakdown. We have proposed a mechanism that is second order in hydroxide, wherein the ionized hydroxyl group of the carbinolamide can act as an intramolecular general base to deprotonate $T_{o^{2-}}$, resulting in amidic hydrolysis and release of aminomethanol anion. This new mechanism of carbinolamide breakdown may also provide valuable insight into the enzymatic mechanism for the hydrolysis of amides and other acyl derivatives.



Scheme 2. Proposed amidic hydrolysis route.

Acknowledgments

This work was supported by the National Science Foundation under CHE-051830 and also a MRI grant under CHE-0722385.

Supplementary data

Synthesis and characterization of **1a–c**, with experimental methods, plots of k_{obsd} versus [HO^-] for **1a–c** with predicted rates based upon k_1' and predicted pK_a's are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.069.

References and notes

1. (a) Vela, M.; Kohn, H. *J. Org. Chem.* **1992**, *57*, 5223–5231; (b) Miyoshi, T.; Miyari, N.; Aoki, H.; Kohsaka, M.; Sakai, H.; Imanaka, H. *J. Antibiot.* **1972**, *25*, 569–575; (c) Miyamura, S.; Ogasawara, N.; Otsuka, H.; Niwayama, S.; Takana, H.; Take, T.; Uchiyama, T.; Ochiai, H.; Abe, K.; Koizumi, K.; Asao, K.; Matuski, K.; Hoshino, T. *J. Antibiot.* **1972**, *25*, 610–612.
2. (a) Asami, Y.; Kakeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett.* **2002**, *4*, 2845–2848; (b) Nakai, R.; Ogawa, H.; Asai, A.; Ando, K.; Agatsuma, T.; Matsumiya, S.; Akinaga, S.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 294–296; (c) Suzuki, S.; Hosoe, T.; Nozawa, K.; Kawai, K.; Yaguchi, T.; Udagawa, S. *J. Nat. Prod.* **2000**, *63*, 768–772; (d) Singh, S. B.; Goetz, M. A.; Jones, E. T.; Bills, G. F.; Giacobbe, R. A.; Herranz, L.; Stevensmiles, S.; Williams, D. L. *J. Org. Chem.* **1995**, *60*, 7040–7042; (e) Kakeya, H.; Takahashi, I.; Okada, G.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 733–735.
3. (a) Young, S. D.; Tamburini, P. P. *J. Am. Chem. Soc.* **1989**, *111*, 1933–1934; (b) Eipper, B. A.; Mains, R. E.; Glembotski, C. C. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 5144–5148; (c) Bradbury, A. F.; Finnie, M. D. A.; Smyth, D. G. *Nature* **1982**, *298*, 686–688.
4. (a) McInnch, J. K.; McInnch, J. D.; May, S. W. *J. Biol. Chem.* **2003**, *278*, 50091–50100; (b) Takada, Y.; Noguchi, T. *Biochem. J.* **1986**, *235*, 391–397.
5. (a) Chung, F. L.; Nath, R. G.; Nagao, M.; Nishikawa, A.; Zhou, G. D.; Randerath, K. *Mutat. Res.* **1999**, *424*, 71–81; (b) Marnett, L. J. *Mutat. Res.* **1999**, *424*, 83–95; (c) Nair, J.; Barbin, A.; Velic, I.; Bartsch, H. *Mutat. Res.* **1999**, *424*, 59–69.
6. (a) Bundgaard, H. In *Design of Prodrugs*; Bundgaard, H., Ed.; Elsevier: Amsterdam, 1985; pp 1–92; (b) Bundgaard, H.; Buur, A. *Int. J. Pharm.* **1987**, *37*, 185–194; (c) Bundgaard, H.; Johansen, M. *Int. J. Pharm.* **1980**, *5*, 67–77; (d) Bundgaard, H.; Johansen, M. *Int. J. Pharm.* **1984**, *22*, 45–56; (e) Johansen, M.; Bundgaard, H. *Arch. Pharm. Chem. Sci. Edn.* **1979**, *7*, 175–192.
7. (a) Tenn, W. J.; French, N. L.; Nagorski, R. W. *Org. Lett.* **2001**, *3*, 75–78; (b) Mennenga, A. G.; Johnson, A. L.; Nagorski, R. W. *Tetrahedron Lett.* **2005**, *46*, 3079–3083; (c) Tenn, W. J.; Murphy, J. L.; Bim-Merle, J. K.; Brown, J. A.; Junia, A. J.; Price, M. A.; Nagorski, R. W. *J. Org. Chem.* **2007**, *72*, 6075–6083; (d) Ankem, R. V.; Murphy, J. L.; Nagorski, R. W. *Tetrahedron Lett.* **2008**, *49*, 6547–6549.
8. (a) More recently, questions concerning the position of deprotonation in the specific-base catalyzed reaction of carbinolamides have arisen. The mechanism shown in Scheme 1 shows the hydroxyl group being deprotonated followed by breakdown into the aldehyde and release of the benzamidate. Limited data concerning the acidity of the protons on the nitrogen of benzamides are available, but the available data suggest that benzamide has a pK_a >19.0 with 4-bromobenzamide and 4-nitrobenzamide having pK_a's of 17.13 and 15.85, respectively. (Ref. 8b,c) Substantial changes to the pK_a of the hydrogen attached to nitrogen have been observed in benzohydroxamic acid (pK_a = 8.88), where, depending upon the conditions of the experiment, deprotonation can occur at either the oxygen or the nitrogen. (Ref. 8d–f) However, the insertion of the methylene unit between the nitrogen and the oxygen, as seen in carbinolamides, should mediate changes in the pK_a of both the oxygen and the nitrogen. For example, the pK_a's of the hydrate of acetaldehyde and 2-hydroxyacetophenone are 13.48 and 13.33, respectively. (Ref. 8g,h) Based upon these comparisons, it is reasonable to expect that the pK_a of the protons on both the nitrogen and the oxygen of carbinolamides will be affected by their proximity to one another but the protons on the oxygen will still be significantly more acidic than those attached to the nitrogen.; (b) Hine, J.; Hine, M. *J. Am. Chem. Soc* **1952**, *74*, 5266–5271; (c) Homer, R. B.; Johnson, C. D. *The Chemistry of Amides*; Interscience: New York, 1970; (d) Wise, W. M.; Brandt,

