# Traceless Solid-Phase Synthesis of Heteroannulated 1,3-Oxazin-6-ones

Jun Che, Makam S. Raghavendra, and Yulin Lam*

*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543*

*Received November 24, 2008*

A microwave-assisted solid-phase synthesis of heteroannulated 1,3-oxazin-6-ones has been developed. Significant rate enhancement was observed for all steps carried out under microwave irradiation, and the overall reaction time was dramatically shortened when compared to the conventional procedures. A representative set of 20 bi- and tricyclic heteroannulated 1,3-oxazin-6-ones was prepared. Key steps in the synthesis are (i) five-member heterocycle formation, (ii) acylation of amine, and (iii) ring closure to give the heteroannulated 1,3-oxazin-6-one.

## Introduction

Fused 1,3-oxazin-6-ones constitute an interesting class of pharmacologically active compounds because they have shown a multitude of biological activities. Benzoxazinones, the most widely studied analogs, are found in some naturally occurring antimicrobial and antifungal agents.[1] They are known to possess anticoagulative,[2] antiviral,[3] and herbicidal[4] activities, are potential inhibitors of HSV-1 and C1r serine protease,[5] chymotrypsin, and pancreatic elastase,[6] and have also found applications in materials and polymer science.[7] The heteroannulated oxazinones like thieno[2,3-*d*]-1,3-ox-azinones,[8] pyrrolo[2,3-*d*]-1,3-oxazin-4-ones,[9] and pyrazolo[3,4-*d*][1,3]oxazin-4-ones[10] are less common in nature but have also attracted much interest because they too have been shown to demonstrate a wide range of biological activities. This multifaceted profile bodes well for the interaction of such heterocycles with a variety of biological targets, which has consequently led to the development of a number of lead compounds based on the fused 1,3-oxazinone scaffold. Over the years numerous solution-phase methodologies for the synthesis of fused heterocyclic oxazinone derivatives have been reported.[10b,11] However for the preparation of large libraries without massive synthetic effort, we envisage that solid-phase synthesis (SPS) which allows convenient handling and distribution of the synthetic intermediates would offer an attractive alternative pathway. To our knowledge, such a process has not been previously demonstrated. Thus, we herein describe a convenient traceless solid-phase approach to bi- and tricyclic heteroannulated 1,3-oxazin-6-ones. Our approach involves, first, the synthesis of the five-membered heterocyclic acylamino ester on solid-support and then cyclization to a fused heterocyclic oxazinone derivative via dibromotetrachloroethane and triphenylphosphine mediated ring closure (Scheme 1).

## Results and Discussion

Wang resin **1** was chosen for our solid-phase studies because it was easily converted to the requisite ester linkage

that could eventually be tracelessly cleaved with concomitant formation of the 1,3-oxazin-6-one ring.
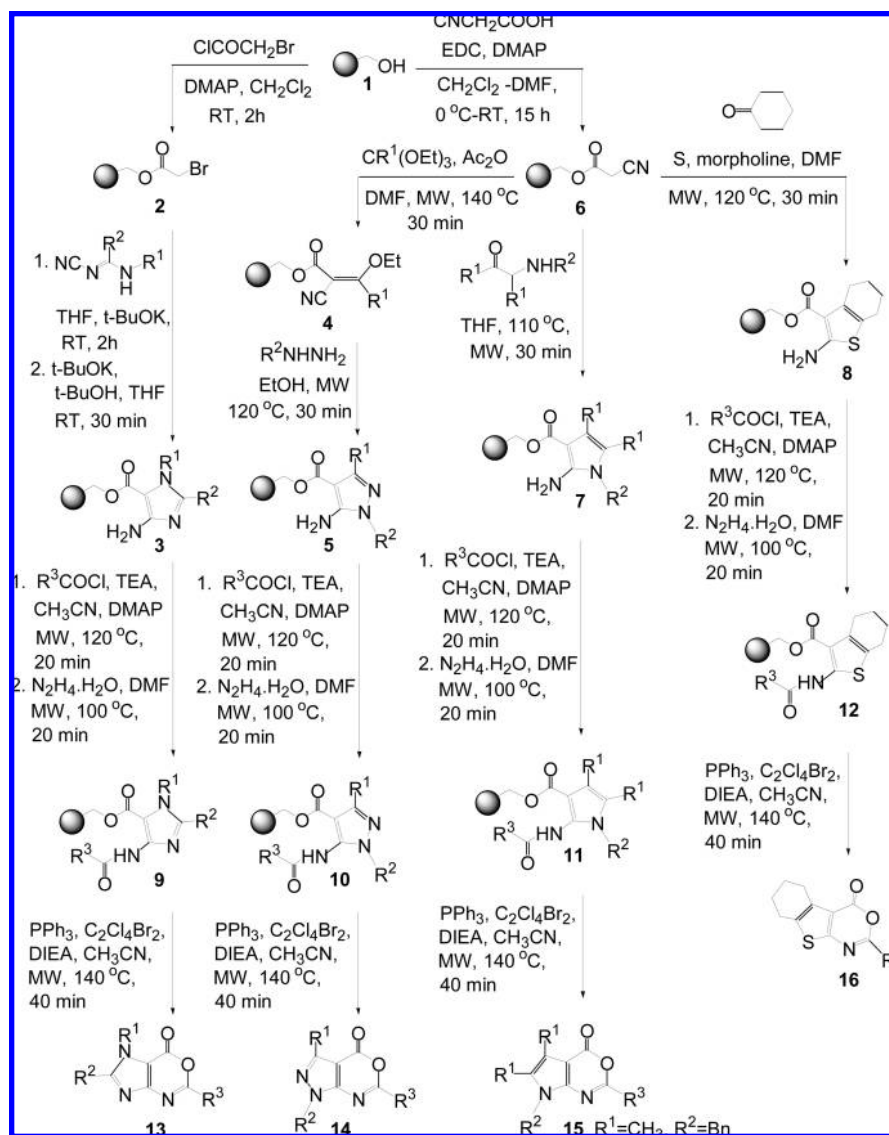
**Synthesis of Polymer-Supported 5-Amino-2,3-disubstituted-3*H*-imidazole 3.** We had recently reported the synthesis of resin **3** from **1** in a 4-step procedure.[12] We herein disclose a modified procedure that provides resin **3** in 3 steps.

