JOC*Note*

pubs.acs.org/joc

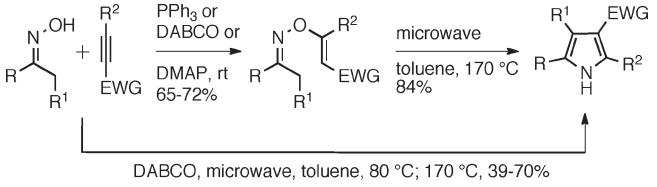
Synthesis of Highly Substituted Pyrroles via Nucleophilic Catalysis

Simbarashe Ngwerume and Jason E. Camp*

School of Chemistry, University of Nottingham, Nottingham NG7 2RD, U.K.

jason.camp@nottingham.ac.uk

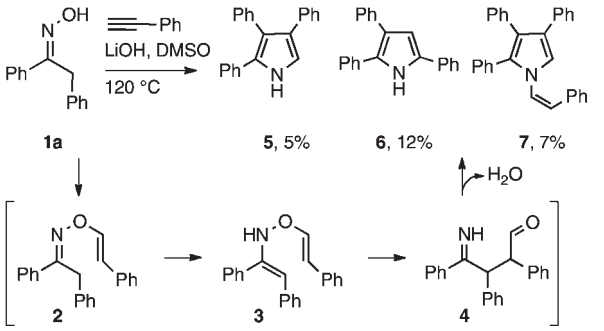
Received June 11, 2010



A nucleophilic catalysis method providing a concise synthesis of di-, tri-, and tetrasubstituted pyrroles is described. This regioselective one-pot method relies on nucleophilic catalysis of the intermolecular addition of oximes to activated alkynes and thermal rearrangement of the in situ generated *O*-vinyl oximes to form pyrroles that contain a functional group handle at the C3/C4 position.

Pyrroles as pharmaceuticals,[1] agrochemicals,[2] and in biological processes[3] are vital to our everyday lives. Due to their importance, extensive research has been conducted on the synthesis of pyrroles.[4] One underutilized method for the synthesis of pyrroles is the reaction of oximes and acetylenes under thermal superbasic conditions (LiOH, DMSO), the Trofimov reaction (Scheme 1).[5,6] Mechanistically, this process is proposed to proceed via initial addition of the anion of oxime **1a** to the alkyne, followed by tautomerization of vinyl oxime **2** to diene **3**. A subsequent [3,3]-sigmatropic rearrangement forms 1,4-iminoaldehyde **4**, which upon cyclodehydration generates pyrrole **5**, in a manner analogous to the

SCHEME 1. Trofimov Pyrrole Synthesis and Proposed Mechanism



Paal-Knorr pyrrole synthesis.[7] Importantly, this reaction provides (a) access to difficult to synthesize pyrroles from unactivated alkynes, and (b) a convergent way to form both a C−C bond and a C−N bond.[8] Unfortunately, the usual reaction conditions are extremely harsh, requiring strong bases/high temperatures. Additionally, the process is unselective, resulting in a mixture of both product regioisomers and distribution (i.e., formation of **5**−**7** from the reaction of oxime **1a** and phenylacetylene). These factors limit the overall synthetic utility of the Trofimov pyrrole synthesis, and therefore, we sought to develop a milder catalytic version to broaden the scope of this important transformation.

At the outset of our research, nothing had been reported on catalytic variants of the Trofimov reaction. During the course of the work outlined here, Anderson et al. described a related study on the selective formation of methyl-substituted pyrroles from *O*-allyl oximes. Vinyl oxime intermediates similar to **2** are formed in situ using an iridium-catalyzed isomerization of preformed allyl oximes, which then underwent a process similar to that outlined in Scheme 1 to form 4-methyl-5-unsubstituted pyrroles (Figure 1).[9] This publication has prompted us to disclose our research in the area of catalytic variants of the Trofimov reaction, which eliminates the need for strongly basic conditions while controlling the regioselectivity of the reaction and increasing the scope/utility of the products. Herein we report the findings from our study, including the development of a one-pot nucleophilic catalysis method for the synthesis of highly substituted pyrroles from the reaction of oximes with electron-deficient alkynes.

