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An Efficient Highly Regioselective Synthesis of 2,3,4-Trisubstituted Pyrroles by Cycloaddition of Polarized Ketene *S*,*S*- and *N*,*S*-Acetals with Activated Methylene Isocyanides†

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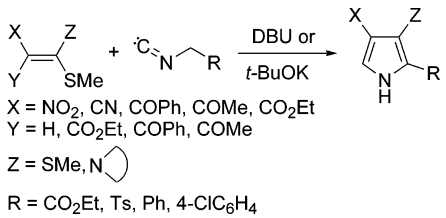

An efficient route for regioselective synthesis of 2,3,4- substituted pyrroles allowing precise control over the introduction of a number of substituents and functionalities (tosyl, carbalkoxy, aryl, cyano, nitro, acetyl, benzoyl, cyclic amines, etc.) at the three positions of the pyrrole ring has been developed via 1,3-dipolar cycloaddition of readily accessible polarized ketene *S*,*S*- and *N*,*S*-acetals with carbanions derived from activated methylene isocyanides.

Introduction

Substituted pyrroles represent an important class of heterocycles which are present in a wide range of natural products[1] such as porphyrins and bioactive molecules[1c,f,2] including the blockbuster drug atorvastatin calcium[3a] as well as important antiinflammatants,[3b] antitumor agents,[3c] and immunosuppressants.[3d] Similarly, polypyrroles are of growing relevance in material science,[2a,4,5] nonlinear optics,[5] and supramolecular chemistry[6] as molecular sensors and devices.[7] Therefore, considerable attention has been paid to develop efficient general methods for the synthesis of pyrroles.[1,8] Previous approaches such as Paal−Knorr cyclization[9] and Hantzsch synthesis[10] involving classical condensation reactions between activated

† Dedicated to Professor S. V. Kessar on his 75th birthday.

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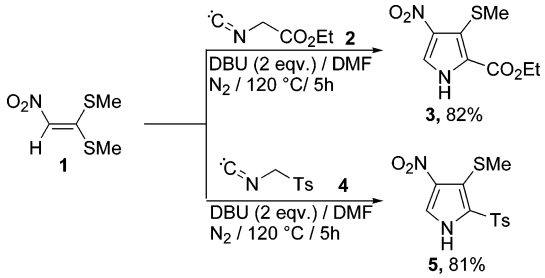
methylene compounds and amino ketones can have limitations in terms of efficiency, functional group compatibility, regiospecificity, and substituent diversity. More recent pyrrole syntheses include transition-metal-based strategies[11] such as the addition of chromium carbene to dipolarophiles,[12] the Cu(0)- or palladium-catalyzed cycloisomerization of alkynylimines,[2a,13] Rh-catalyzed N−H insertion[14] or a combination of isonitrile and 1,3-diketone insertion,[15] palladium- and ruthenium-catalyzed multicomponent reactions,[16] and other methods.[17,18] Among the cycloaddition approaches,[19] the reaction between an activated alkene and an activated methylene isocyanide under basic conditions also represents an efficient method for the synthesis of substituted and annulated pyrroles. The reaction of nitroalkenes (or arenes) with isocyanoacetate is known as Barton−Zard synthesis,[20] whereas the reaction of various Michael acceptors and TosMIC (*p*-toluenesulfonylmethyl isocyanide) is called Van Leusen synthesis.[21] Both of these cycloadditions proceed with elimination of either nitrous acid or toluenesulfinate, respectively, in the final pyrrole ring formation step. Several variations of the Barton−Zard reaction with various activated olefins and nitroarenes yielding substituted and annulated pyrroles have been reported.[22] Recently, these cycloadditions have also been extended to activated acetylenes under either a copper[1f] or a phosphine[23] catalysis. As part of our ongoing studies on synthetic applications of polarized ketene dithioacetals for heterocycle synthesis,[24,25] we herein report a facile base-induced [3 + 2] cycloaddition of these intermediates with various activated methylene isocyanides, furnishing 2,3,4-substituted pyrroles in high yields.