W. W. *J. Am. Chem. Soc.* **1955**, *77*, 1058–1059; (e) Decouzon, M.; Exner, O.; Gal, J. F.; Maria, P. C. *J. Org. Chem.* **1990**, *55*, 3980–3981; (f) Podlaha, J.; Ciisarova, I.; Soukupova, L.; Schraml, J.; Exner, O. *J. Chem. Res. (S)* **1998**, 520–521; (g) Bell; McTigue *J. Chem. Soc.* **1960**, 2983; (h) Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205.

9. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1987.
10. The differences in the ρ-values between Bundgaard's work (Ref. 6e) and that reported here, and in Ref. 7c, can, in part, be attributed to differences in the ionic strengths at which the two studies were performed.
11. (a) Bunton, C. A.; Nayak, B.; O'Connor, C. *J. Org. Chem.* **1968**, *33*, 572–575; (b) Slebocka-Tilk, H.; Bennet, A. J.; Keillor, J. W.; Brown, R. S.; Guthrie, J. P.; Jodhan, A. *J. Am. Chem. Soc.* **1990**, *112*, 8507–8514.
12. Brown, R. S. In *The Amide Linkage*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-Interscience: New York, 2000.
13. (a) Young, J. K.; Pazhanisamy, S.; Schowen, R. L. *J. Org. Chem.* **1984**, *49*, 4148–4152; (b) Eriksson, S. O. *Acta Chem. Scand.* **1968**, *22*, 892–906; (c) DeWolfe, R. H.; Newcomb, R. C. *J. Org. Chem.* **1971**, *36*, 3870–3878; (d) Pollack, R. M.; Dumsha, T. C. *J. Am. Chem. Soc.* **1973**, *95*, 4463–4465; (e) Biechler, S. S.; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 432–437.
14. (a) Kirby, A. J. *Adv. Phys. Org. Chem* **1980**, *17*, 183–278. and references therein; (b) Fife, T. H.; Chauffe, L. *J. Org. Chem.* **2000**, *65*, 3579–3586; (c) Fernandes, N. M.; Fache, F.; Rosen, M.; Nguyen, P.-L.; Hansen, D. E. *J. Org. Chem.* **2008**, *73*, 6413–6416; (d) Wu, Z.; Ban, F.; Boyd, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 6994–7000.
15. Liu, B.-Y.; Brown, R. S. *J. Org. Chem.* **1993**, *58*, 732–734.