To begin, the formation of vinyl oximes from the addition of oximes to activated alkynes was investigated. Importantly, we wanted to develop a synthesis of vinyl oximes that

(1) For example, see: (a) Pinna, G. A.; Curzu, M. M.; Sechi, M.; Chelucci, G.; Maciocco, E. *Il Farmaco* **1999**, *54*, 542–550. (b) Murineddu, G.; Loriga, G.; Gavini, E.; Peanna, A. T.; Mulè, A. C.; Pinna, G. A. *Arch. Pharm. Med. Chem.* **2001**, *334*, 393–398.

(2) Walter, H. *Z. Naturforsch.* **2008**, *63b*, 351–362.

(3) For example, see: Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256.

(4) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Blackwell Science: Oxford, UK, 2010.

(5) For a review, see: Mikhaleva, A. I.; Hyun, S.; Trofimov, B. A. *Heterocycles* **1994**, *37*, 1193–1232. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491–2515.

(6) For examples of Trofimov reactions, see: (a) Petrova, O. V.; Sobenina, L. N.; Ushakov, I. A.; Mikhaleva, A. I.; Hyun, S.; Trofimov, B. A. *ARKIVOC* **2009**, *iv*, 14–20. (b) Trofimov, B. A.; Schmidt, E. A.; Mikhaleva, A. I.; Pozo-Gonzaol, C.; Pomposo, J. A.; Salsamendi, M.; Protzuk, N. I.; Zorina, N. V.; Afonin, A. V.; Vashchenko, A. V.; Levanova, E. P.; Levkovskaya, G. G. *Chem.—Eur. J.* **2009**, *15*, 6435−6445 and references therein.

(7) For a recent microwave-assisted Paal-Knorr pyrrole synthesis, see: Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389–392.

(8) For examples of the use of the Trofimov reaction in synthesis, see: (a) Gonzales, F.; Sanz-Cervera, J. F.; William, R. M. *Tetrahedron Lett.* **1999**, *40*, 4519–4522. (b) Pinna, G. A.; Pirisi, M. A.; Chelucci, G.; Mussinu, J. M.; Murineddu, G.; Lorga, G.; D'Aquila, P. S.; Serra, G. *Bioorg. Med. Chem.* **2002**, *10*, 2485–2496. (c) Murineddu, G.; Cignarella, G.; Chelucci, G.; Loriga, G.; Pinna, G. A. *Chem. Pharm. Bull.* **2002**, *50*, 754–759. (d) Vasil'tsov, A. M.; Ivanov, A. V.; Mikhaleva, A. I.; Trofimov, B. A. *Tetrahedron Lett.* **2010**, *51*, 1690–1692.

(9) Wang, H.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290–2293.

DOI: 10.1021/jo1011448 Published on Web 08/18/2010

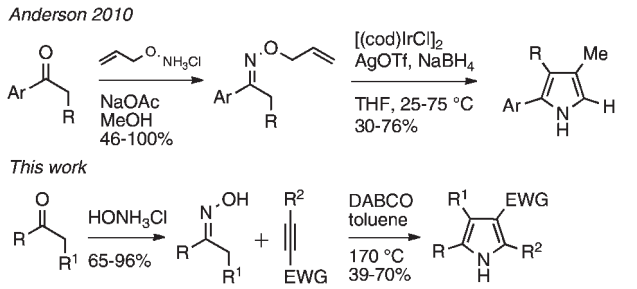
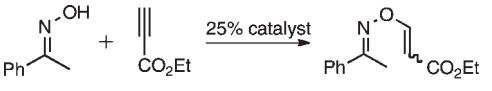


FIGURE 1. Catalytic synthesis of pyrroles from oximes.

TABLE 1. *O*-Vinyl Oxime Formation via Nucleophilic Catalysis



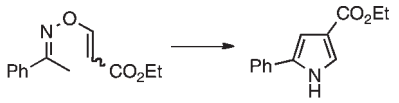
entry	catalyst/conditions	yield (%) *E*:*Z* ratio
1	PPh_3, DCM, −10 °C−rt, 20 h	65, 9:1
2	DMAP, DCM, −10 °C−rt, 20 h	71, 9:1
3	DABCO, DCM, −10 °C−rt, 20 h	72, 8:1
4	DABCO, toluene, −10 °C−rt, 20 h	66, 8:1
5	PPh_3, toluene-d_8,40 °C, microwave, 10 min	55,[a] 8:1
6	PPh_3, toluene-d_8,60 °C, microwave, 10 min	70,[a] 8:1
7	PPh_3, toluene-d_8,80 °C, microwave, 10 min	80,[a] 9:1
8	PPh_3, toluene-d_8,100 °C, microwave, 10 min	71,[a] 10:1

