

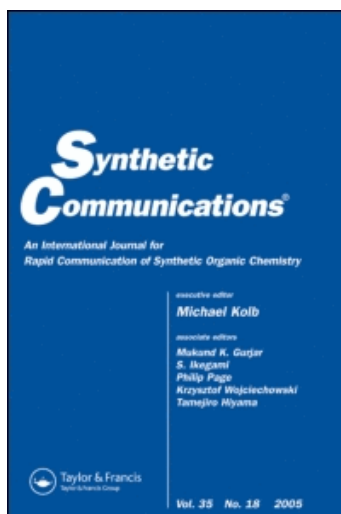
This article was downloaded by: [Monash University]

On: 20 June 2010

Access details: Access Details: [subscription number 907465080]

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Synthetic Communications

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597304>

### Facile Preparation of 1,2-Diketones

Pawel Nowak<sup>a</sup>; David Malwitz<sup>a</sup>; Derek C. Cole<sup>a</sup>

<sup>a</sup> Chemical Sciences, Wyeth Research, Pearl River, New York, USA

Online publication date: 17 June 2010

**To cite this Article** Nowak, Pawel , Malwitz, David and Cole, Derek C.(2010) 'Facile Preparation of 1,2-Diketones', Synthetic Communications, 40: 14, 2164 — 2171

**To link to this Article:** DOI: 10.1080/00397910903219575

**URL:** <http://dx.doi.org/10.1080/00397910903219575>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

## FACILE PREPARATION OF 1,2-DIKETONES

Pawel Nowak, David Malwitz, and Derek C. Cole

Chemical Sciences, Wyeth Research, Pearl River, New York, USA

*Easily accessible lead-like libraries of heterocyclic molecules useful for high-throughput screening are of continuous interest to the pharmaceutical industry. A number of drug-like libraries are derived from aromatic 1,2-diketones; however, nonsymmetrical 1,2-diketones are challenging to prepare. This communication describes a simple and practical synthesis of 1,2-diketones based on a controlled cross benzoin-like condensation reaction.*

**Keywords:** Cross-benzoin condensation; 1,2-diketones

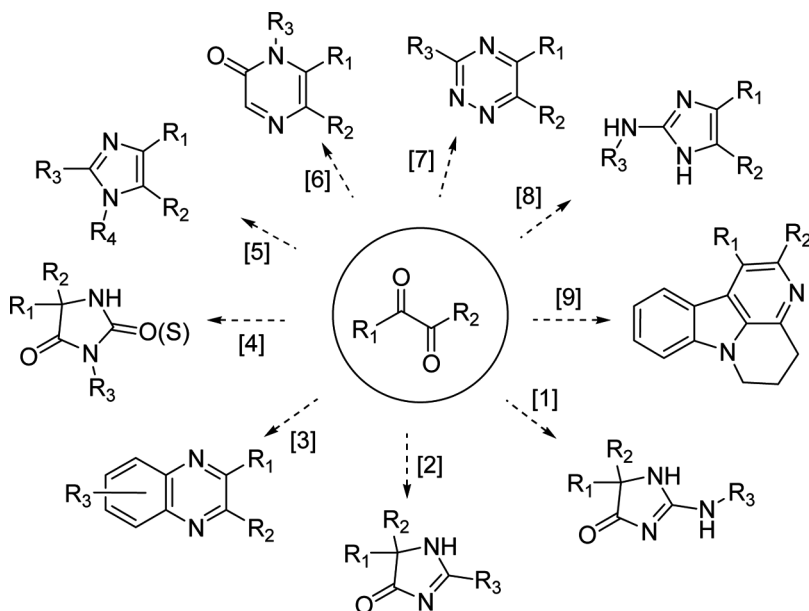
### INTRODUCTION

The ability of the pharmaceutical industry to quickly screen large numbers of compounds using high-throughput screening (HTS) technologies continues to stimulate the demand for preparation of arrays of novel small molecules. An increased access to chemical diversity is needed to target all of biological space and to increase the number of “drugable” targets. Literature precedents indicate that a number of drug-like heterocyclic libraries (Scheme 1) may be prepared starting from 1,2-diketones, such as 2-amino-1*H*-imidazol-4(5*H*)-ones,<sup>[1]</sup> 1*H*-imidazol-4(5*H*)-ones,<sup>[2]</sup> quinoxalines,<sup>[3]</sup> imidazolidine-2,4-diones and 2-thioxoimidazolidin-4-ones,<sup>[4]</sup> imidazoles,<sup>[5]</sup> pyrazin-2(1*H*)-ones,<sup>[6]</sup> 1,2,4-triazines,<sup>[7]</sup> 1*H*-imidazol-2-amines,<sup>[8]</sup> and canthine-like alkaloids.<sup>[9]</sup>