Prior to the SPS of resin **3**, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications required for solid-phase format. Benzyl alcohol **17** was reacted with bromoacetyl chloride at room temperature to afford benzyl 2-bromoacetate **18** in quantitative yield (Scheme 2). When compound **18** was condensed with *N*-butyl-*N*′-cyanobenzimidamide (Scheme 2, $R^1 = C_6H_5$ and $R^2 = C_4H_9$) in the presence of *t*-BuOK, 5-amino-3-butyl-2-phenyl-3H-imidazole-4-carboxylic acid benzyl ester **20a** was obtained directly in 95% yield. However when the reaction was carried out with *N*-benzyl-*N*′-cyanobenzimidamide, the intermediate **19** ($R^1 = C_6H_5$ and $R^2 = CH_2C_6H_5$) was the major product (70%), and only a small portion of **20b** (20%) was obtained. Attempts to obtain **20b** directly from **18** resulted in poor yields. With **19** in hand, we proceeded to treat it with *t*-BuOK in mixed *t*-BuOH and THF which gave **20b** in 50% yield. The overall yield of **20** obtained via this procedure was higher than the yield obtained through the 4-step synthesis. In addition, it would provide a slightly shorter SPS of resin **3**.

With the solution-state procedure established, we proceeded to demonstrate the solid-phase synthesis of resin **3**. Wang resin **1** was reacted with bromoacetyl chloride in the presence of DMAP. The formation of resin **2** was amenable to KBr FTIR monitoring (i.e., disappearance of the OH stretch at 3566 cm$^{-1}$ and the appearance of a strong C=O stretch at 1748 cm$^{-1}$) Resin **2** was then treated with various imidamides to give the cyanoimino intermediate which according to FTIR analysis shows a CN stretch at 2183 cm$^{-1}$. Further treatment of this intermediate with *t*-BuOK and *t*-BuOH gave resin **3** whose formation was monitored by FTIR for the disappearance of the CN stretch and a shift in the C=O stretch from 1739 to 1671 cm$^{-1}$.

---

* To whom correspondence should be addressed. E-mail: chmlamyl@nus.edu.sg. Fax: (65)-6779-1691.

**Scheme 1.** SPS of Heteroannulated 1,3-Oxazin-6-ones



**Scheme 2.** Solution-Phase Synthesis
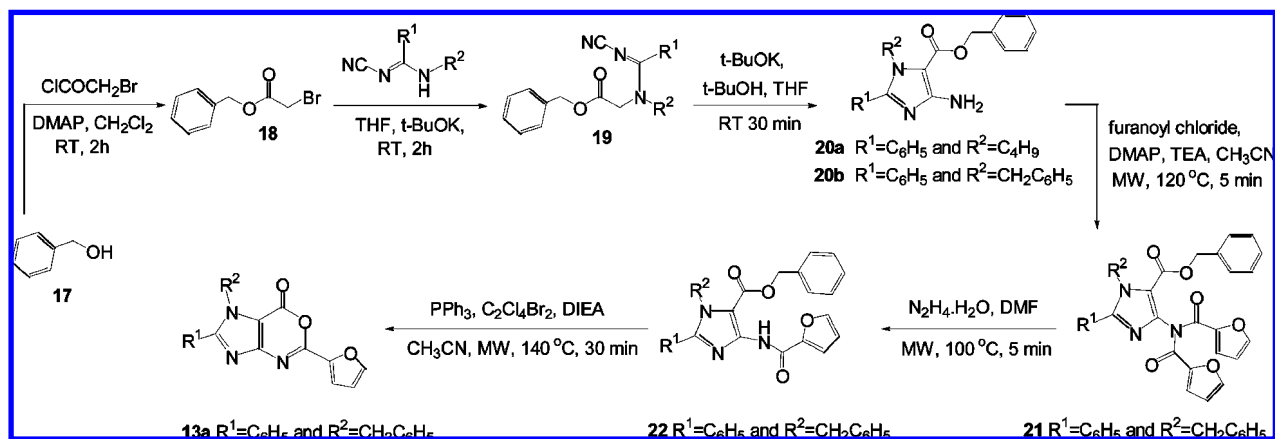


**Synthesis of Polymer-Supported 5-Amino-1,3-trisubstituted-1H-pyrazole 5, 2-Amino-1,4,5-dimethyl-1H-pyrrole 7, and 5-Amino-2,3-disubstituted-thiophene 8.** The key intermediate, resin **6**, was prepared by esterifying cyanoacetic acid with resin **1** using a procedure reported by Zaragoza.[13] Resin **6**, whose formation was monitored by

FTIR for the CN stretch at 2264 cm$^{-1}$, was then treated with triethyl orthoformate (7 equiv) and acetic anhydride (8 equiv) in toluene at 100 °C for 36 h to give resin **4**, which could not be reliably analyzed on the FTIR. Hence we proceeded with the condensation of resin **4** with phenyl hydrazine (5 equiv) in ethanol/DMF (1:1) at 80 °C for 12 h to provide

resin **5**, which was amenable to FTIR monitoring (i.e., disappearance of CN stretch).

To prepare resin **5** more expeditiously, we have explored the reactions under microwave conditions. For the evaluation of the microwave-assisted formation of resin **4**, we carried out a systematic variation of the reaction time and temperature with triethyl orthoformate and acetic anhydride in DMF as a representative example. We discovered that the reaction was completed within 30 min at 140 °C and subsequent treatment of resin **4** with phenyl hydrazine in ethanol-DMF (1:1) solvent at 120 °C for 30 min gave resin **5**. To illustrate the versatility of this methodology, a representative set of resin **5** was prepared.