[a]Percent conversion to product based on NMR analysis.

would be viable under the subsequent thermal rearrangement (vide infra). Yavari and Ramazani reported a method for the synthesis of vinyl oximes based on the use of triphenylphosphine (PPh_3) as a nucleophilic catalyst.[10,11] Building upon this research, a number of nucleophilic catalysts (PPh_3, DMAP, and DABCO) were shown to effect the formation of vinyl oxime **9b**. Reaction of acetophenone oxime (**1b**) with ethyl propiolate (**8**) in either DCM or toluene at rt cleanly afforded the desired product **9b**, as an inseparable mixture of *E*:*Z*-alkene isomers (Table 1, entries 1−4).[12] Next, the thermal stability of this reaction was investigated by analyzing the contents of the crude reaction mixture after microwave irradiation.[13] The optimal temperature for the formation of vinyl oxime **9b** was found to be 80 °C (Table 1, entries 5−8).

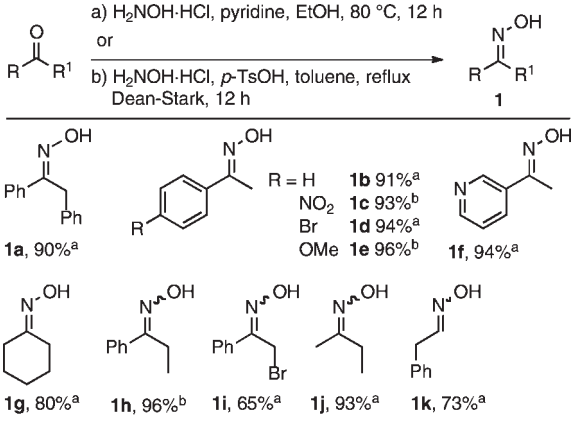
The second phase of this work was directed toward the thermal rearrangement of vinyl oxime **9b** to 2,4-disubstituted pyrrole **10b**. Previous research on the thermal rearrangement[14] of vinyl oximes to pyrroles demonstrated that the reaction is dependent upon the nature of the substrate with

TABLE 2. Thermal Rearrangement of Vinyl Oximes to Pyrroles



entry	solvent/conditions	result/yield (%)
1	none, thermal, 100 °C, 26 h	**9b**
2	none, thermal, 120 °C, 28 h	**9b**
3	none, thermal, 140 °C, 24 h	**9b**
4	DMSO, microwave, 120 °C, 45 min	**9b**
5	toluene, microwave, 100 °C, 45 min	**9b**
6	toluene, microwave, 120 °C, 45 min	**9b**
7	toluene, microwave, 140 °C, 45 min	**9b**
8	toluene, microwave, 170 °C, 45 min	**10b**/84

SCHEME 2. Substituted Oxime Formation



electron-withdrawing groups requiring increased temperatures.[15] Neat thermolysis for extended reaction times at temperatures up to 140 °C using traditional heating did not afford any of the desired pyrrole **10b** (Table 2). In contrast, DMSO at 120 °C, a solvent and temperature that have been shown to result in the formation of pyrroles from unsubstituted vinyl oximes,[16] only afforded starting material **9b**. To overcome the activation barrier for conversion of vinyl oximes with electron-withdrawing groups to pyrroles, **9b** was heated in toluene to 170 °C in a microwave reactor, which gave the desired pyrrole **10b** in 84% isolated yield.

We next investigated a one-pot synthesis of pyrroles from oximes and activated alkynes. A series of oximes were initially synthesized under standard conditions (Scheme 2).[17,18] Oximes **1a**−**1f** were isolated as the (*E*)-oximes, as determined by correlation to literature precedent, while oximes **1h**−**1k** were isolated as isomers.

Oximes **1a**−**1k** were then reacted with activated alkynes, ethyl propiolate (**8**) or dimethylacetylenedicarboxylate (**12**), to form highly substituted pyrroles **10** or **13**, respectively

(10) (a) Yavari, I.; Ramazani, A. *Synth. Commun.* **1997**, *27*, 1449–1454. (b) For a review of PPh_3 as a nucleophilic catalyst, see: Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544.

