

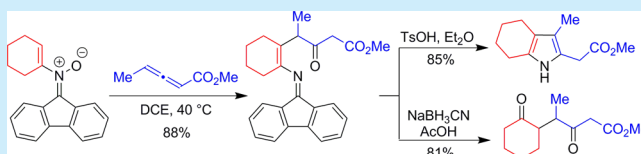
Synthesis of 1,4-Enamino Ketones by [3,3]-Rearrangements of Dialkenylhydroxylamines

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Supporting Information

ABSTRACT: The synthesis of 1,4-enamino ketones has been achieved through the [3,3]-rearrangement of dialkenylhydroxylamines generated from the addition of *N*-alkenylnitrones to electron-deficient allenes. The mild conditions required for this reaction, and the simultaneous installation of a fluorenyl imine *N*-protecting group as a consequence of the rearrangement, avoid spontaneous cyclization of the 1,4-enamino ketones to form the corresponding pyrroles and allow for the isolation and controlled divergent functionalization of these reactive intermediates. The optimization, scope, and tolerance of the new method are discussed with demonstrations of the utility of the products for the synthesis of pyrroles, 1,4-diones, and furans.

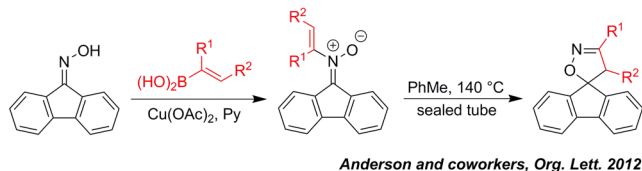
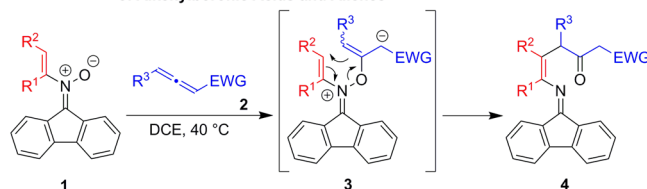


[3,3]-Rearrangements of dialkenylhydrazines and dialkenylhydroxylamines are important transformations that are employed as the key C–C bond forming steps in the Piloty–Robinson and Trofimov pyrrole syntheses.^{1–3} Unfortunately, the conditions required to generate these intermediates and to achieve these transformations limit their scope and generality.^{4–6} We surmised that dialkenylhydroxylamines could alternatively be accessed through the addition of an *N*-alkenylnitron to an allene.^{7,8} This route could then be used to circumvent limitations of the pyrrole syntheses mentioned above as well as provide access to isolable [3,3]-rearrangement products for divergent functionalization prior to heterocycle formation. Our recent discovery that *N*-alkenyl fluorenone oximes can be prepared by a copper-mediated C–N bond-forming reaction between fluorenone oxime and alkenyl boronic acids facilitated our study (Scheme 1a).⁹ Herein, we describe the generation of dialkenylhydroxylamines **3** by the addition of *N*-alkenylnitrones **1** to activated allenes **2** and a

subsequent spontaneous [3,3]-rearrangement to give 1,4-enamino ketones **4** (Scheme 1b). Isolation of these compounds with a fluorenone imine protecting group, installed as a consequence of the [3,3]-rearrangement, provided the opportunity for their straightforward conversion to tetrasubstituted pyrroles, 1,4-diones, and tetrasubstituted furans. Considered in sequence with our reported *N*-alkenylnitron synthesis, this two-step procedure can be described as an oxime-mediated oxidative coupling of alkenyl boronic acids and allenes to form 1,4-diones and 1,4-dione derivatives.

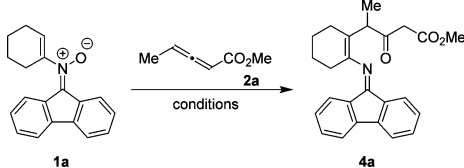
The synthesis of 1,4-enamino ketone **4a** was initially observed when *N*-cyclohexenyl nitron **1a** was treated with allenolate **2a** in toluene at 40 °C. A solvent screen showed that the preparation of **4a** was most efficient in 1,2-dichloroethane (DCE) but also occurred in dioxane, acetonitrile, DMF, and *t*-BuOH (Table 1, entries 1–6). Decomposition of the reaction mixture was observed at higher temperatures, but isolation of **4a** was possible in attenuated yields when the reaction was run at 25 °C (Table 1, entries 7–9). In addition to solvent and temperature, several acidic and basic additives were also tested to determine their effect on the synthesis of **4a**, but none improved the yield of the desired product.¹⁰ The conditions described in Table 1, entry 5, were determined to be optimal conditions for the synthesis of **4a** and were used for further exploration of the scope of the method.¹¹