SCHEME 1



Results and Discussion

We first examined the cycloaddition of nitroketene *S*,*S*-acetal **1**[26] with ethyl isocyanoacetate (**2**) under varying reaction conditions in the presence of different bases (NaH, BuLi, *t*-BuOK, DBU). Under optimized conditions, when **1** was reacted with **2** in the presence of DBU as the base in DMF at 120 °C, analysis of the reaction mixture revealed formation of only one product, which was characterized as ethyl 4-nitro-3-(methylthio)pyrrole-2-carboxylate (**3**) (82%) on the basis of its spectral and analytical data (Scheme 1). It should be noted that unlike previous reactions of nitroalkene/arene with ethyl iso-

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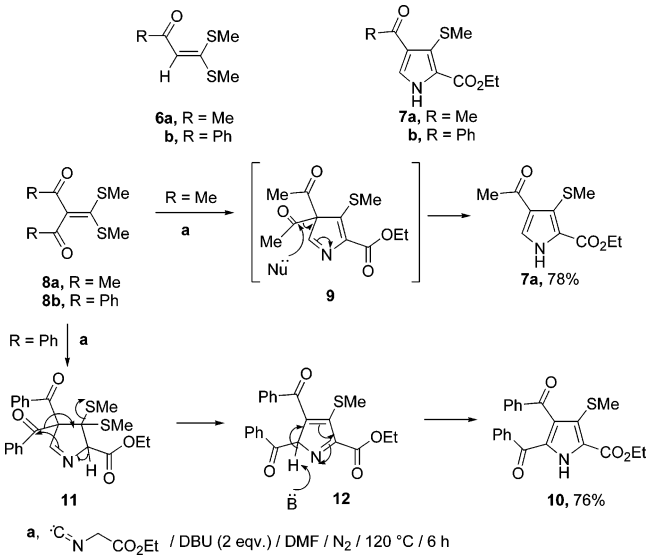
SCHEME 2



cyanoacetate, the nitro group is retained in the 4-position of the product pyrrole **3** with elimination of the methylthio group (Scheme 1). A similar trend was observed when nitroketene *S*,*S*-acetal **1** was subjected to cycloaddition with tosylmethyl isocyanide (**4**) under identical conditions, furnishing the pyrrole **5** (81%) with a tosyl group incorporated in the 2-position.

With the success of these two reactions, we next extended this pyrrole-forming reaction to α-acetyl- and α-benzoylketene dithioacetals **6a,b**[27] and **2** with a view to prepare 4-acetyl/benzoylpyrroles **7a,b**. However, the ketene dithioacetal **6a** or **6b** failed to give the desired pyrroles under the influence of various bases (NaH, *t*-BuOK, DBU, LiHMDS, etc.) under different conditions, yielding either the unreacted ketene dithioacetals **6a,b** or an intractable reaction mixture under more drastic conditions. In one of the reactions, pyrrole **7b** was obtained in low yield (20%) when ketene dithioacetal **6b** was reacted with **2** in the presence of NaH in THF (10 h). The lower reactivity of acylketene dithioacetals **6a,b** appears to be due to poor activation of the double bond as a Michael acceptor.[28] We therefore examined the reaction of diacylketene dithioacetals **8a,b** with **2** assuming that the introduction of another electron-withdrawing group at the α-position of **6a,b** will enhance the reactivity of the double bond in **8a,b** as a Michael acceptor. Also, it was anticipated that the initial cycloadduct such as 4,4-diacyl-4*H*-pyrrole **9** from diacylketene dithioacetal **8a**[27a] and **2** should undergo facile aromatization to the product 4-acylpyrrole **7a** via cleavage of one of the acyl groups (Scheme 2). Indeed we were pleased to find that **8a** reacted cleanly with ethyl isocyanoacetate according to our prediction under earlier described reaction conditions, furnishing the expected 4-acetyl-2-carbethoxy-3-(methylthio)pyrrole (**7a**) in 78% yield (Scheme 2). The corresponding dibenzoylketene dithioacetal **8b**[29] also underwent facile cycloaddition with ethyl isocyanoacetate under these conditions to give only one product. However, a precise analysis of spectroscopic data revealed the product structure to be 4,5-dibenzoyl-2-carbethoxy-3-(methylthio)pyrrole (**10**) (instead of **7b**), which is probably formed by the rearrangement of the benzoyl group to the 5-position in the 4,4-dibenzoyl-2*H*-pyrrole intermediate **11** via **12** as shown in Scheme 2. The reaction of ketene dithioacetal **8a** with tosylmethyl isocyanide also proceeded in a similar fashion under identical reaction conditions, yielding the corresponding 2-tosyl-4-acetylpyrrole **13** in 79% yield (Scheme 3 and Table 1, entry 1).