(11) For a related nucleophilic catalysis approach to *N*-hydroxy pyrroles, see: Hekmatshoar, R.; Nouri, R.; Beheshtiha, S. Y. S. *Heteroat. Chem.* **2008**, *19*, 100−103 and references therein.

(12) For use of nucleophilic catalysts in the related Morita−Baylis−Hillman reaction, see: (a) Spivey, A. C.; Areniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436–5441. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062.

(13) For a review on microwave-assisted multicomponent reactions for the synthesis of heterocycles, see: Bagley, M. C.; Lubinu, M. C. *Top. Heterocycl. Chem.* **2006**, 31–58.

(14) Please note that unsubstituted vinyl oximes have been shown to explode violently at elevated temperatures. See: Trofimov, B. A.; Mikhaleva, A. I.; Vasol'tsov, A. M.; Schmidt, E. Y.; Tarasova, O. A.; Morozova, L. V.; Sobenina, L. N.; Preiss, T.; Henkelmann, J. *Synthesis* **2000**, 1125–1132.

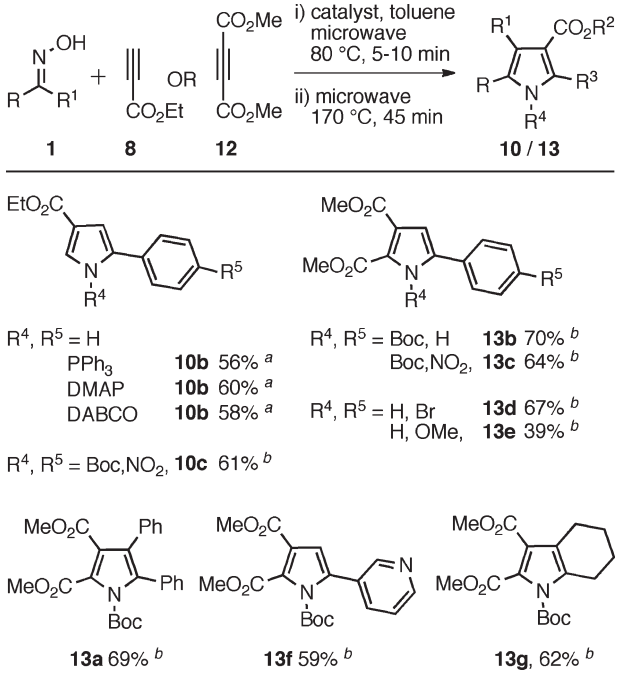
(15) For examples, see: (a) Sheradsky, T. *Tetrahedron Lett.* **1970**, 25–26. (b) Pinna, G. A; Sechi, M.; Paglietti, G.; Pirisi, M. A. *J. Chem. Res.* (*S*) **2003**, 117−120 and references therein.

(16) Schmidt, E. Y.; Zorina, N. V.; Zaitsez, A. B.; Mikhaleva, A. I.; Vasil'tsov, A. M.; Audebert, P.; Clavier, G.; Méallet-Renault, R.; Pansu, R. B. *Tetrahedron Lett.* **2004**, *45*, 5489–5491.

(17) Cui, Y.; Yasutomi, E.; Otani, Y.; Yoshinaga, T.; Ido, K; Sawada, K.; Kawahata, M.; Yamaguchi, K; Ohwada, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6386–6389.

(18) See Supporting Information for details on the synthesis and characterization of oximes **1a**−**1k**.

SCHEME 3. One-pot Pyrrole Synthesis from Oximes and Activated Alkynes



[a] 10% catalyst [b] 10% DABCO catalyst

(Scheme 3). Several features of the one-pot method are noteworthy. It was found that a 5−10 min microwave pulse at 80 °C prior to increasing the temperature to 170 °C was necessary in order to form pyrroles. This method proved to be very expedient and high yielding for α-methyl-α-aromatic ketoximes. For example, subjection of acetophenone oxime (**1b**) and **8** to the optimized conditions gives NH-pyrrole **10b** in good yield regardless of the nucleophilic catalyst that was employed. DABCO was used in all subsequent reactions due to its ease of purification from the reaction mixture and low catalyst loading. The doubly activated alkyne **12** gave higher yields of the corresponding pyrroles **13a**−**g** under the reaction conditions. Importantly, tetrasubstituted pyrroles **13a** and **13g** were synthesized in good yields from the respective oximes. For increased yields and ease of purification, as the polymerization of NH-pyrroles is well-documented,[19] it was sometimes necessary to add di-*tert*-butyl dicarbonate directly to the crude reaction mixture to afford *N*-Boc-pyrroles. Unfortunately, oxime substitution other than methyl (**1h**, **1i**), which lacked an aromatic group and were acyclic (**1j**) or aldoximes (**1k**), did not afford the desired pyrroles in significant yields. We believe that this is a result of the instability of the compounds to the high reaction temperatures necessary for a thermal rearrangement, leading to degradation/polymerization.[7]