Rapid access to arrays of heterocycles derived from 1,2-diketones is limited by the lack of commercial availability or efficient synthetic procedures of diverse nonsymmetrically substituted 1,2-diketones. 1,2-Diketones are prepared by simple oxidation of 2-hydroxyketones, and aryl-substituted 2-hydroxyketones are typically prepared using benzoin condensation. However, practical application of the classical benzoin condensation is limited to symmetrically substituted products because coupling of two different aldehydes generally leads to mixtures of products. Several solutions to this problem have been reported<sup>[10]</sup>; however, these suffer from lengthy preparations and uncommon reagents. We sought to develop a controlled cross-condensation of two carbonyl partners that could be readily performed and would lead directly to the desired 1,2-diketones. The two-step procedure we report here relies on readily available and inexpensive off-the-shelf aldehyde and acid chloride reagents and involves conversion of the aldehyde to the corresponding trimethylsilyl

Received June 16, 2009.

Address correspondence to Pawel Nowak, Chemical Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA. E-mail: nowakp@wyeth.com



Scheme 1. Examples of heterocycles derived from 1,2-diketones.



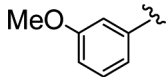
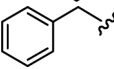

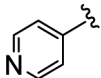
cyanohydrin followed by coupling with the acid chloride and deprotection to yield the unsymmetrical 1,2-diketone.

## RESULTS AND DISCUSSION

The introduction of trimethylsilyl cyanide<sup>[11]</sup> reagent allowed for a quick and efficient access to protected cyanohydrins. Six examples were prepared in excellent yields following the Evans protocol<sup>[12]</sup> (Table 1). The reaction proceeded at very mild conditions in chloroform at room temperature with zinc iodide as catalyst. In the case of 4-pyridinecarboxaldehyde, reaction with trimethylsilyl cyanide in the presence of zinc iodide produced only polymeric material; however, when the reaction was run in the absence of catalyst, the trimethylsilyl cyanohydrin of 4-pyridinecarboxaldehyde was produced in 83% yield.

Various combinations of bases and solvents, including NaH, lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LiTMP), and lithium hexamethyldisilazane (LiHMDS) in toluene, Et<sub>2</sub>O, and tetrahydrofuran (THF), were tried for the deprotonation of trimethylsilyl cyanohydrins and coupling with the acid chlorides. The reaction was found to proceed in greatest yields with LiHMDS in THF at low (−78 °C) temperature.<sup>[4j,k]</sup> Originally, we intended to moderate the reactivity of the lithium anion by stoichiometric addition of copper salts; however, this was not needed as the reaction with acid chlorides proceeded cleanly in the absence of these additives, and no double addition of the anion to the carbonyl group was observed. The intermediate keto-cyanohydrins could be isolated; however, it was more convenient to regenerate the second carbonyl group in a one-pot process.

**Table 1.** Preparation of trimethylsilyl cyanohydrins

$  \begin{array}{ccc}  \text{R}_1-\text{C}(=\text{O})\text{H} & \xrightarrow[\text{CHCl}_3, 4\text{h, rt}]{\text{TMSCN, ZnI}_2} & \text{R}_1-\text{C}(\text{OTMS})(\text{CN})  \end{array}  $		
No.	R <sub>1</sub>	Yield (%) <sup>a</sup>
1		97
2		98
3		98
4		94
5		92
6		0 (83) <sup>b</sup>

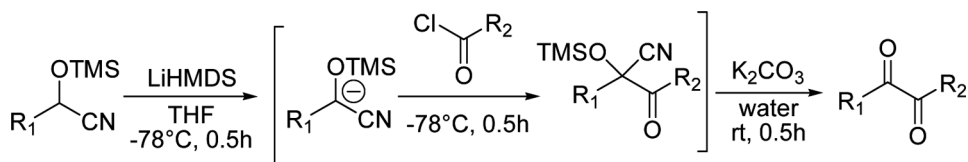
<sup>a</sup>Isolated yields after distillation.<sup>b</sup>Reaction in the absence of ZnI<sub>2</sub> catalyst.