Resin **6** was also applied to the preparation of resins **7** and **8**. In the synthesis of resin **7** via a modified Bayomi procedure,[14] 3-benzylaminobutan-2-one, which was prepared in 73% yield by refluxing 2-hydroxybutanone and benzylamine in cyclohexane for 2 h, was slowly stirred under reflux with resin **6** for 12 h to provide resin **7**, whose formation was amenable to FTIR monitoring. On the other hand, under microwave irradiation at 110 °C and with THF as solvent, the reaction was found to be completed within 30 min.

The synthesis of resin **8** was achieved by adapting the Gewald's synthesis[15] whereby a three-component condensation of a cyclic ketone, resin **6**, and elemental sulfur was carried out in the presence of morpholine. Under conventional heating conditions, the reaction required 18 h and a reflux temperature of 60 °C. However under microwave irradiation at 120 °C, the same reaction was found to be completed in 30 min and the formation of resin **8** was again monitored by FTIR for the disappearance of the CN stretch.

**Solid-Phase Synthesis of the 1,3-Oxazin-6-one.** To establish the reaction conditions required for the 1,3-oxazin-6-one ring formation, we carried out a solution-phase study of the reaction strategy (Scheme 2). Compound **20b** was treated with furanoyl chloride in the presence of TEA and DMAP at room temperature[16] and under reflux. Both reaction conditions provided the diacylated compound **21** (∼85%) and monoacylated **22** (∼10%) in 12 and 1 h, respectively. Compound **21** was then refluxed with hydrazine monohydrate in dioxane-isopropanol for 90 min to facilitate deacylation and afford **22** in 94% yield. Subsequent treatment of **22** with $C_2Cl_4Br_2$ (1.1 equiv) and $PPh_3$ (1.1 equiv) in the presence of TEA (3 equiv)[16] provided **13a** (74% yield) and unreacted **22**. Attempts to completely consume the residual **22** by prolonging the reflux time or doubling the amount of reagents used only led to a small increase in the yield of **13a** but not the complete consumption of **22**. We then decided to first treat **22** with $Br_2C_2Cl_4$ (1.5 equiv), $PPh_3$ (1.5 equiv), and DIEA (3 equiv) under reflux for 8 h. Thereafter a second portion of the reagents was added and the reflux was continued for another 8 h. This resulted in the complete consumption of **22** and **13a** was obtained in 95% yield. However the major drawback to this procedure is the long reaction times and to circumvent this problem, we once again turned to microwave irradiation.

When **20b** was heated with furanoyl chloride, DMAP and TEA in the microwave reactor at 120 °C, complete conversion was observed within 5 min giving compounds **21** and **22** in 88% and 5% yields, respectively (Scheme 2). Compound **21** was then heated at 100 °C with hydrazine monohydrate in DMF under microwave irradiation. The reaction proceeded rapidly and was completed in 5 min, giving **22** in quantitative yield. For the ring closure reaction, we used the protocol established for conventional heating conditions and by varying the temperature and reaction time, the microwave-assisted ring closure reaction was found to occur optimally at 140 °C and the reaction was completed in 30 min, giving **13a** in 96% yield.

To translate the reaction procedure onto solid-phase format, we treated resin **3** with furanoyl chloride, DMAP, and TEA under microwave irradiation for 20 min. This acylation reaction could not be reliably monitored by FTIR. Hence without performing any characterization of the resin, it was further microwaved at 100 °C with hydrazine monohydrate in DMF for 20 min to give resin **9**, which again could not be reliably analyzed on the FTIR. Thus we proceeded to treat resin **9** with dibromotetrachloroethane and $PPh_3$ in the presence of DIEA to provide **13**. Optimization of the reaction conditions showed that the best overall yield (18%) was obtained when the reaction mixture was microwave irradiated at 140 °C for 40 min. To illustrate the versatility of this methodology, the synthetic procedure was extended to resins **5**, **7**, and **8** and a representative set of 20 bi- and tricyclic heteroannulated 1,3-oxazin-6-ones was prepared (Figure 1) in 16−36% overall yield, indicating an average yield of at least 70% for each step of the reaction.

In summary, an efficient microwave-assisted SPS route to bi- and tricyclic heteroannulated 1,3-oxazin-6-ones has been devised. The target compounds were obtained in good yields. To our knowledge, this is the first example of a synthesis of heteroannulated 1,3-oxazin-6-ones on solid-phase.

## Experimental Section

**General Procedures.** Wang resin was purchased from Tianjin Nankai Hecheng Science and Technology Co (100−200 mesh, 1.4 mmol/g, 1% divinylbenzene cross-linking). All other chemical reagents were obtained from either Aldrich, Merck, Lancaster, or Fluka and used without further purification. The solid-phase room reactions were agitated on a flask shaker SF1 (Stuart Scientific). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. Flash column chromatograph was performed with silica gel (Merck, 70−230 mesh).