In summary, we have developed a concise, robust, and flexible nucleophilic catalysis/microwave irradiation method for the formation of vinyl oximes and pyrroles from oximes and electron-deficient alkynes. In particular, we note the amenability of this method to the regioselective generation of 2,4-disubstituted and 2,3,5-trisubstituted pyrroles. Importantly, this method provides a functional group handle at C3/C4 for further manipulations and negates the need for strongly basic conditions. To the best of our knowledge, this is the first example of a catalytic one-pot method for the direct synthesis of pyrroles from oximes and activated alkynes, and we anticipate that it will find wide application due to its simple operating procedure.

(19) Thompson, A.; Butler, R. J.; Grundy, M. N.; Laltoo, A. B. E.; Robertson, K. N.; Cameron, T. S *J. Org. Chem.* **2005**, *70*, 3753–3756.

Experimental Section

Ethyl 3-(1-phenylethylideneaminooxy)acrylate (9b). To a stirred solution of DABCO (36 mg, 0.30 mmol) and (*E*)-acetophenone oxime (**1b**, 400 mg, 3.0 mmol) in dry dichloromethane (8 mL) at −10 °C was added dropwise a mixture of ethyl propiolate (**8**, 0.28 mL, 3.0 mmol) in dichloromethane (3 mL) over 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (9:1 petroleum/EtOAc) to afford ethyl 3-(1-phenylethylideneaminooxy)acrylate (**9b**, 497 mg, 72%) as an inseparable *E*:*Z* mixture (8:1) as a colorless oil: IR ($CHCl_3$) ν (cm^{-1}) 3180, 2961, 2872, 2728, 1701, 1615, 1573, 1465, 1312, 1129, 1048, 896, 840, 640 cm^{-1}. (*E*)-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 12.6 Hz, 1H), 7.67−7.74 (m, 2H), 7.37−7.46 (m, 3H), 5.71 (d, J = 12.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.6, 161.9, 160.3, 134.5, 130.4, 128.6, 126.9, 126.9, 97.3, 59.8, 14.3, 13.5. (*Z*)-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.77 (m, 2H), 7.49 (d, J = 7.5 Hz, 1H), 7.45−7.49 (m, 3H), 4.94 (d, J = 7.5 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.48 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.2, 159.9, 159.2, 134.5, 130.2, 128.3, 125.9, 94.3, 59.7, 14.1, 13.5; HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_3Na$, 256.1052; found, 256.1055.

Ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (10b). A solution of ethyl 3-(1-phenylethylideneaminooxy)acrylate (**9b**, 100 mg, 0.49 mmol) in dry toluene (2.5 mL) was heated to 170 °C for 45 min under microwave irradiation. The solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (3:1 petroleum/EtOAc) to afford ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (**10b**, 72 mg, 84%) as an orange oil: IR ($CHCl_3$) ν (cm^{-1}) 3699, 3631, 2992, 2943, 2888, 2838, 1708, 1626, 1486, 1392, 1217, 1073, 891, 838, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65−8.89 (m, 1H), 7.50−7.52 (m, 1H), 7.47−7.50 (m, 2H), 7.36−7.43 (m, 2H), 7.23−7.30 (m, 1H), 6.93−6.92 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.9, 133.0, 131.7, 129.0, 127.0, 124.1, 118.1, 106.7, 59.9, 14.5; HRMS (ESI) m/z calcd for $C_{13}H_{13}NO_2Na$, 238.0844; found, 238.0845.

General Procedure A: Synthesis of NH-Pyrroles. To a stirred solution of catalyst (0.10 equiv) and oxime (1.0 equiv) at −10 °C in dry toluene was added dropwise an alkyne (1.0 equiv) over 15 min. The reaction mixture was allowed to warm to rt and was subjected to a two-stage microwave irradiation sequence (stage 1, 80 °C, 5−10 min; stage 2, 170 °C, 45 min). The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to afford the NH-pyrrole.