Inspired by the success of these reactions, we further extended our studies to other doubly activated ketene dithioacetals **8c**[27a] and **8d**[27a] (derived from ethyl acetoacetate and ethyl cyanoacetate) with a view to demonstrate the versatility of the reaction for incorporation of various electron-withdrawing groups (CO_2-Et, CN) in the 4-position (or 3-position) of the pyrrole ring. Thus, the reaction of **8c** and **8d** with **2** also proceeded smoothly according to our earlier prediction, yielding the desired 2,4-dicarbethoxy-3-(methylthio)pyrrole (**7c**) and 2-carbethoxy-4-cyano-3-(methylthio)pyrrole (**7d**) in 72% and 80% yields by cleavage of acetyl or carbethoxy groups, respectively (Scheme 3 and Table 1, entries 3 and 4). Similarly, the ketene dithioacetal **8d** reacted smoothly with tosylmethyl isocyanide under these conditions with the loss of the carbethoxy group to give 2-tosyl-4-cyanopyrrole **14** in 86% yield (entry 4, Table 1).

As a further test for substrate and functional group compatibility in this efficient pyrrole synthesis, cycloadditions of a few

SCHEME 3

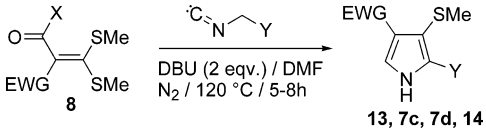


TABLE 1. Synthesis of 2,4-Substituted 3-(Methylthio)pyrroles

Entry	8	2, 4	Product	% Yield
1	**8a**	**4**	**13**	79
2	**8c**	**2**	**7c**	72
3	**8d**	**2**	**7d**	80
4	**8d**	**4**	**14**	86

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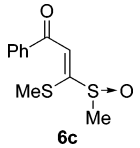
(28) Attempted cycloaddition of monomethyl sulfoxide **6c**[27b] with ethyl isocyanoacetate in the presence of DBU as the base yielded only deoxygenated ketene dithioacetal **6b**, and no trace of pyrrole **7b** could be isolated from the reaction mixture.



6c

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SCHEME 4

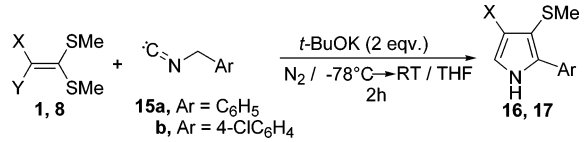
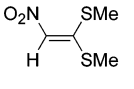
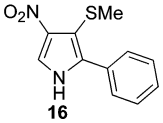
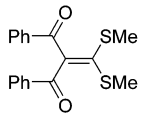
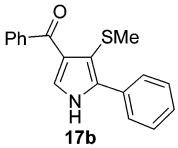
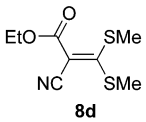
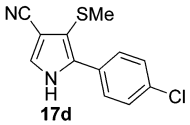
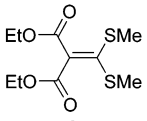
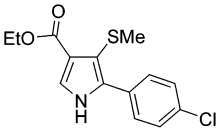


TABLE 2. Synthesis of 4-Substituted 2-Aryl-3-(methylthio)pyrroles

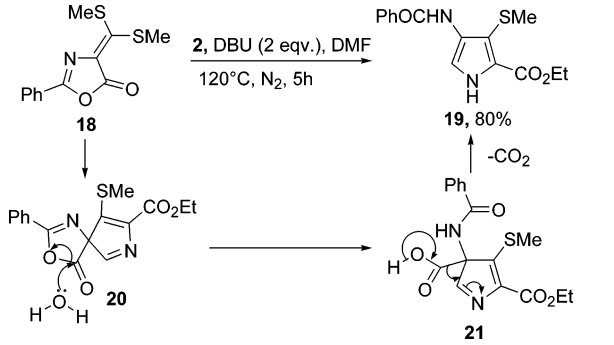
Entry	1, 8	15	16, 17	% Yield
1	 **1**	**15a**	 **16**	65
2	 **8b**	**15a**	 **17b**	74
3	 **8d**	**15b**	 **17d**	84
4	 **8e**	**15b**	 **17e**	86

polarized ketene dithioacetals with arylmethyl isocyanides were examined. However, the reaction of nitroketene *S*,*S*-acetal **1** with benzyl isocyanide (**15a**) using DBU as the base afforded the expected 2-phenyl-3-(methylthio)-4-nitropyrrole (**16**) in poor yield (9%). The lower yield of the pyrrole **16** appears to be due to insufficient basicity of DBU for deprotonation of benzyl isocyanide. This was evident by performing the reaction in the presence of a stronger base such as potassium *tert*-butoxide, when the pyrrole **16** was obtained in an improved yield of 65% (Scheme 4 and Table 2, entry 1). Similarly, a few of the doubly activated ketene dithioacetals **8b**, **8d**, and **8e**[27a] were also reacted with either **15a** or 4-chlorobenzyl isocyanide (**15b**), furnishing various substituted 2-arylpyrroles **17b, 17d**, and **17e** in high yields (Table 2, entries 2−4).