Several *N*-alkenylnitrones were tested under the optimized reaction conditions to determine the scope of the transformation (Table 2). Cycloalkenylnitron substituents were discovered to be particularly amenable to the preparation of imine-protected 1,4-enamino ketones **4**, and cyclohexenyl, cycloheptenyl, and cyclooctenyl groups were well-tolerated by the transformation (Table 2, entries 1–3). *N*-Cyclopentenyl nitrones were also efficient substrates, but enamino ketone **4d** was sensitive to

Scheme 1. [3,3]-Rearrangement of Dialkenylhydroxylamines Generated from *N*-Alkenylnitronesa) Previous work – Preparation and Rearrangement of *N*-AlkenylnitronesAnderson and coworkers, *Org. Lett.* 2012b) This work – *N*-Alkenylnitrones as Intermediates for the Oxidative Coupling of Alkenylboronic Acids and Allenes

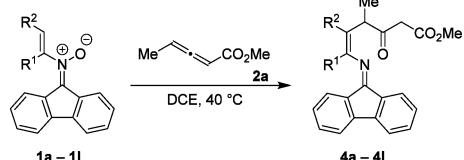
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Table 1. Optimization of the Addition of *N*-Alkenylnitrone 1a to Allenolate 2a and Rearrangement to 4a


entry	solvent	temp (°C)	yield ^a (%)
1	PhMe	40	63
2	dioxane	40	65
3	MeCN	40	80
4	DMF	40	54
5	DCE	40	89
6	<i>t</i> -BuOH	40	72
7	DCE	80	dec
8	DCE	60	56
9	DCE	25	66

^aDetermined by ¹H NMR spectroscopy using CH₂Br₂ as a reference: 1a (1 equiv), 2a (3–4 equiv), 0.1 M, 18 h.

Table 2. Scope of *N*-Alkenylnitrone Reagent



entry	4	yield (%) ^a	entry	4	yield (%) ^a
1		88	7		94
2		60	8		67
3		68	9		57
4		30	10		78
5		63	11		77
6		92	12		64

^aPercent isolated yield. Conditions: 1 (1 equiv), allenolate 2a (3–4 equiv), 0.1 M in DCE, 40 °C, 18–24 h.

purification on silica gel (Table 2, entry 4). Substituted cyclohexenylnitrones with alkyl, ester, and ketal substituents smoothly underwent the addition and rearrangement to give

enamino ketones 4e–i (Table 2, entries 5–9). Monosubstituted enamino ketones 4g–i were isolated as 1:1 mixtures of diastereomers. Gratifyingly, nitrones with heterocyclic substituents such as 1j and 1k were also well-tolerated (Table 2, entries 10 and 11), and nitrone 1l with a linear alkenyl group gave the corresponding product 4l in good yield. These examples describe the generality of the method for the synthesis of imino-protected, 1,4-enamino ketones and offer an alternative route to enamine displacements of α -halogenated ketones or oxidative couplings of enamines and silyl enol ethers for the preparation of mono-enamino-functionalized 1,4-diones.^{12–14}

In addition to the nitrones discussed above, the scope of the allene component of the transformation was tested to determine the range of the method for installing the ketone fragment of the products. As shown in Table 3, when methyl allenates with

Table 3. Scope of Allene Reagent


entry	2	R ¹	EWG	yield (%) ^a
1	2b	<i>n</i> -Bu	CO ₂ Me	4m (81)
2	2c	<i>i</i> -Pr	CO ₂ Me	4n (89)
3	2d	Bn	CO ₂ Me	4o (94)
4	2e	Me	CO ₂ Ph	4p (80)
5	2f	Me		4q (89)
6	2g	Me		4r (85)
7	2h	Me		4s (77)
8	2i	Me	SO ₂ Ph	4t (75)
9	2j	Me		4u (84)