Dimethyl 5-(4-bromophenyl)-1*H*-pyrrole-2,3-dicarboxylate (13d). Pyrrole **13d** was synthesized according to general procedure A. To DABCO (10 mg, 0.09 mmol) and (*E*)-1-(4-bromophenyl)ethanone oxime (**1d**, 200 mg, 0.9 mmol) in dry toluene (2.5 mL) was added dimethylacetylenedicarboxylate (**12**, 0.15 mL, 0.9 mmol), and the resultant mixture was subjected to the two-stage microwave irradiation sequence (stage 1, 80 °C, 5 min; stage 2, 170 °C, 45 min). After workup, the residue was purified by flash column chromatography on silica gel (7:1 petroleum/EtOAc) to afford dimethyl 5-(4-bromophenyl)-1*H*-pyrrole-2,3-dicarboxylate (**13d**, 197 mg, 67%) as an orange

oil: IR ($CHCl_3$) ν (cm^{-1}) 3689, 3634, 3423, 3087, 2887, 2087, 1721, 1653, 1565, 1489, 1398, 1180, 998, 899, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75−9.97 (br s, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 6.91 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.1, 160.6, 133.7, 132.2, 131.0, 126.3, 122.9, 122.2, 121.5, 110.9, 52.3, 51.9; HRMS (ESI) m/z calcd for $C_{14}H_{12}BrNO_4Na$, 359.9847; found, 359.9849.

General Procedure B: Synthesis of N-Boc-Pyrroles. To a stirred solution of DABCO (0.10 equiv) and oxime (1.0 equiv) at −10 °C in dry toluene was added dropwise an alkyne (1.0 equiv) over 15 min. The reaction mixture was allowed to warm to rt and was subjected to a two-stage microwave irradiation sequence (stage 1, 80 °C, 5−10 min; stage 2, 170 °C, 45 min). To the cooled crude mixture were added di-*tert*-butyl dicarbonate (2.0 equiv), DMAP (0.10 equiv), and triethylamine (1.0 equiv), and the resultant mixture was stirred at rt for 30 min. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to afford the *N*-Boc-pyrrole.

1-*tert*-Butyl 2,3-dimethyl 5-phenyl-1*H*-pyrrole-1,2,3-tricarboxylate (13b). Pyrrole **13b** was synthesized according to general procedure B. To DABCO (17 mg, 0.15 mmol) and (*E*)-acetophenone oxime (**1b**, 200 mg, 1.48 mmol) in dry toluene (2.5 mL) was added dimethylacetylenedicarboxylate (**12**, 0.24 mL, 1.48 mmol), and the resultant mixture was subjected to the two-stage microwave irradiation sequence (stage 1, 80 °C, 10 min; stage 2, 170 °C, 45 min). Di-*tert*-butyl dicarbonate (645 mg, 2.96 mmol), DMAP (18 mg, 0.15 mmol), and triethylamine (0.15 mL, 1.48 mmol) were added. After workup, the residue was purified by flash column chromatography on silica gel (12:1 petroleum/EtOAc) to afford 1-*tert*-butyl 2,3-dimethyl 5-phenyl-1*H*-pyrrole-1,2,3-tricarboxylate (**13b**, 367 mg, 70%) as an orange oil: IR ($CHCl_3$) ν (cm^{-1}) 3694, 3631, 3482, 3008, 2912, 2838, 2019, 1750, 1603, 1534, 1447, 1332, 1126, 965, 846, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.40 (m, 3H), 7.33 (m, 2H), 6.52 (s, 1H), 3.98 (s, 3H), 3.84 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.3, 162.9, 147.8, 135.7, 132.5, 129.7, 129.2, 128.2, 127.9, 117.4, 112.5, 86.2, 53.1, 51.9, 27.2; HRMS (ESI) m/z calcd for $C_{19}H_{21}NO_6Na$, 382.1267; found, 382.1267.

Acknowledgment. We gratefully acknowledge financial support from the School of Chemistry at the University of Nottingham.

Supporting Information Available: All experimental procedures, analytical data, and copies of ^1H and ^{13}C NMR spectra of all newly synthesized products. This material is available free of charge via the Internet at http://pubs.acs.org.