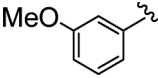

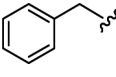








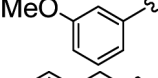

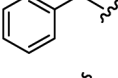




The use of tetrabutylammonium fluoride, a common reagent for this type of transformation, led to a complex mixture of products, but simple treatment with aqueous potassium carbonate gave the desired diketones in good to excellent yields (Table 2). The conditions turned out to be incompatible with the 4-pyridinyl substrates, as no diketones were isolated when the deprotonated 4-pyridyltrimethylsilylcyanohydrin was quenched with benzoyl chloride (entry 6) or when phenyltrimethylsilyl cyanohydrin was quenched with isonicotinoyl chloride (entry 11).

In conclusion, we have developed a simple, reliable, and short synthesis of 1,2-diketones relying only on easily available, inexpensive, and diverse off-the-shelf aldehydes and acid chlorides.

## EXPERIMENTAL

Melting points were determined in a Mel-Temp II instrument and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded on a Thermo-Nicolet Nexus 470 instrument. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured on a Bruker Spectrospin 300-MHz instrument. Mass spectra (MS) were obtained using a Bruker Apex II FTICR mass spectrometer equipped with an actively shielded 9.4-tesla superconducting magnet (Magnex Scientific Ltd.) and an external Bruker Apollo electrospray ionization (ESI) source. Elemental analyses were measured on a Perkin-Elmer 2400 series II instrument.

**Table 2.** Preparation of 1,2-diketones from TMS cyanohydrins and acid chlorides

No.	R <sub>1</sub>	R <sub>2</sub>	Yield (%)
1			87
2			92
3			91
4			71
5			61
6			0
7			89
8			73
9			65
10			94
11			0

**3-Methoxy- $\alpha$ -[(trimethylsilyl)oxy]-benzeneacetonitrile<sup>[13]</sup>**  
**(Table 1, Entry 3)**

3-Methoxybenzaldehyde (6.81 g, 50.0 mmol) and trimethylsilyl cyanide (5.95 g, 60.0 mmol) were dissolved in chloroform (10 mL). The solution was cooled in a cold water bath (10 °C), and zinc iodide (80 mg, 0.25 mmol) was added. After 4 h of stirring, the solution was diluted with Et<sub>2</sub>O (200 mL) and washed with aqueous sodium thiosulfate (50 mL) and saturated sodium bicarbonate (50 mL). The organic solution was dried with magnesium sulfate and evaporated. The remaining liquid was distilled

in a Kugelrohr apparatus in a vacuum (0.1 mm Hg) to provide a light yellow oil (11.77 g, 98%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.32 (dd, 1H,  $J_1 = 9.0$   $J_2 = 8.5$  Hz), 7.06–7.00 (m, 1H), 6.91 (dd, 1H,  $J_1 = 9.0$   $J_2 = 3.5$  Hz), 5.46 (s, 1H), 3.82 (s, 3H), 0.23 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  160, 137.7, 130.0, 119.1, 118.5, 114.8, 111.8, 63.6, 55.2, –0.3; IR (KBr): 1251, 1066, 1035  $\text{cm}^{-1}$ ; M/S:  $m/e$  ( $\text{M} + \text{NH}_4$ ) $^+$  253.1 (22%), ( $\text{M} + \text{H}$ ) $^+$  236.1 (100%). Anal. calcd. for  $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{Si}$ : C, 61.24; H, 7.28; N, 5.95. Found: C, 61.18; H, 7.15; N, 6.06.

Other cyanohydrines (Table 1) were prepared in the same manner, except for entry 6, where the reaction was run without zinc iodide catalyst.