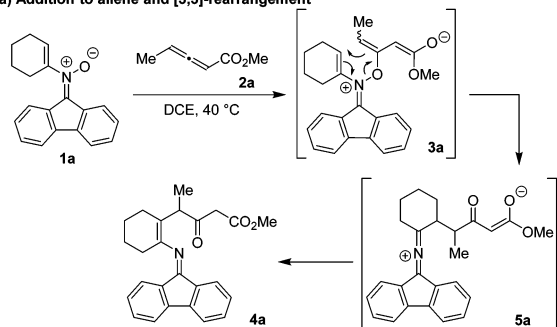
^aPercent isolated yield. Conditions: 1a (1 equiv), 2 (3–4 equiv), 0.1 M in DCE, 40 °C, 18–24 h.

isopropyl, butyl, and benzyl substituents were treated with nitrone 1a, enamino ketones 4m–o were isolated in good yield (Table 3, entries 1–3). These results suggest that the cascade rearrangement is tolerant of various substitution patterns at this position. Several different allenates, including phenyl, styrenyl, allyl, and propargyl esters, smoothly underwent addition and rearrangement with 1a (Table 3, entries 4–7). In addition, allenes with alternative electron-withdrawing groups, such as sulfonyl and Weinreb amide functionalities, were equally effective substrates for the preparation of functionalized 1,4-enamino ketones (Table 3, entries 8 and 9).

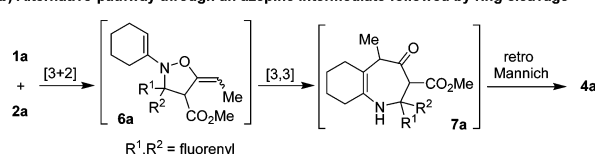
A proposed mechanism for the conversion of mixtures of *N*-alkenylnitrones and allenes to 1,4-enamino ketones is illustrated in Scheme 2a. Addition of nitrone 1a to electron-deficient allene 2a could form intermediate 3a, which could then undergo a [3,3]-rearrangement to form azallenium 5a and a subsequent proton transfer to form 4a.¹⁵ Alternatively, a [3 + 2]-cycloaddition to form exomethylene isoxazoline 6a could also predicate a [3,3]-rearrangement to form azepine 7a (Scheme 2b). A subsequent retro-Mannich reaction could then cleave the azepine to form 4a.¹⁶ The pathway illustrated in Scheme 2b,

Scheme 2. Proposed Mechanism

a) Addition to allene and [3,3]-rearrangement



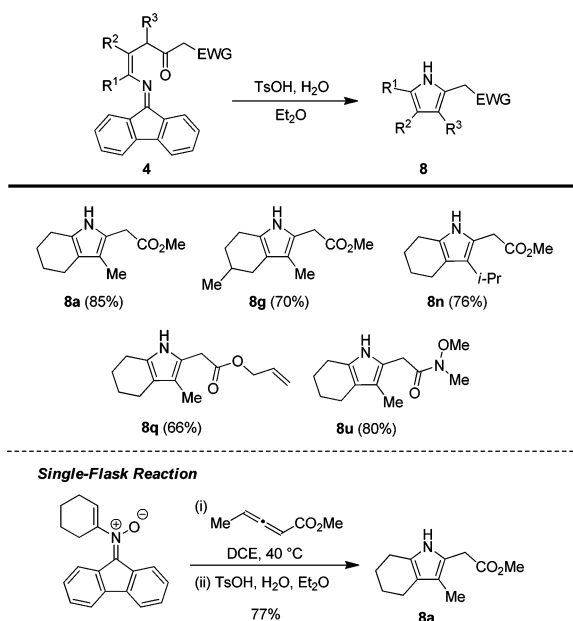
b) Alternative pathway through an azepine intermediate followed by ring cleavage



however, seems less likely than the pathway illustrated in Scheme 2a due to the sterically hindered and electronically deactivated fluorenyl imine which would be unlikely to undergo a [3 + 2]-cycloaddition.¹⁷

With several 1,4-enamino ketone products in hand, we decided to investigate the reactivity of these unusual imino-protected intermediates. Hydrolysis conditions were tested to remove the fluorenone imine and assess the use of these compounds for the preparation of highly substituted pyrroles. A mixture of *p*-toluenesulfonic acid (TsOH) and H₂O in ether was determined to be optimal for removal of the fluorenone imine from **4a** and the synthesis of tetrasubstituted pyrrole **8a** (Scheme 3). These conditions were tolerated by a variety of 1,4-enamino ketones **4** and provided tetrasubstituted pyrroles with cyclohexyl, -CH₂CO₂R, and Weinreb amide functional groups.¹⁸ The hydrolysis of **4a** can also be performed as a two-step, single-flask