^{1}H and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 or DPX 500 Fourier Transform spectrometer. Chemical shifts were reported in $\delta$ (ppm), relative to the internal standard of tetramethylsilane (TMS). The signals observed were described as s (singlet), d (doublet), t (triplet), and m (multiplet). The number of protons (n) for a given resonance was indicated as nH. All Infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectrometry was performed on a Finnigan MAT 95/XL-T spectrometer under electron impact (EI) and electrospray
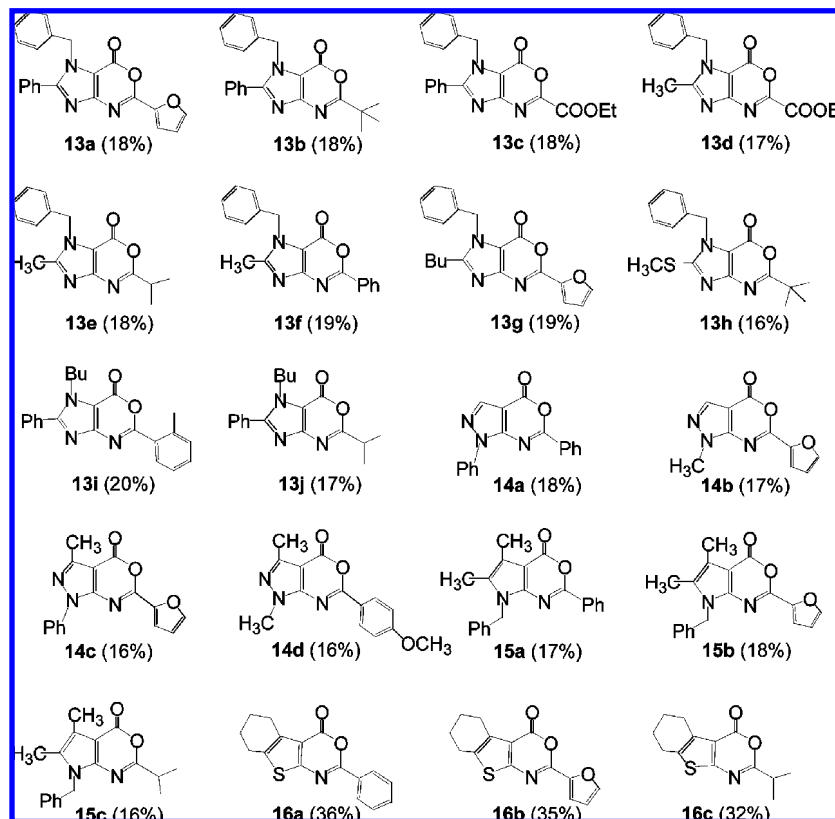
**Figure 1.** Library of **13**−**16**.

ionization (ESI) techniques. Microwave reactions were performed on the Biotage Initiator microwave synthesizer.

**Synthesis of Benzyl 2-Bromoacetate 18.** 2-Bromoacetyl chloride (0.2361 g, 1.50 mmol) was dissolved in dichloromethane (5 mL), and the solution was added dropwise into a mixture of benzyl alcohol (0.1081 g, 1.00 mmol), DMAP (0.0240 g, 0.02 mmol), and dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 2 h, then quenched with water (20 mL), and extracted with EtOAc (10 mL × 3). The combined organic layer was dried with MgSO$_4$, filtered, concentrated, and purified by column chromatography (EtOAc/Hexane = 1:40) to give **18** as a pale yellow liquid (0.4201 g, 99% yield). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.90 (s, 2 H, C*H*$_2$Br), 5.25 (s, 2 H, PhC*H*$_2$), 7.41−7.44 (m, 5 H, Ar*H*). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 25.9, 67.9, 128.4, 128.5, 128.6, 135.0, 167.0. HRMS (EI, C$_9$H$_9$BrO$_2$) calcd: 227.9786, found 227.9790.

**Synthesis of *N*-Alkyl-*N*′-cyanoalkanimidamide and *N*-Alkyl-*N*-cyanoacetimidamide. Preparation of the Ethyl *N*-Cyanoacetimidate.** Cyanamide (0.42 g, 10 mmol) was dissolved in trimethoxyethane (5.47 mL, 30 mmol), and the reaction was heated at 70 °C for 12 h. Thereafter, the reaction mixture was concentrated and purified by column chromatography (EtOAc/Hexane = 1:5) to give ethyl *N*-cyanoacetimidate (0.97 g, 87%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.24−1.27 (t, 3 H, *J* = 7.3 Hz, OCH$_2$C*H*$_3$), 2.30 (s, 3 H, CC*H*$_3$), 4.18−4.22 (m, 2 H, *J* = 7.2 Hz, OC*H*$_2$CH$_3$). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 13.3, 20.6, 65.5, 113.8, 181.7. HRMS (ESI, C$_5$H$_9$N$_2$O + H) cacld: 113.0709, found 113.0704.

Ethyl *N*-cyanobenzimidate and methyl *N*-cyanopentanimidate were prepared in the same manner.

**Ethyl *N*-Cyanobenzimidate.** $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.44−1.48 (t, 3 H, *J* = 7.0 Hz, OCH$_2$CH$_3$), 4.45−4.52 (m, 2 H, *J* = 7.1 Hz, OCH$_2$CH$_3$), 7.49−8.09 (m, 5 H, ArH). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 13.1, 65.7, 112.9, 127.9, 128.1, 128.9, 133.0, 173.8. HRMS (ESI, C$_{10}$H$_{11}$N$_2$O + H) calcd: 175.0866, found 175.0873. Yield: 82%.

**Methyl N-Cyanopentanimidate.** $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 0.90−0.93 (t, 3 H, *J* = 7.6 Hz, CH$_2$CH$_2$CH$_2$C*H*$_3$), 1.32−1.40 (m, 2 H, CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.63−1.69 (m, 2 H, CH$_2$-C*H*$_2$CH$_2$CH$_3$), 2.66−2.69 (t, 2 H, *J* = 7.6 Hz, C*H*$_2$CH$_2$-CH$_2$CH$_3$), 3.84 (s, 3 H, OC*H*$_3$). $^{13}$CNMR (CDCl$_3$, 125 MHz): $\delta$ 13.4, 22.0, 27.6, 34.2, 56.2, 113.6, 185.4. HRMS (ESI, C$_7$H$_{13}$N$_2$O + H) calcd: 141.1022, found 141.1017. Yield: 83%

**Preparation of *N*-Benzyl-*N*′-cyanobenzimidamide.** To a solution of ethyl *N*-cyanobenzimidate (0.1741 g, 1 mmol) in THF (5 mL) was added benzylamine (0.2141 g, 2 mol), and the reaction mixture was stirred at room temperature for 4 h. Thereafter, the reaction mixture was concentrated and purified by column chromatography (EtOAc/CH$_2$Cl$_2$ = 1:2) to give *N*-benzyl-*N*′-cyanobenzimidamide (0.2115 g, 90%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.62−4.63 (d, 2 H, *J* = 5.7 MHz, PhC*H*$_2$), 6.57 (s, 1 H, N*H*), 7.26−7.60 (m, 10 H, Ar*H*). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 46.6, 117.2, 127.1, 128.1, 128.2, 128.9, 129.1, 132.1, 132.3, 136.2, 170.3. HRMS (ESI, C$_{15}$H$_{12}$N$_3$ − H) calcd: 234.1028, found 234.1037.