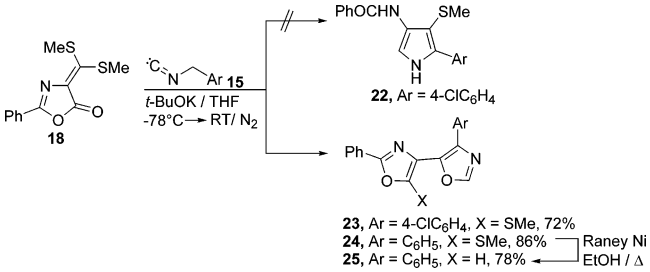
To further probe the efficiency of the reaction for the synthesis of a pyrrole ring with diverse functionalities, the cycloaddition of ketene dithioacetal **18**[30] (derived from 2-phenyloxazolone) with **2** was examined as shown in Scheme 5. Thus, when **18** was reacted with **2** under earlier described reaction conditions, product analysis revealed formation of only one product (80%), which after spectroscopic characterization was found to be ethyl 4-(benzoylamino)-3-(methylthio)pyrrole-2-carboxylate (**19**). Although the initial cycloadduct, i.e., spiropyrroleisoxazolone **20** could not be isolated, the probable mechanism for the formation of observed product **19** appears to be the ring opening of the isoxazolone ring in the intermediate **20** by some nucleophilic species such as water during workup followed by aromatization of the resulting intermediate **21** by elimination of carbon dioxide (Scheme 5).

(30) Tripathy, P. K.; Roy, J.; Mukerjee, A. K. *Indian J. Chem., Sect.B: Org. Chem. Incl. Med. Chem.* **1986**, *25B*, 1275−1276.

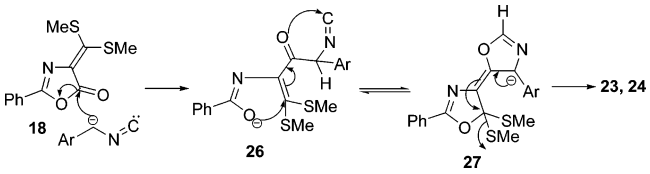
SCHEME 5



SCHEME 6



SCHEME 7

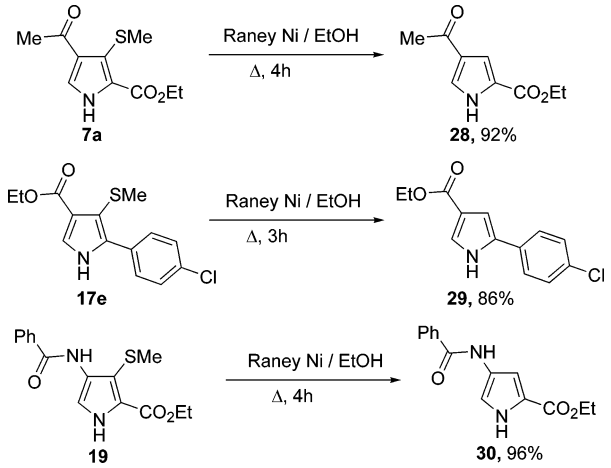


Interestingly, when **18** was reacted with **15b** in the presence of *t*-BuOK at −78 °C, workup of the reaction mixture did not afford the expected 2-aryl-4-(benzoylamino)-3-(methylthio)-pyrrole **22**. The product isolated (72%) was found to be unexpected bisoxazole derivative **23** on the basis of its spectral, analytical, and X-ray crystallographic data (Scheme 6). Reaction of **18** with **15a** under identical conditions similarly afforded the bisoxazole **24** in 86% yield (Scheme 6). Desulfurization of **24** with Raney Ni in refluxing ethanol gave the dethiomethylated bisoxazole **25** in 78% yield (Scheme 6). The probable mechanism for the formation of bisoxazoles **23**−**24** from **18** and **15** is shown in Scheme 7. The carbanion from benzyl isocyanide appears to undergo nucleophilic addition to the carbonyl group of **18**, resulting in the cleavage of the lactone ring and formation of imidate anion **26**. Subsequent cascade intramolecular conjugate addition of the anion **26** to the activated bis(methylthio)-methylene double bond and intramolecular addition of a nucleophilic carbonyl oxygen to the isonitrile group followed by aromatization of the newly formed oxazole ring via elimination of the methylmercapto anion affords the bisoxazoles **23** and **24** in good yields. However, we are unable to explain at this stage the different behaviors of carbethoxymethyl isocyanide and phenylmethyl isocyanide anions toward **18** (1,4-addition vs 1,2-addition), leading to formation of different products.