Scheme 3. Hydrolysis of Imine-Protecting Group To Give Tetrasubstituted Pyrroles

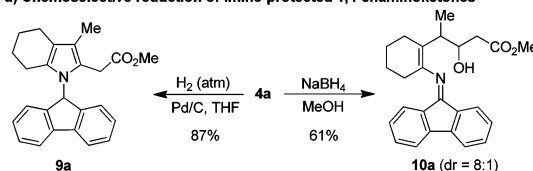


process with the addition and rearrangement reaction providing direct conversion of *N*-alkenylnitron **1a** to tetrasubstituted pyrrole **8a** in good yield. Pyrroles with 2-CH₂CO₂R groups have previously been prepared by the treatment of α -aminated ketones with β -ketoesters.¹⁹ The transformation described above provides a simple, alternative route to these compounds through an oxime-mediated coupling of an alkenyl boronic acid and an electron-deficient allene.

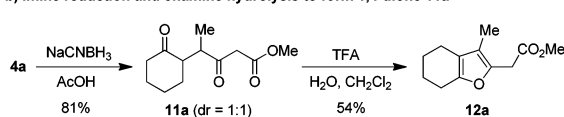
To further pursue the use of imino-protected 1,4-enamino ketones **4** as synthetic intermediates, we also screened conditions for chemoselective reductions. As shown in Scheme 4,

Scheme 4. Synthetic Diversification of Isolated 1,4-Enamino Ketones by Selective Reduction Methods

a) Chemoselective reduction of imine-protected 1,4-enaminoketones



b) Imine reduction and enamine hydrolysis to form 1,4-dione 11a



hydrogenation of fluorenone imine **4a** with Pd/C gave a fluorenyl amine which cyclized to the corresponding *N*-fluorenylpyrrole **9a**. In contrast, reduction of **4a** with NaBH₄ gave δ -hydroxyenamine **10a**. To our delight, a NaCNBH₃ reduction of **4a** in acetic acid gave 1,4-dione **11a**, which could also be subsequently converted to tetrasubstituted furan **12a**.²⁰ These experiments imply that [3,3]-rearrangements of dialkenylhydroxylamines, triggered by the addition of *N*-alkenylnitrones to allenes, can provide rapid access to 1,4-diones and their derivatives. These transformations provide alternative routes to oxidative enolate couplings and Stetter reactions to access these challenging fragments.^{21,22}

In summary, we have discovered a new method for the generation of dialkenylhydroxylamines through the addition of *N*-alkenylnitrones to electron-deficient allenes and the synthesis of 1,4-enamino ketones by a subsequent spontaneous [3,3]-rearrangement. This new route to dialkenylhydroxylamines has a broader scope than the Trofimov reaction, and the mild reaction conditions allow for the isolation of a novel fluorenylimine-protected 1,4-enamino ketone intermediate. Simple functionalization methods have been shown to be effective for the conversion of these compounds to pyrroles, 1,4-diones, and furans. Ongoing work in our laboratory is focused on controlling the stereochemistry of these rearrangements and further exploring the synthetic utility of the imino-protected enamino ketone rearrangement products.