*N*-Benzyl-*N*′-cyanopentanimidamide, *N*-benzyl-*N*′-cyanopentanimidamide, and *N*-benzyl-*N*′-cyanoacetimidamide were prepared in the same manner.

*N*-Benzyl-*N*′-cyanopentanimidamide. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 0.0.93−0.96 (t, 3 H, *J* = 7.6 Hz, CH$_2$-CH$_2$CH$_2$C*H*$_3$), 1.35−1.42 (m, 2 H, CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.66−1.73 (m, 2 H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 2.54−2.57 (t, 2 H, *J* = 7.6 Hz, C*H*$_2$CH$_2$CH$_2$CH$_3$), 4.46−4.47 (d, 2 H, *J* = 5.7 Hz, PhC*H*$_2$), 7.28−7.33 (m, 5 H, Ar*H*), 8.23 (s, 1 H, N*H*). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 13.4, 22.0, 28.6, 34.6, 45.3, 118.0, 127.3, 127.6, 128.3, 136.5, 175.2. HRMS (EI, C$_{13}$H$_{17}$N$_3$) calcd: 215.1422, found 215.1415.

*N*-Phenyl-*N*′-cyanopentanimidamide. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 0.091−0.94 (t, 3 H, *J* = 7.6 Hz, CH$_2$-CH$_2$CH$_2$C*H*$_3$), 1.31−1.38 (m, 2 H, CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.56−1.60 (m, 2 H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 3.37−3.41 (m, 2 H, C*H*$_2$-CH$_2$CH$_2$CH$_3$), 6.95 (s, 1 H, N*H*), 7.38 −7.52 (m, 5 H, Ar*H*). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 13.6, 20.0, 30.4, 42.4, 127.1, 128.7, 131.7, 132.5, 170.3. HRMS (ESI, C$_{12}$H$_{14}$N$_3$ − H) calcd: 200.1180, found 200.1178.

*N*-Benzyl-*N*′-cyanoacetimidamide. ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 2.26 (s, 3 H, N = CC*H*$_3$), 4.39−4.40 (d, 2 H, *J* = 5.7 Hz, PhC*H*$_2$), 7.28−7.37 (m, 5 H, Ar*H*), 9.25 (s, 1H, N*H*). ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ 20.4, 44.7, 118.0, 127.3, 127.7, 128.5, 137.2, 171.5. HRMS (ESI, C$_{10}$H$_{10}$N$_3$ − H) calcd: 172.0880, found 172.0874.

**Preparation of Methyl *N*-Benzyl-*N*′-cyanocarbamim-idothioate.** To a solution of dimethyl cyanocarbonimi-dodithioate (0.1460 g, 1 mmol) in ethanol (5 mL) was added benzylamine (0.2141 g, 2 mol), and the reaction mixture was stirred at room temperature for 4 h. Thereafter, the reaction mixture was filtered and precipitate was washed with EtOAC to give methyl *N*-benzyl-*N*′-cyano carbamimidothioate (0.17 g, 90%). ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 2.62 (s, 3 H, SC*H*$_3$), 4.48−4.50 (d, 2 H, *J* = 5.6 Hz, PhC*H*$_2$), 7.26−7.36 (m, 5 H, Ar*H*), 8.89 (s, 1 H, N*H*). ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ 14.0, 46.1, 115.7, 127.2, 127.3, 128.3, 137.4, 170.2. HRMS (EI, C$_{10}$H$_{11}$SN$_3$) calcd: 205.0674, found 205.0674.

**Synthesis of Benzyl 2-(*N*-Benzyl-*N*′-cyanobenzimida-mido)acetate 19.** *N*-benzyl-*N*′-cyanobenzimidamide (0.4002 g, 2 mmol) and *t*-BuOK (0.2244 g, 2.0 mmol) were dissolved in THF (5 mL) and then added to **18** (0.2280 g, 1 mmol). The reaction mixture was stirred at room temperature for 2 h, then concentrated, and purified by column chromatography (EtOAc/CH$_2$Cl$_2$ = 1:3) to give intermediate **19** as a yellow oil containing both the E- and Z-isomers (0.2683 g, 70% yield) and **20b** (0.0767 g, 20%). For **19**: ^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.83−4.26 (s, 2 H, PhC*H*$_2$N), 4.50−4.93 (s, 2 H, NC*H*$_2$-CO),5.10−5.23 (s, 2 H, OC*H*$_2$), 7.10−7.51 (m, 15 H, Ar*H*). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 48.3, 50.8, 51.9, 55.2, 67.4, 67.5, 116.3, 116.7, 126.3, 126.5, 127.1, 127.2, 128.1, 128.3, 128.4, 128.4, 128.5, 128.6, 128.6, 128.7, 128.8, 129.0, 129.1, 129.4, 131.0, 131.1, 131.2, 131.5, 134.3, 134.4, 134.6, 135.0, 167.3, 167.8, 174.4, 174.6. HRMS (EI, C$_{24}$H$_{21}$N$_3$O$_2$) calcd: 383.1634, found 383.1621.

**Synthesis of 5-Amino-3-benzyl-2-phenyl-3*H*-imidazole-4-carboxylic Acid Benzyl Ester 20b.** Compound **19** (0.2513 g, 0.66 mmol) was dissolved in anhydrous THF (5 mL), and a solution of *t*-BuOK (0.1612 g, 1.32 mmol) in anhydrous *t*-BuOH (0.0978 g, 1.32 mmol) was added. The reaction mixture was stirred at room temperature for 30 min.