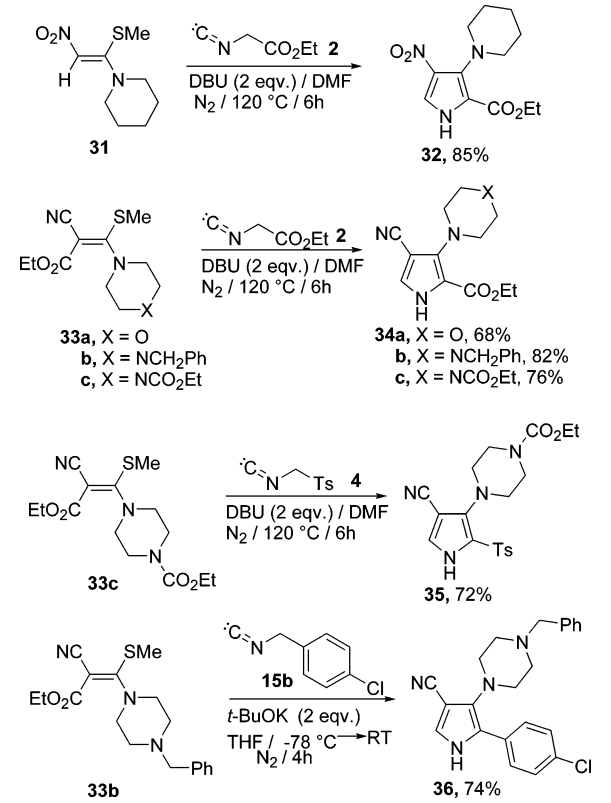
A few of the newly synthesized pyrroles (**7a**, **17e**, **19**) were dethiomethylated with Raney Ni in refluxing ethanol, furnishing the corresponding 3-unsubstituted pyrroles **28**−**30** in good yields (Scheme 8).

Finally, to further add a point of diversity at the 3-position of the newly synthesized pyrroles, reaction of a few polarized

SCHEME 8



SCHEME 9



ketene *N*,*S*-acetals (derived from cyclic secondary amines) with **2, 4**, and **15b** was examined (Scheme 9). It should be noted that such push−pull enamines have not been studied earlier as dipolarophiles in this isocyanide cycloaddition reaction. The desired *N*,*S*-acetals **31**[31a] and **33a**−**c**[31b,c] were prepared by direct displacement of one of the methylthio groups in the respective ketene dithioacetals by the appropriate secondary amines. Thus, when the nitroketene *N*,*S*-acetal **31** was reacted with **2** under standard reaction conditions, the corresponding 4-nitro-3-(*N*-piperidino)-2-carbethoxypyrrole (**32**) was obtained in 85% yield (Scheme 9). Similarly, the corresponding *N*-morpholino and *N*-piperazino *N*,*S*-acetals **33a**−**c** underwent smooth cycloaddition with various activated methylene isocyanides **(2, 4, 15b)** under similar conditions, affording the respective 2-substituted 3-(*N*-cycloamino)-4-cyanopyrroles **34a-c**, **35**, and **36** in overall high yields (Scheme 9), thus demonstrating further the substrate and functional group compatibility of this versatile pyrrole synthesis.

Conclusion

In summary, we have developed a concise and efficient protocol for regioselective synthesis of 2,3,4-substituted pyrroles from readily available polarized ketene *S*,*S*- and *N*,*S*-acetals and activated methylene isocyanides. The methodology allows precise control over the introduction of a number of substituents and functionalities (tosyl, carbalkoxy, aryl, cyano, nitro, acetyl, benzoyl, cyclic amines, etc.) at the three positions of the pyrrole ring. The reaction is particularly promising for the introduction of electron-withdrawing groups at the 3-position (or 4-position) of the pyrrole ring. The reaction of nitroketene *S*,*S*-acetal with ethyl isocyanoacetate is to our knowledge the first example of the Barton−Zard reaction in which a nitro group is retained in the 4-position of the pyrrole ring. Some of the prepared pyrroles are useful intermediates for the synthesis of biologically important compounds (distamycin, netropsin, etc.).[32] Further application of this methodology is under way in our laboratory.