### (3-Methoxyphenyl)phenylethanedione<sup>[14]</sup> (Table 2, Entry 3)

Hexamethyldisilazane (0.75 g, 4.67 mmol) was dissolved in THF, and the solution was cooled in an ice bath. N-Butyllithium (1.70 mL, 2.5 M solution in hexanes, 4.25 mmol) was added. After 5 min, the solution was cooled to  $-78^\circ\text{C}$  and cannulated to a solution of 3-methoxy- $\alpha$ -[(trimethylsilyl)oxy]-benzeneacetonitrile (1.00 g, 4.25 mmol) in THF (15 mL), which was also cooled to  $-78^\circ\text{C}$ . After 30 min, this solution was cannulated to a solution of benzoyl chloride (0.72 g, 5.10 mmol) in THF (15 mL) cooled to  $-78^\circ\text{C}$ . After another 30 min, the solution was warmed up to  $0^\circ\text{C}$  in an ice bath for 15 min, and it was quenched with 10% aqueous potassium carbonate (40 mL) and extracted with  $\text{Et}_2\text{O}$ . The mixture was shaken in a separatory funnel for 10 min. Diethyl ether (50 mL) was added, and the mixture was extracted. The organic phase was dried with magnesium sulfate and concentrated to provide the crude product as a yellow solid (1.0 g), which was sufficiently pure for library preparations. The product could be purified by flash chromatography (gradient from 100% hexane to 50:50 hexane/ethyl acetate) to yield yellow crystals (0.92 g, 90%). Mp  $91\text{--}93^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.32 (dd, 1H,  $J_1 = 9.0$   $J_2 = 8.5$  Hz), 7.06–7.00 (m, 1H), 6.91 (dd, 1H,  $J_1 = 9.0$   $J_2 = 3.5$  Hz), 5.46 (s, 1H), 3.82 (s, 3H), 0.23 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  194.5 (2 $\times$ ), 160.1, 134.9, 134.2, 133.0, 130.0, 129.9, 129.0, 123.2, 121.9, 112.8, 55.5; IR (KBr): 1670, 1255, 1030  $\text{cm}^{-1}$ ; M/S:  $m/e$  ( $2\text{M} + \text{H}$ ) $^+$  481.2 (100%), ( $\text{M} + \text{H}$ ) $^+$  241.1 (47%). Anal. calcd. for  $\text{C}_{15}\text{H}_{12}\text{O}_3$ : C, 74.99; H, 5.03; N, 0. Found: C, 74.97; H, 4.77; N, 0.

Other 1,2-diketones (Table 2, entries 1, 2, 4–11) were prepared in the same manner.

## REFERENCES

- (a) Bishop, M. M.; Lindoy, L. F.; Miller, D. J.; Turner, P. A comparative investigation of supramolecular structures involving copper(II) complexes of imidazolinylalkanimidamides. *J. Chem. Soc., Dalton Trans.* **2002**, 4128–4133; (b) Schramm, H. W. Reactions of carbonic acid diamides with  $\alpha$ -hydroxy ketones and  $\alpha$ -diketones, part 4: Reactions of substituted biguanides with benzil in ethanol under the influence of sodium ethanolate. *Scientia Pharmaceutica* **1991**, 59, 123–133; (c) Nishimura, T.; Kitajima, K. Reaction of guanidines with  $\alpha$ -diketones: Syntheses of 4,5-disubstituted-2-aminoimidazoles and 2,6-unsymmetrically substituted imidazo[4,5-d]imidazoles. *J. Org. Chem.* **1979**, 44, 818–824; (d) Hoffmann, C. New derivatives of 5,5-diphenylhydantoin, II. *Bull. Soc. Chim. Fr.* **1950**, 659–660.