Thereafter, the reaction mixture was quenched with saturated ammonium chloride and extracted with CH$_2$Cl$_2$. The combined organic layer was dried with MgSO$_4$, filtered, concentrated, and purified by column chromatography (EtOAc/Hexane = 1:2) to give **20b** (0.1265 g, 50% yield) ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.08 (s, 2 H, N*H*$_2$), 5.17 (s, 2 H, NC*H*$_2$),5.45 (s, 2 H, OC*H*$_2$), 6.94−7.52 (m, 15 H, Ar*H*). ^{13}C NMR (CDCl$_3$, 125 MHZ): δ 49.6, 65.5, 102.5, 125.6, 125.6, 127.1, 128.1, 128.5, 128.6, 128.6, 129.0, 129.4, 129.7, 129.8, 136.0, 138.0, 150.1, 160.7. HRMS (EI, C$_{24}$H$_{21}$N$_3$O$_2$) calcd: 383.1634, found 383.1630.

**Acylation of 20b.** To a solution of compound **20b** (0.1022 g, 0.27 mmol) in CH$_3$CN (5 mL) was added furanoyl chloride (0.1044 g, 0.81 mmol), TEA (0.1034 g, 0.81 mmol), and DMAP (0.0065 g, 0.054 mmol). The reaction mixture was heated at 120 °C under microwave irradiation for 5 min. Thereafter, it was concentrated and purified by column chromatography (EtOAc/Hexane = 1: 3 to EtOAc/CH$_2$Cl$_2$ = 1: 2) to give both **21** (0.1337 g, 88% yield) and **22** (0.0092 g, 5% yield). For **21**: ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.07 (s, 2 H, NC*H*$_2$), 5.62 (s, 2 H, PhC*H*$_2$), 6.42−7.48 (m, 21 H, Ar*H*). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 49.9, 66.4, 112.0, 117.7, 119.1, 125.4, 127.4, 128.0, 128.3, 128.3, 128.6, 128.7, 129.3, 130.1, 135.3, 137.1, 143.0, 145.9, 145.9, 147.5, 150.7, 158.5, 160.4. HRMS (ESI, C$_{34}$H$_{25}$N$_3$O$_6$ + H) calcd: 572.1822, found 572.1818.

**Deacylation of 21.** Compound **21** (0.1237 g, 0.22 mmol) was dissolved in DMF, and hydrazine monohydrate (0.0331 g, 0.66 mmol) was added to the solution. The reaction mixture was heated at 100 °C under microwave irradiation for 5 min. Thereafter, the reaction mixture extracted with ethyl acetate, and the combined organic layer was dried with MgSO$_4$, filtered, concentrated, and purified by column chromatography (EtOAc/CH$_2$Cl$_2$ = 1: 2) to give **22** (0.1013 g, 98% yield). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.22 (s, 2 H, NC*H*$_2$), 5.53 (s, 2 H, PhC*H*$_2$), 6.48−7.60 (m, 18 H, Ar*H*), 9.92 (s, 1 H, N*H*). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 49.9, 66.8, 108.1, 112.3, 115.6, 125.5, 127.4, 128.5, 128.5, 128.6, 128.7, 128.8, 129.0, 129.6, 130.0, 135.0, 137.3, 144.5, 146.7, 147.8, 151.2, 154.4, 160.3. HRMS (EI, C$_{29}$H$_{23}$N$_3$O$_4$) calcd: 477.1689, found 477.1683.

**Synthesis of 1-Benzyl-5-furan-2-yl-2-phenyl-1*H*-imi-dazo[4,5-*d*][1,3]oxazin-7-one 13a.** Compound **22** (0.0834 g, 0.1744 mmol) was dissolved in anhydrous CH$_3$CN (5 mL); the PPh$_3$ (0.0686 g, 0.2616 mmol), C$_2$Cl$_4$Br$_2$ (0.0852 g, 0.2616 mmol), and DIEA (0.0676 g, 0.5232 mmol) were added to the solution, and the reaction mixture was heated at 140 °C under microwave irridation for 15 min. After that another portion of PPh$_3$ (0.0457 g, 0.1744 mmol), C$_2$Cl$_4$Br$_2$ (0.0568 g, 0.1744 mmol), and DIEA (0.0451 g, 0.3488 mmol) was added to the reaction vessel, and the reaction mixture was further heated at 140 °C under microwave irridation for 15 min. Thereafter, the reaction mixture was concentrated and purified by column chromatography (EtOAc/Hexane = 1:3) to give **13a** (0.1924 g, 96% yield). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.65 (s, 2 H, PhC*H*$_2$), 6.59−7.68 (m, 13 H, Ar*H*). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 50.0, 110.9, 112.6, 117.0, 126.5, 128.2, 128.3, 128.9, 129.0, 129.4, 130.9,

135.9, 144.7, 146.8, 152.0, 153.2, 156.0, 156.7. HRMS (ESI, $C_{22}H_{15}N_3O_3$ + Na) calcd: 392.1011, found 392.1006.

**Procedure for the Preparation of Benzyl Bromoacetate Resin 2.** Wang resin **1** (2 g, 2.8 mmol) was swollen in dichloromethane (15 mL) for 30 min, and then DMAP (0.628 g, 0.56 mmol) was added to it. 2-Bromoacetyl chloride (0.6610 g, 1.50 mmol) was dissolved in dichloromethane (5 mL) and added dropwise to the resin mixture, which was shaken at room temperature for 2 h. Thereafter, the resin was filtered, washed with DMF (20 mL × 3), $H_2O$ (20 mL × 3), EtOH (20 mL × 3), $CH_2Cl_2$ (20 mL × 3), and $Et_2O$ (20 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the Preparation of Resin-Bound Substituted Imidazole 3.** Resin **2** (1.1214 g, 1.4 mmol) was swollen in THF (15 mL) for 30 min. The respective imidamide (2.8 mmol) and *t*-BuOK (2.8 mmol) were added, and the resin mixture was shaken at room temperature for 2 h. Thereafter, the resin was filtered, washed with DMF (10 mL × 3), $H_2O$ (10 mL × 3), EtOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3) and dried overnight in a vacuum oven at 50 °C.