Experimental Section

General Procedure for the Synthesis of Substituted Pyrroles from Various Polarized Ketene *S*,*S*- and *N*,*S*-Acetals via Ethyl Isocyanoacetate/TosMIC (3, 5, 7a, 7c, 7d, 10, 13, 14, 19, 32, 34a, 34b, 34c, 35). DBU (6.0 mmol) was added dropwise to a stirring solution of the corresponding ketene *S*,*S*-acetal (or *N*,*S*-acetal) (3.0 mmol) and ethyl isocyanoacetate (0.58 g, 6.0 mmol) (or TosMIC, 1.2 g, 6.0 mmol) in DMF (40 mL) under a nitrogen atmosphere. The resulting mixture was heated at 120 °C with constant stirring for 5−6 h (monitored by TLC). It was then cooled and poured into a saturated NH_4Cl solution (100 mL). The mixture was extracted with chloroform (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and distilled under reduced pressure to give crude products. The crude products were purified by column chromatography over silica gel using hexane−EtOAc (7:3) as the eluent.

Data for ethyl 3-(methylthio)-4-nitropyrrole-2-carboxylate (3): yield 82% (0.57 g); white solid; mp 134−135 °C ($CHCl_3$−hexane); R_f 0.2 (7:3 hexane−EtOAc); IR (KBr) 3247, 2990, 1673, 1498, 1363, 1309 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3H), 2.48 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.81 (d, J = 3.9 Hz, 1H), 9.75 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.4, 61.8, 120.3, 122.9, 123.7, 143.1, 159.4; MS *m*/*z* (rel intens) 231 (M + 1, 100); HRMS (EI) *m*/*z* calcd for $C_8H_{10}N_2O_4S$ 230.0361, found 230.0357.

Data for ethyl 4-acetyl-3-(methylthio)pyrrole-2-carboxylate (7a): yield 78% (0.53 g); white crystalline solid; mp 132−133 °C ($CHCl_3$−hexane); R_f 0.3 (7:3 hexane−EtOAc); IR (KBr) 3138, 2980, 1708, 1636, 1528, 1377, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 2.52 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 7.52 (d, J = 3.4 Hz, 1H), 10.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.8, 29.0, 61.0, 123.9, 124.8, 127.4, 128.2, 160.0, 193.7; MS *m*/*z* (rel intens) 228 (M + 1, 100); HRMS (EI) *m*/*z* calcd for $C_{10}H_{13}NO_3S$ 227.0616, found 227.0608.

(31) (a) Manjunatha, S. G.; Reddy, K. V.; Rajappa, S. *Tetrahedron Lett.* **1990**, *31*, 1327−1330. (b) Kuwayama, Y.; Kataoka, S. *Yakugaku Zasshi* **1965**, *85*, 387−390. (c) Kumar, A.; Aggarwal, V.; Ila, H.; Junjappa, H. *Synthesis* **1980**, 748−751.

(32) (a) Lown, J. W.; Krowicki, K. *J. Org. Chem.* **1985**, *50*, 3774−3779. (b) Wang, Y.; Wright, S. C.; Larrick, J. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 459−461.

Data for ethyl 4-cyano-3-(methylthio)pyrrole-2-carboxylate (7d): yield 80% (0.5 g); white solid; mp 92−93 °C ($CHCl_3$−hexane); R_f 0.2 (7:3 hexane−EtOAc); IR (KBr) 3237, 2984, 2227, 1692, 1436, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3H), 2.58 (s, 3H), 4.37 (q, J = 7.2 Hz, 2H), 7.10 (d, J = 2.7 Hz, 1H), 10.07 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 18.7, 61.6, 99.2, 114.7, 118.9, 124.5, 136.8, 160.0; MS *m/z* (rel intens) 210 (M^+, 70); HRMS (EI) *m/z* calcd for $C_9H_{10}N_2O_2S$ 210.0463, found 210.0447.

Data for ethyl 4,5-dibenzoyl-3-(methylthio)pyrrole-2-carboxylate (10): yield 76% (0.9 g); yellow solid; mp 114−116 °C (EtOAc−hexane); R_f 0.2 (7:3 hexane−EtOAc); IR (CH_2Cl_2) 3261, 2988, 1712, 1655, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.3 Hz, 3H), 2.29 (s, 3H), 4.39 (q, J = 7.3 Hz, 2H), 7.08 (t, J = 7.8 Hz, 2H), 7.15 (t, J = 7.8 Hz, 2H), 7.28−7.38 (m, 6H), 10.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.0, 61.7, 124.2, 126.6, 128.1, 128.2, 128.5, 128.9, 129.0, 130.8, 132.7, 133.0, 137.4, 138.6, 159.2, 186.2, 191.8; MS *m/z* (rel intens) 394 (M + 1, 70); HRMS (EI) *m/z* calcd for $C_{22}H_{19}NO_4S$ 393.1035, found 393.1021.