2. (a) Rio, G.; Ranjon, A. 2,5,5-Triphenylimidazolin-4-one, a new synthesis: Study of its formation by the old synthesis from benzil and benzamidine. *Bull. Soc. Chim. Fr.* **1958**, 543–551; (b) Gillman, K. W.; Higgins, M. A.; Poindexter, G. S.; Browning, M.; Clarke, W. J.; Flowers, S.; Grace, J. E.; Hogan, J. B.; McGovern, R. T.; Iben, L. G.; Mattson, G. K.; Ortiz, A.; Rassnick, S.; Russell, J. W.; Antal-Zimanyi, I. Synthesis and evaluation of 5,5-diphenylimidazolones as potent human neuropeptide Y5 receptor antagonists. *Bioorg. Med. Chem.* **2006**, *14*, 5517–5526.
3. For some examples, see (a) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. General microwave-assisted protocols for the expedient synthesis of quinoxalines and heterocyclic pyrazines. *Tetrahedron Lett.* **2004**, *45*, 4873–4876; (b) Li, Z.; Li, W.; Sun, Y.; Huang, H.; Ouyang, P. Room-temperature facile synthesis of quinoxalines catalyzed by amidosulfonic acid. *J. Het. Chem.* **2008**, *45*, 285–288; (c) Li, A.-R.; Johnson, M. G.; Liu, J.; Chen, X.; Du, X.; Mihalic, J. T.; Deignan, J.; Gustin, D. J.; Duquette, J.; Fu, Z.; Zhu, L.; Marcus, A. P.; Bergeron, P.; McGee, L. R.; Danao, J.; Lemon, B.; Carabeo, T.; Sullivan, T.; Ma, J.; Tang, L.; Tonn, G.; Collins, T. L.; Medina, J. C. Optimization of the heterocyclic core of the quinazolinone-derived CXCR3 antagonists. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 688–693; (d) Palanki, M. S. S.; Dneprovskaya, E.; Doukas, J.; Fine, R. M.; Hood, J.; Kang, X.; Lohse, D.; Martin, M.; Noronha, G.; Soll, R. M.; Wrasidlo, W.; Yee, S.; Zhu, H. Discovery of 3,3'-(2,4-diaminopteridine-6,7-diyl)diphenol as an isozyme-selective inhibitor of PI3 K for the treatment of ischemia reperfusion injury associated with myocardial infarction. *J. Med. Chem.* **2007**, *50*, 4279–4294; (e) Zhang, L.; Qiu, B.; Xiong, B.; Li, X.; Li, J.; Wang, X.; Li, J.; Shen, J. Quinoxalinyurea derivatives as a novel class of JSP-1 inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2118–2122; (f) Rong, F.; Chow, S.; Yan, S.; Larson, G.; Hong, Z.; Wu, J. Structure–activity relationship (SAR) studies of quinoxalines as novel HCV NS5B RNA-dependent RNA polymerase inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1663–1666.
4. For some examples, see (a) Muccioli, G. G.; Martin, D.; Scriba, G. K. E.; Poppitz, W.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. Substituted 5,5'-diphenyl-2-thioxoimidazolidin-4-one as CB1 cannabinoid receptor ligands: Synthesis and pharmacological evaluation. *J. Med. Chem.* **2005**, *48*, 2509–2517; (b) Peretto, I.; Forlani, R.; Fossati, C.; Giardina, G. A. M.; Giardini, A.; Guala, M.; La Porta, E.; Petrillo, P.; Radaelli, S.; Radice, L.; Raveglia, L. F.; Santoro, E.; Scudellaro, R.; Scarpitta, F.; Bigogno, C.; Misiano, P.; Dondio, G. M.; Rizzi, A.; Armani, E.; Amari, G.; Civelli, M.; Villetti, G.; Patacchini, R.; Bergamaschi, M.; Delcanale, M.; Salcedo, C.; Fernandez, A. G.; Imbimbo, B. P. Discovery of diaryl imidazolidin-2-one derivatives, a novel class of muscarinic M3 selective antagonists (part 1). *J. Med. Chem.* **2007**, *50*, 1571–1583; (c) Muccioli, G. G.; Wouters, J.; Scriba, G. K. E.; Poppitz, W.; Poupaert, J. H.; Lambert, D. M. 1-Benzhydryl-3-phenylurea and 1-benzhydryl-3-phenylthiourea derivatives: New templates among the CB1 cannabinoid receptor inverse agonists. *J. Med. Chem.* **2005**, *48*, 7486–7490; (d) Muccioli, G. G.; Poupaert, J. H.; Wouters, J.; Norberg, B.; Poppitz, W.; Scriba, G. K. E.; Lambert, D. M. A rapid and efficient microwave-assisted synthesis of hydantoins and thiohydantoins. *Tetrahedron* **2003**, *59*, 1301–1307.
5. For some examples, see (a) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. Efficient synthesis of imidazoles from aldehydes and 1,2-diketones using microwave irradiation. *Org. Lett.* **2004**, *6*, 1453–1456; (b) Kim, D.-K.; Lim, J.-H.; Lee, J. A.; Dewang, P. M. Synthesis and biological evaluation of trisubstituted imidazole derivatives as inhibitors of p38 $\alpha$  mitogen-activated protein kinase. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4006–4010; (c) Mader, M.; de Dios, A.; Shih, C.; Bonjouklian, R.; Li, T.; White, W.; Lopez de Uralde, B.; Sanchez-Martinez, C.; del Prado, M.; Jaramillo, C.; de Diego, E.; Martin, C.; Luisa, M.; Dominguez, C.; Montero, C.;