The dried resin was swollen in THF (15 mL) for 30 min and then *t*-BuOK (2.8 mmol) and *t*-BuOH (2.8mmol) were added to it. The resin mixture was shaken at room temperature for 30 min. Thereafter, the resin was filtered, washed with DMF (10 mL × 3), $H_2O$ (10 mL × 3), EtOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the Preparation of the Cyanoacetic Acid Resin 6.** Resin **1** (0.8571 g, 1.2 mmol) was preswelled in $CH_2Cl_2$ (10 mL) for 30 min. Cyanoacetic acid (0.2552 g, 3.0 mmol) was added, and the reaction mixture was cooled in an ice-bath. When the reaction mixture was ice-cold, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC, 0.5751 g, 3.0 mmol) in DMF (4 mL) was added dropwise to the ice-cold reaction mixture, followed by a solution of DMAP (50 mg) in DMF (2 mL), and the reaction mixture was shaken at room temperature for 15 h. The resin was then filtered, washed with DMF (1 mL × 3), $H_2O$ (10 mL × 3), MeOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the Preparation of 2-Cyano-3-ethoxy-3-substituted Acrylate Resin 4.** Resin **6** (3 mmol) was swelled in DMF (25 mL) for 30 min. The respective triethylorthoester (2.2 mmol) and acetic anhydride (0.2552 g, 2.5 mmol) were added to the swollen resin solution, and the reaction mixture was heated at 140 °C under microwave irradiation for 30 min. The resin was then filtered, washed with DMF (1 mL × 3), $H_2O$ (10 mL × 3), EtOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the Preparation of 5-Amino-1,3-disubstituted-1H-pyrazole-4-carboxylate Resin 5.** Resin **4** (3 mmol) was swelled in DMF (25 mL) for 30 min. The respective hydrazine (1.5 mmol) in ethanol (3 mL) was added to the swollen resin solution, and the reaction mixture was heated at 120 °C under microwave irradiation for 30

min. The resin was then filtered, washed with DMF (1 mL × 3), $H_2O$ (10 mL × 3), EtOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the Preparation of 2-Amino-1,4,5-trisubstituted-1H-pyrrole-3-carboxylate Resin 7.** Resin **6** (3 mmol) was swelled in THF (25 mL) for 30 min. The respective 3-substituted amino-2-ketone (15 mmol) was added to the swollen resin solution, and the reaction mixture was heated at 110 °C under microwave irradiation for 30 min. The resin was then filtered, washed with DMF (1 mL × 3), $H_2O$ (10 mL × 3), MeOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the Preparation of 2-Aminobenzo[b]thiophene Resin 8.** Resin **6** (3 mmol) was swollen in DMF (25 mL) for 30 min. The respective cyclic ketone (9 mmol) and sulfur powder (0.2886 g, 9 mmol) were added, and the resin mixture and shaken at room temperature for 5 min. Thereafter, a solution of morpholine (0.5226 g, 6 mmol) in DMF (5 mL) was added dropwise to the resin mixture, and the mixture was subsequently heated at 120 °C under microwave irradiation for 30 min. The resin was then filtered, washed with DMF (1 mL × 3), $H_2O$ (10 mL × 3), MeOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the Preparation of the Resin-Bound Monoacylated Imidazole 9−12.** Resin **3**, **5**, **7**, or **8** (1.4 mmol) was swollen in $CH_3CN$ (15 mL) for 30 min. The respective acid chloride (4.2 mmol), TEA (0.585 mL, 4.2 mmol), and DMAP (0.0342 g, 0.28 mmol) were added, and the resin mixture was heated at 120 °C under microwave irradiation for 20 min. Thereafter, the resin was filtered, washed with DMF (10 mL × 3), $H_2O$ (10 mL × 3), EtOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried in a vacuum oven at 50 °C for 1 h.

The dried resin was swollen in DMF (15 mL) for 30 min, and hydrazine monohydrate (0.2103 g, 4.2 mmol) was added to it. The resin mixture was heated at 100 °C under microwave irradiation for 20 min. Thereafter, the resin was filtered, washed with DMF (10 mL × 3), $H_2O$ (10 mL × 3), EtOH (10 mL × 3), $CH_2Cl_2$ (10 mL × 3), and $Et_2O$ (10 mL × 3), and dried overnight in a vacuum oven at 50 °C.

**General Procedure for the 1,3-Oxazin-6-one Ring Formation.** The respective resin **9−12** (1.4 mmol) was swollen in $CH_3CN$ (15 mL) for 1 h, and thereafter, $PPh_3$ (0.7344 g, 2.8 mmol), $C_2Cl_4Br_2$ (0.9005 g, 2.8 mmol), and DIEA (0.5438 g, 4.2 mmol) were added to the resin mixture. The resin mixture was heated at 140 °C under microwave irradiation for 20 min, and thereafter, a second portion of $PPh_3$ (0.5508 g, 2.1 mmol), $C_2Cl_4Br_2$ (0.6754 g, 2.1 mmol), and DIEA (0.5438 g, 4.2 mmol) was added; then, the resin mixture was further heated at 140 °C under microwave irridation for another 20 min. After which, the resin was filtered and washed with EtOAc (10 mL × 3) and $CH_2Cl_2$ (10 mL × 3). The combined organic filtrate and washings were concentrated and purified by column chromatography to give the respective compounds **13−16**.

**Supporting Information Available.** $^1$H and $^{13}$C NMR spectra of compounds **13a−j**, **14a−d**, **15a−c**, **16a−c**, **18**, **19**, **20b**, **21**, and **22**, IR spectra of resin **2**, **3a**, **5−12**, and the diacetylated resin **3a**, **5**, **7**, and **8**, and a crystallographic file in CIF format of **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

(1) (a) Mayama, S.; Matsuura, Y.; Iida, H.; Tani, T. *Physiol. Plant Pathol.* **1982**, *20*, 189–199. (b) Mayama, S.; Tani, T.; Matsuura, Y.; Ueno, T.; Fukami, H. *Physiol. Plant Pathol.* **1981**, *19*, 217–226.