■ ASSOCIATED CONTENT

S Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For seminal and recent examples of the Piloty–Robinson pyrroles synthesis, see: (a) Piloty, O. *Chem. Ber.* **1910**, *43*, 489. (b) Robinson, R.; Robinson, G. M. *J. Chem. Soc.* **1918**, *43*, 639. (c) Posvic, H.; Dombro, R.; Ito, H.; Telinski, T. *J. Org. Chem.* **1974**, *39*, 2575. (d) Baldwin, J. E.; Bottaro, J. C. *J. Chem. Soc., Chem. Commun.* **1982**, 624. (e) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 3941. (f) Alekseyev, R. S.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2011**, *47*, 584.
- (2) For seminal examples and reviews of the Trofimov reaction, see: (a) Sheradaky, T. *Tetrahedron Lett.* **1970**, *11*, 25. (b) Mikhaleva, A. I.; Zaitsev, A. B.; Trofimov, B. A. *Russ. Chem. Rev.* **2002**, *71*, 563. (c) Trofimov, B. A. *Curr. Org. Chem.* **2002**, *6*, 1121. (d) Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193. (e) Trofimov, B. A. *Adv. Heterocycl. Chem.* **1990**, *51*, 177. (f) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E. Y.; Sobenina, L. N. *Adv. Heterocycl. Chem.* **2010**, *99*, 209.
- (3) For recent examples and limitations of the Trofimov reaction, see: (a) Petrova, O. V.; Sobenina, L. N.; Ushakov, I. A.; Mikhaleva, A. I.; Hyun, S. H.; Trofimov, B. A. *ARKIVOC* **2009**, *4*, 14. (b) Trofimov, B. A.; Tarasova, O. A.; Mikhaleva, A. I.; Kalinina, N. A.; Sinogovskaya, L. M.; Henkelmann, J. *Synthesis* **2000**, 1585. (c) Petrova, O. V.; Sobenina, L. N.; Mikhaleva, A. I. *Chem. Heterocycl. Compd.* **2013**, *48*, 1628.
- (4) For an example of a copper-catalyzed dialkenylation of a hydrazine followed by cyclization to the corresponding pyrrole, see: Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973.
- (5) For examples of the addition of oximes to activated alkynes, see: (a) Ngwerume, S.; Camp, J. E. *Chem. Commun.* **2011**, *47*, 1857. (b) Ngwerume, S.; Camp, J. E. *J. Org. Chem.* **2010**, *75*, 6271. (c) Madabhushi, S.; Vangipuram, V. S.; Mallu, K. K. R.; Chinthala, N.; Beeram, C. R. *Adv. Synth. Catal.* **2012**, *354*, 1413.
- (6) For examples of Ir-catalyzed isomerizations of O-allyl oximes to form O-vinyl oximes, see: (a) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290. (b) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Kapadia, R.; Londino, H. N.; Anderson, L. L. *J. Org. Chem.* **2011**, *76*, 3203.
- (7) For recent examples of nitron [3 + 2] cycloadditions with allenes involved in cascade processes and metal-catalyzed examples of these transformations, see: (a) Bhella, S. S.; Pannu, A. P. S.; Elango, M.; Kapoor, A.; Hundal, M. S.; Ishar, M. P. S. *Tetrahedron* **2009**, *65*, 5928. (b) Kapur, A.; Kumar, K.; Singh, L.; Singh, P.; Elango, M.; Subramanian, V.; Gupta, V.; Kanwal, P.; Ishar, M. P. S. *Tetrahedron* **2009**, *65*, 4593. (c) Wu, X.; Na, R.; Liu, H.; Liu, J.; Wang, M.; Zhong, J.; Guo, H. *Tetrahedron Lett.* **2012**, *53*, 342. (d) Li, G.-H.; Zhou, W.; Li, X.-X.; Bi, Q.-W.; Wang, Z.; Zhao, Z.-G.; Hu, W.-X.; Chen, Z. *Chem. Commun.* **2013**, *49*, 4770.
- (8) For recent examples of other types of additions of nitrones and allenes, see: (a) Stoll, A. H.; Blakey, S. B. *Chem. Sci.* **2011**, *2*, 112. (b) Xu, C.-P.; Huang, P.-Q.; Py, S. *Org. Lett.* **2012**, *14*, 2034. (c) Wu, L.; Shi, M. *Chem.—Eur. J.* **2010**, *16*, 1149.
- (9) Mo, D.-L.; Wink, D. J.; Anderson, L. L. *Org. Lett.* **2012**, *14*, 5180.
- (10) See the Supporting Information for an expanded optimization table.
- (11) Preparation of **4a** can be achieved in attenuated yield (40 – 50%) from the corresponding oxime through a two-step, single-flask, Chan–Lam coupling followed by the addition of **2a**.
- (12) For examples of the preparation of azabutadienes by addition/elimination and isomerization, see: (a) Barluenga, J.; Joglar, J.; Fustero, S.; Gotor, V.; Krueger, C.; Romao, M. *J. Chem. Ber.* **1985**, *118*, 3652. (b) Grigg, R.; Stevenson, P. J. *Synthesis* **1983**, 1009.