- Shepherd, T.; Dally, R.; Toth, J. E.; Chatterjee, A.; Pleite, S.; Blanco-Urgoiti, J.; Perez, L.; Barberis, M.; Lorite, M. J.; Jambrina, E.; Nevill, C. R.; Lee, P. A.; Schultz, R. C.; Wolos, J. A.; Li, L. C.; Campbell, R. M.; Anderson, B. D. Imidazolyl benzimidazoles and imidazo[4,5-b]pyridines as potent p38 $\alpha$  MAP kinase inhibitors with excellent in vivo anti-inflammatory properties. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 179–183; (d) Kokare, N. D.; Sangshetti, J. N.; Shinde, D. B. One-pot efficient synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles and 2,4,5-triaryl-1H-imidazoles using oxalic acid catalyst. *Synthesis* **2007**, 2829–2834; (e) Williams, D. R.; Lee, M.-R.; Song, Y. A.; Ko, S.-K.; Kim, G.-H.; Shin, I. Synthetic small molecules that induce neurogenesis in skeletal muscle. *J. Am. Chem. Soc.* **2007**, *129*, 9258–9259.
6. (a) Kaftory, M.; Shteyman, V.; Lavy, T.; Scheffer, J. R.; Yang, J.; Enkelmann, V. Discrimination in the solid-state photodimerization of 1-methyl-5,6-diphenylpyrazin-2-one. *Eur. J. Org. Chem.* **2005**, 847–853; (b) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Hartman, G. D.; Huff, J. R.; Huber, H. E.; Duggan, M. E. Allosteric Akt (PKB) inhibitors: Discovery and SAR of isozyme selective inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 761–764.
  7. (a) Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W. Broadening the scope of 1,2,4-triazine synthesis by the application of microwave technology. *Tetrahedron Lett.* **2003**, *44*, 1123–1127; (b) Potewar, T. M.; Lahoti, R. J.; Daniel, T.; Srinivasan, K. V. Efficient synthesis of 3,5,6-trisubstituted-1,2,4-triazines in the Brønsted acidic ionic liquid, 1-n-butylimidazolium tetrafluoroborate ([Hbim]BF<sub>4</sub>). *Synth. Commun.* **2007**, *37*, 261–269; (c) Nongkhlaw, R. L.; Myrboh, B. Novel one-pot synthesis of substituted 1,2,4-triazines. *Heterocycl. Commun.* **2006**, *12*, 67–72; (d) Rostamizadeh, S.; Sadeghi, K. One-pot synthesis of 1,2,4-triazines. *Synth. Commun.* **2002**, *32*, 1899–1902; (e) Neipp, C. E.; Ranslow, P. B.; Wan, Z.; Snyder, J. K. Dienophilicity of imidazole in inverse electron demand Diels–Alder reactions. *Tetrahedron Lett.* **1997**, *38*, 7499–7502; (f) Tanaka, A.; Sakai, H.; Ishikawa, T.; Motoyama, Y.; Takasugi, H. Studies on anti-platelet agents, V: Synthesis and structure–activity relationship of 3-substituted 5,6-bis(4-methoxyphenyl)-1,2,4-triazines. *Chem. Pharm. Bull.* **1994**, *42*, 1835–1840; (g) Harada, K. 1,2,4-Triazine chemistry, 10: Dihydro-1,2,4-triazines: Structural studies of 5,6-diaryldihydro-1,2,4-triazines through the reactions with dimethyl acetylenedicarboxylate. *J. Org. Chem.* **1980**, *45*, 4587–4593; (h) O'Rourke, M.; Lang, S. A., Jr.; Cohen, E. 3-Aryl-as-triazines as potential anti-inflammatory agents. *J. Med. Chem.* **1977**, *20*, 723–726.
  8. (a) Gore, V. K.; Ma, V. V.; Tamir, R.; Gavva, N. R.; Treanor, J. J. S.; Norman, M. H. Structure–activity relationship (SAR) investigations of substituted imidazole analogs as TRPV1 antagonists. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5825–5830; (b) also see Ref. 1(b).
  9. (a) Lindsley, C. W.; Wisnoski, D. D.; Wang, Y.; Leister, W. H.; Zhao, Z. A “one pot” microwave-mediated synthesis of the basic canthine skeleton: Expedient access to unnatural  $\beta$ -carboline alkaloids. *Tetrahedron Lett.* **2003**, *44*, 4495–4498; (b) Lindsley, C. W.; Bogusky, M. J.; Leister, W. H.; McClain, R. T.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Ross, C. W., III; Hartman, G. D. Synthesis and biological evaluation of unnatural canthine alkaloids. *Tetrahedron Lett.* **2005**, *46*, 2779–2782.
  10. For example, see (a) Page, P. C. B.; Graham, A. E.; Park, B. K. A convenient preparation of symmetrical and unsymmetrical 1,2-diketones: Application to fluorinated phenytoin synthesis. *Tetrahedron* **1992**, *48*, 7265–7274; (b) Rozwadowska, M. D. Cyanohydrins as substrates in benzoin condensation: Regiocontrolled mixed benzoin condensation. *Tetrahedron* **1985**, *41*, 3135–3140; (c) Demir, A. S.; Reis, O. A convenient and selective synthesis of unsymmetrical benzoin via the cyanide ion-catalyzed cleavage of benzils. *Tetrahedron* **2004**, *60*, 3803–3811; (d) Demir, A. S.; Reis, O.; Igdir, C.; Esiringu, I.; Eymur, S. Generation of acyl anion equivalents from acylphosphonates via phosphonate–phosphate rearrangement: A highly practical method for cross-benzoin reaction. *J. Org.*