General Procedure for the Synthesis of Substituted Pyrroles from Various Polarized Ketene *S,S*- and *N,S*-Acetals via Benzyl Isocyanide/4-Chlorobenzyl Isocyanide (16, 17b, 17d, 17e, 36) and Bisoxazoles 23 and 24. Potassium *tert*-butoxide (6.0 mmol) (dissolved in 20 mL of THF) was added dropwise to a stirring solution of the corresponding ketene *S,S*-acetal (or *N,S*-acetal) (3.0 mmol) and benzyl isocyanide (0.53 g, 4.5 mmol) (or 4-chlorobenzyl isocyanide, 0.68 g, 4.5 mmol) in THF (60 mL) at −78 °C under a nitrogen atmosphere. The resulting mixture was further stirred at room temperature for 2−3 h (monitored by TLC). It was then poured into a saturated NH_4Cl solution (100 mL). The mixture was extracted with chloroform (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and distilled under reduced pressure to give crude products. The crude products were purified by column chromatography over silica gel using hexane−EtOAc (7:3) as the eluent.

Data for 3-(methylthio)-4-nitro-2-phenyl-1*H*-pyrrole (16): yield 65% (0.46 g); yellow solid; mp 92−94 °C ($CHCl_3$−hexane); R_f 0.4 (4:1 hexane−EtOAc); IR (KBr) 3208, 2920, 1479, 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 7.37−7.47 (m, 3H), 7.62−7.64 (m, 2H), 7.82 (d, J = 3.7 Hz, 1H), 9.56 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 108.2, 121.8, 128.2, 128.7, 130.3, 135.8, 138.4, 193.2; MS *m/z* (rel intens) 235 (M + 1, 100); HRMS (EI) *m/z* calcd for $C_{11}H_{10}N_2O_2S$ 234.0463, found 234.0457.

Data for ethyl 5-(4-chlorophenyl)-4-(methylthio)pyrrole-3-carboxylate (17e): yield 96% (0.8 g); white crystalline solid; mp 180−182 °C ($CHCl_3$−hexane); R_f 0.3 (4:1 hexane−EtOAc); IR (KBr) 3288, 2980, 1687, 1481, 1332, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 2.32 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 3.4 Hz, 1H), 7.57 (d, J = 7.7 Hz, 2H), 8.99 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.1, 59.9, 113.2, 118.7, 125.4, 128.7, 129.3, 129.9, 133.8, 134.6, 164.0; MS *m/z*, (rel intens) 295 (M^+, 100), (M + 2, 33); HRMS (EI) *m/z* calcd for $C_{14}H_{14}ClNO_2S$ 295.0434, found 295.0421.

Data for ethyl 4-(benzoylamino)-3-(methylthio)pyrrole-2-carboxylate (19): yield 80% (0.73 g); white solid; mp 142−144 °C (EtOAc−hexane); R_f 0.2 (7:3 hexane−EtOAc); IR (KBr) 3268, 2984, 1681, 1645, 1574, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 2.26 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 7.40−7.49 (m, 3H), 7.56 (d, J = 2.7 Hz, 1H), 7.83 (d, J = 7.1 Hz, 2H), 8.11 (s, 1H), 9.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.2, 60.8, 107.9, 114.9, 122.9, 127.0, 128.0, 128.7, 131.8, 134.3, 161.1, 164.4; MS *m/z* (rel intens) 304 (M^+, 100); HRMS (EI) *m/z* calcd for $C_{15}H_{16}N_2O_3S$ 304.0881, found 304.0851.

Data for 4′-(4-chlorophenyl)-5-(methylthio)-2-phenyl-4,5′-bioxazolyl (23): yield 72% (0.51 g); white crystalline solid; mp 128−130 °C ($CHCl_3$−hexane); R_f 0.6 (3:1 hexane−EtOAc); IR (KBr) 3126, 2929, 1476, 1094, 1020, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.36 (d, J = 8.5 Hz, 2H), 7.47 (dd, J = 5.0, 1.8 Hz, 3H), 7.84 (d, J = 8.6 Hz, 2H), 8.00 (s, 1H), 8.02−8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 126.46, 126.52, 128.5, 128.9, 129.2, 129.7, 131.1, 131.8, 134.1, 136.9, 137.9, 144.4, 150.5, 163.0; MS *m/z* (rel intens) 368 (M^+, 100), 370 (M + 2, 33); HRMS (EI) *m/z* calcd for $C_{19}H_{13}N_2O_2SCl$ 368.0386, found 368.0334.