- (13) For examples of the preparation of 1,4-enamino ketones by enamine additions to α -halogenated ketones, α,β -unsaturated ketones, and 1,2-diones, see: (a) Lopez-Alvarado, P.; Garcia-Granda, S.; Alvarez-Rua, C.; Avendano, C. *Eur. J. Org. Chem.* **2002**, 1702. (b) Schank, K.; Leider, R.; Lick, C.; Glock, R. *Helv. Chim. Acta* **2004**, *87*, 869. (c) Koulouri, S.; Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M. *J. Org. Chem.* **2005**, *70*, 8780. (d) Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, *70*, 3277. (e) Bremner, J. B.; Samosorn, S. *Aust. J. Chem.* **2003**, *56*, 871. (f) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515.
- (14) For examples of oxidative couplings of enamines and silyl enol ethers, see: (a) Narasaka, K.; Okauchi, T.; Tanaka, K.; Murikami, M. *Chem. Lett.* **1992**, 2099. (b) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (c) Li, Q.; Fan, A.; Lu, Z.; Cui, Y.; Lin, W.; Jia, Y. *Org. Lett.* **2010**, *12*, 4066.
- (15) For examples of fluorenone-substituted azaallenium salts, see: (a) Frey, H.; Mehlhorn, A.; Ruehlmann, K. *Tetrahedron* **1987**, *43*, 2945. (b) Al-Talib, M.; Jibril, I.; Jochims, J. C.; Huttner, G. *Tetrahedron* **1985**, *41*, 527. (c) Al-Talib, M.; Jochims, J. C. *Chem. Ber.* **1984**, *117*, 3222.
- (16) For related examples of [3 + 2] cycloadditions and rearrangements of N-alkyl- and N-arylnitrones with electron-deficient allenes, see: (a) Padwa, A.; Matzinger, M.; Tomioka, Y.; Venkatraman, M. K. *J. Org. Chem.* **1988**, *53*, 955. (b) Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. J. *J. Org. Chem.* **1989**, *54*, 2862. (c) Wilkens, J.; Kuehling, A.; Blechert, S. *Tetrahedron* **1987**, *43*, 3237. (d) Wirth, T.; Blechert, S. *Synlett* **1994**, 717.
- (17) No intermediates, such as **5a** or **6a**, were observed by either ^1H or ^{13}C NMR spectroscopy when the conversion of a mixture of **1a** and **2a** to **4a** was monitored in DCE- d_4 . A mixture of **1a** and DMAD gave only a trace amount of [3 + 2] cycloaddition product when stirred at 25–60 °C. At further elevated temperatures, alternative rearrangement activity was observed; see ref 9.
- (18) We chose to demonstrate the utility of enamino ketones **4** by converting a representative set of examples to pyrroles **8**. The hydrolysis and condensation process appeared to be general.
- (19) For examples of the preparation of 2- $\text{CH}_2\text{CO}_2\text{R}$ pyrroles from α -amino ketones and β -ketoesters, see: (a) Freifeld, I.; Shojaei, H.; Langer, P. *J. Org. Chem.* **2006**, *71*, 4965. (b) Tang, P. C.; Su, Y. D.; Feng, J.; Fu, J. H.; Yang, J. L.; Xiao, L.; Peng, J. H.; Li, Y. L.; Zhang, L.; Hu, B.; Zhou, Y.; Li, F. Q.; Fu, B. B.; Lou, L. G.; Gong, A. S.; She, G. H.; Sun, W. H.; Mong, X. T. *J. Med. Chem.* **2010**, *53*, 8140. (c) Clezy, P. S.; Duncan, M. W.; Ravi, B. N.; Van Thuc, L. *Aust. J. Chem.* **1986**, *39*, 399.
- (20) Dione **10a** was isolated as a 1:1 mixture of diastereomers.
- (21) For recent reviews of the Stetter reaction, see: (a) Rovis, T. *Chem. Lett.* **2008**, *37*, 2. (b) Vora, H. M.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3. (c) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189. (d) Johnson, J. S. *Curr. Opin. Drug Discovery* **2007**, *10*, 691.
- (22) For a recent review and examples of oxidative enolate coupling reactions to form 1,4-diones, see: (a) Guo, F.; Clift, M. D.; Thomson, R. *J. Eur. J. Org. Chem.* **2012**, 4881. (b) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912. (c) Clift, M. D.; Taylor, C. T.; Thomson, R. *J. Org. Lett.* **2007**, *9*, 4667. (d) Avetta, C. A., Jr.; Konkol, L. C.; Taylor, C. N.; Dugan, K. C.; Stern, C. L.; Thomson, R. *J. Org. Lett.* **2008**, *10*, 5621.