- Chem.* **2005**, *70*, 10584–10587, and references therein; (e) Linghu, X.; Bausch, C. C.; Johnson, J. S. Mechanism and scope of the cyanide-catalyzed cross silyl benzoin reaction. *J. Am. Chem. Soc.* **2005**, *127*, 1833–1840; (f) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. Applications of optically active aryl cyanohydrins in the synthesis of  $\alpha$ -hydroxy aldehydes,  $\alpha$ -hydroxy ketones, and  $\beta$ -hydroxy amines. *Aust. J. Chem.* **1990**, *43*, 2045–2062; (g) Pirrung, M. C.; Shuey, S. W. Photoremovable protecting groups for phosphorylation of chiral alcohols: Asymmetric synthesis of phosphotriesters of (–)-3',5'-dimethoxybenzoin. *J. Org. Chem.* **1994**, *59*, 3890–3897, and references therein; (h) Denkermann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Muller, M. Development of a donor–acceptor concept for enzymatic cross-coupling reactions of aldehydes: The first asymmetric cross-benzoin condensation. *J. Am. Chem. Soc.* **2002**, *124*, 12084–12085; (i) Katritzky, A. R.; Wang, Z.; Lang, H.; Feng, D. Novel and facile syntheses of alkenyl, alkynyl, and aryl 1,2-diketones. *J. Org. Chem.* **1997**, *62*, 4125–4130; (j) Huenig, S.; Wehner, G. Trimethylsilyl cyanide as an umpolung reagent, II: Nucleophilic acylation of aldehydes and ketones with anionic 1,4-O,O-silyl group migration. *Chem. Ber.* **1979**, *112*, 2062–2067; (k) Huenig, S.; Wehner, G. Nucleophilic acylation with masked acyl anions, III: Synthesis of  $\alpha$ -hydroxyketones. *Synthesis* **1975**, 391–392.
11. (a) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981; (b) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer: Berlin, 1983; (c) *Advances in Silicon Chemistry 1*, G. Larson (Ed.); JAI: Greenwich, CT, 1991; (d) Groutas, W. C.; Felker, D. Synthetic applications of cyanotrimethylsilane, iodotrimethylsilane, azidotrimethylsilane, and methylthiotrimethylsilane. *Synthesis* **1980**, 861–868; (e) Livinghouse, T. Trimethylsilyl cyanide: Cyanosilation of p-benzoquinone. *Org. Synth. Coll.* **1990**, *7*, 517.
  12. Evans, D. A.; Truesdale, L. K.; Carroll, G. L. C. Cyanosilylation of aldehydes and ketones: Convenient route to cyanohydrin derivatives. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56.
  13. Mai, K.; Patil, G. Facile synthesis of  $\alpha$ -amino nitriles. *Tetrahedron Lett.* **1984**, *25*, 4583–4856.
  14. Leonard, N. J.; Rapala, R. T.; Herzog, H. L.; Blout, E. R. The ultraviolet absorption spectra of alkoxy- and hydroxybenzils. *J. Am. Chem. Soc.* **1949**, *71*, 2997–3002.