General Procedure for Raney Ni Dethiomethylation/Reduction. Raney Ni (W_2) (ca. 1 g) was added to an ethanolic solution (20 mL) of the appropriate substrate (**7a**, **17e**, **19**, or **24**) (2 mmol), and the suspension was heated at reflux with stirring for 2−3 h (monitored by TLC). It was then filtered through a sintered glass funnel and washed with hot ethanol. The filtrate was concentrated to afford a viscous residue which was purified by column chromatography over silica gel with hexane−EtOAc (7:3) as the eluent to give the pure products.

Data for ethyl 4-(benzoylamino)pyrrole-2-carboxylate (30): yield 96% (0.5 g); white solid; mp 212−214 °C ($CHCl_3$−hexane); R_f 0.2 (3:2 hexane−EtOAc); IR (KBr) 3338, 2981, 1683, 1644, 1569, 1391, 1263, 1214, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 1.12 (t, J = 7.1 Hz, 3H), 4.07 (q, J = 7.2 Hz, 2H), 6.78 (d, J = 1.7 Hz, 1H), 7.19−7.29 (m, 3H), 7.35 (d, J = 1.7 Hz, 1H), 7.72 (dd, J = 7.6, 1.4 Hz, 2H), 9.52 (s, 1H), 10.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 14.1, 59.6, 106.5, 114.5, 119.7, 124.2, 127.0, 127.8, 130.7, 134.3, 160.7, 164.5; MS *m/z* (rel intens) 259 (M + 1, 100); HRMS (EI) *m/z* calcd for $C_{14}H_{14}N_2O_3$ 258.1004, found 258.1003.

Data for ethyl 4-nitro-3-piperidinopyrrole-2-carboxylate (32): yield 85% (0.68 g); yellow crystalline solid; mp 110−112 °C ($CHCl_3$−hexane); R_f 0.2 (1:1 hexane−EtOAc); IR (KBr) 3248, 2936, 1663, 1559, 1361, 1294 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3H), 1.59 (d, J = 4.4 Hz, 2H), 1.68 (br s, 4H), 3.16 (d, J = 4.6 Hz, 4H), 4.33 (q, J = 7.1 Hz, 2H), 7.65 (s, 1H), 9.37 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 24.0, 26.4, 53.0, 60.9, 113.2, 122.8, 122.9, 131.9, 159.5; MS *m/z* (rel intens) 269 (M + 1, 100); HRMS (EI) *m/z* calcd for $C_{12}H_{17}N_3O_4$ 267.1219, found 267.1211.

Data for ethyl 4-(4-cyano-2-(ethoxycarbonyl)-1*H*-pyrrol-3-yl)piperazine-1-carboxylate (34c): yield 76% (0.77 g); white solid; mp 98−100 °C ($CHCl_3$−hexane); R_f 0.5 (1:1 hexane−EtOAc); IR (DCM solution) 3246, 2982, 2222, 1682, 1688, 1552, 1413, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 3.26 (br s, 4H), 3.54 (d, J = 4.8 Hz, 4H), 4.09 (q, J = 7.1 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 7.15 (d, J = 4.0 Hz, 1H), 9.72 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 14.6, 44.0, 51.5, 60.8, 61.5, 88.6, 112.3, 116.0, 128.0, 145.4, 155.5, 159.2; MS *m/z* (rel intens) 320 (M^+, 89), 321 (M + 1, 100); HRMS (EI) *m/z* calcd for $C_{15}H_{20}N_4O_4$ 320.1484, found 320.1482.

Data for 4-(4-*N*-benzyl-*N*-piperazino)-5-(4-chlorophenyl)-3-cyanopyrrole (36): yield 74% (0.84 g); white solid; mp 163−165 °C ($CHCl_3$−hexane); R_f 0.6 (3:2 hexane−EtOAc); IR (KBr) 3294, 2929, 2220, 1490, 1456, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (br s, 4H), 3.08 (br s, 4H), 3.53 (s, 2H), 7.06 (d, J = 2.9 Hz, 1H), 7.17−7.27 (m, 7H), 7.56 (d, J = 8.3 Hz, 2H), 9.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 53.6, 63.1, 90.0, 116.9, 122.2, 125.2, 127.0, 127.1, 128.2, 128.9, 129.2, 129.6, 132.7, 136.2, 138.0; MS *m/z* (rel intens) 376 (M^+, 100), 378 (M + 2, 30); HRMS (EI) *m/z* calcd for $C_{15}H_{20}N_4O_4$ 376.1454, found 376.1451.

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Supporting Information Available: ^1H and ^{13}C NMR spectral data of all new compounds and CIF files containing the X-ray crystallographic data of compounds **7a**, **23**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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