(2) (a) Wu, C. C.; Wang, T. W.; Wang, W. Y.; Hsieh, P. W.; Wu, Y. C. *Eur. J. Pharmacol.* **2005**, *527*, 37–43. (b) Jakobsen, P.; Ritsmar, P. B.; Persson, E. *Bioorg. Med. Chem.* **2000**, *8*, 2095–2103. (c) Hsieh, P.-W.; Hwang, T.-L.; Wu, C.-C.; Chang, F.-R.; Wang, T.-W.; Wu, Y.-C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2786–2789. (d) Persson, E.; Jakobsen, P.; Worsaae, H. PCT Int. Appl. WO 9948878, 1999.

(3) (a) Tsuruoka, H.; Yabe, Y.; Furukawa, H.; Yamamoto, I.; Miyamoto, S.; Hata, T. Jpn. Kokai Tokkyo Koho JP 11322611, 1999. (b) Hsieh, P. W.; Chang, F. R.; Chang, C. H.; Cheng, P. W.; Chiang, L. C.; Zeng, F. L.; Lin, K. H.; Wu, Y. C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4751–4754.

(4) (a) Hamprecht, G.; Varwig, J.; Wuerzer, B. Ger. Offen. DE 3000309, 1981. (b) Doyle, W. C., Jr. U.S. Patent US 3970652, 1976. (c) Doyle, W. C., Jr. U.S. Patent US 3914121, 1975.

(5) (a) Jarvest, R. L.; Parratt, M. J.; Debouck, Christine, M.; Gorniak, J. G.; Jennings, L. J.; Serafinowska, H. T.; Strickler, J. E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2463–2466. (b) Gilmore, J. L.; Hays, S. J.; Caprathe, B. W.; Lee, C.; Emmerling, M. R.; Michael, W.; Jaen, J. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 679–682. (c) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060–1067.

(6) Neumann, U.; Stuerzebecher, J.; Leistner, S.; Vieweg, H. *J. Enz. Inhib.* **1991**, *4*, 227–232.

(7) (a) Jakisch, L.; Komber, H.; Böhme, F. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 655–667. (b) Jakisch, L.; Komber, H.; Böhme, F. *Macromol. Mater. Eng.* **2007**, *292*, 557–570. (c) Hegewald, J.; Jakisch, L.; Pionteck, J. *Synth. Met.* **2009**,in press.

(8) (a) Jarvest, R. L.; Pinto, I. L.; Ashman, S. M.; Dabrowski, C. E.; Fernandez, A. V.; Jennings, L. J.; Lavery, P.; Tew, D. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 443–448. (b) Jakobsen, P.; Hornemann, A. M.; Persson, E. PCT Int. Appl. WO 2000030646, 2000. (c) Jakobsen, P.; Horneman, A. M.; Persson, E. *Bioorg. Med. Chem.* **2000**, *8*, 2803–2812. (d) Ward, J.; Jain, R.; James, D.; Verheij, H. J.; Schultz, J. C. C. PCT Int. Appl. WO 2006044826, 2006. (e) Pato, J.; Keri, G.; Orfi, L.; Waczek, F.; Horvath, Z.; Banhegyi, P.; Szabadkai, I.; Marosfalvi, J.; Hegymegi-Barakonyi, B.; Szekelyhidi, Z.; Greff, Z.; Choidas, A.; Bacher, G.; Missio, A.; Koul, A. U.S. Patent. US 2004171603, 2004. (f) Missio, A.; Bacher, G.; Koul, A.; Choidas, A. PCT Int. Appl. WO 2003084947, 2003. (g) Witter, D.; Castelhano, A. L. PCT Int. Appl. WO 2003053944, 2003. (h) Linschoten, M. PCT Int. Appl. WO 2004108139, 2004.

(9) Player, M. R.; Sowell, J. W., Sr.; Williams, G. R.; Cowley, G. T. *J. Heterocycl. Chem.* **1994**, *31*, 209–214.

(10) (a) Jakobsen, P.; Horneman, A. M.; Persson, E. *Bioorg. Med. Chem.* **2000**, *8*, 2803–2812. (b) Jakobsen, P.; Hornemann, A. M.; Persson, E. PCT Int. Appl. WO 2000030646, 2000.

(11) (a) El Haddad, M.; Akssira, M. *Molecules* **2001**, *6*, M271. (b) Achakzi, D.; Ertas, M.; Appel, R.; Wamhoff, H. *Chem. Ber.* **1981**, *114*, 3188–3194. (d) Jarvest, R. L.; Jennings, L. J. A.; Pinto, I. L. PCT Int. Appl. WO 9727200, 1997. (f) Witter, D.; Castelhano, A. L. PCT Int. Appl. WO 2003053944, 2003. (g) Player, M. R.; Sowell, J. W., Sr.; Williams, G. R.; Cowley, G. T. *J. Heterocycl. Chem.* **1994**, *31*, 209–214. (h) Bayomi, S. M. *J. Chin. Chem. Soc.* **1992**, *39*, 101–104.

(12) He, R.; Ching, S. M.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 923–928.

(13) Zaraogoza, F. *Tetrahedron Lett.* **1997**, *38*, 7291.

(14) (a) Laks, J. S.; Ross, J. R.; Bayomi, S. M.; Sowell, J. W. *Synthesis* **1985**, 291–293. (b) Bayomi, S. M. *J. Drug. Res.* **1985**, *16*, 147–153. (c) Bayomi, S. M. *J. Chin. Chem. Soc.* **1992**, *39*, 101–104.

(15) Gewald, K.; Schinke, E.; Bottcher, H. *Chem. Ber.* **1966**, *99*, 94.

(16) Jakobsen, P.; Horneman, A. M.; Persson, E. *Bioorg. Med. Chem.* **2000**, *8*, 2803–2812.