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Facile structural elucidation of imidazoles and oxazoles based on NMR spectroscopy and quantum mechanical calculations

Michal Weitman [a], Lena Lerman [a], Shmuel Cohen [b,‡], Abraham Nudelman [a,*], Dan T. Major [a,*], Hugo E. Gottlieb [a,*]

[a] Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel
[b] Department of Inorganic Chemistry, The Hebrew University, Jerusalem 91904, Israel

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ABSTRACT

The reaction of 1,2,3-tricarbonyl derivatives with hexamethylenetetramine and ammonium acetate in acetic acid provides an unambiguous approach to the synthesis of imidazoles, whereas the Bredereck reaction of α-haloketones in formamide, yields both imidazoles and oxazoles. Herein we describe a facile methodology for distinguishing between these heterocyclic compounds based on a combination of NMR spectroscopy and quantum mechanical calculations. In the NMR data the oxazole C-2 has a chemical shift of ca. 150 ppm whereas in the imidazoles it is found at ca. 135 ppm, with a $^{1}J_{C\text{-}H}$ of ca. 250 Hz for the oxazoles and ca. 210 Hz for the imidazoles. $^{1}J_{C\text{-}H}$ values can be easily obtained from a gated-decoupled ^{13}C spectrum, and even more trivially, from the separation of the H-2 ^{13}C satellites in the ^{1}H spectra. Additionally, the computed NMR data, obtained from density functional theory, are found to be in good agreement with the experimental data and serve as valuable tools in identifying the products of the Bredereck reaction.

1. Introduction

In the course of studies dealing with inhibitors of the HIV reverse transcriptase we reported the synthesis of a family of tricyclic derivatives of Formula **I**, based on a scaffold of two benzene rings and a five-membered heterocyclic imidazole or thiazole ring. The initial structures of this scaffold were derived from molecular modeling studies, which predicted that the most promising candidates would be compounds having a carboxamido substituent on the heterocyclic ring.[1] Subsequent studies involved modification of the scaffold by elongation of the distance between the aromatic rings leading to compounds of Formula **II**, which by virtue of the linking methylene group would have a greater degree of rotational freedom and possible additional receptor-binding interaction capabilities than compounds of Formula **I** (Fig. 1).

The early approach to the synthesis of the imidazole moiety was based on the Bredereck reaction involving treatment of an α-haloketone with formamide at elevated temperatures.[2a] Despite the fact that imidazoles prepared by this procedure are claimed to be obtained in 30–70% yields, in our hands the products were isolated only in 2–7% yields,[1] attributed to the presence of the carboxamido or carboxylate ester substituents found in the starting materials. Further structural analysis, described in this manuscript, of the compounds, which were earlier assigned as possessing Formula **I**, revealed that these were oxazoles and not imidazoles. Moreover Bredereck and co-workers[2c] reported that under certain conditions the products of the reaction were oxazoles and not imidazoles and that the oxazoles could be converted to the corresponding imidazoles when heated in formamide at high temperatures. Herein we describe a facile and unambiguous method for distinguishing between the imidazoles and oxazoles based on the $^{1}J_{CH}$ parameter of their respective NMR spectra. The structural assignments are further supported by theoretical calculations. To clarify the mechanism of the transformations involved in the Bredereck reaction we followed one such example in the NMR tube and were able to identify intermediates.

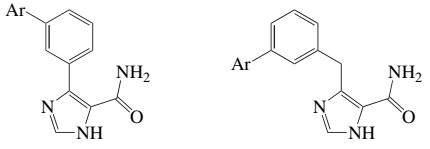

Figure 1. Tricyclic carboxamido-substituted imidazoles.

* Corresponding authors. Tel./fax: +972 3 5318314.
E-mail address: nudelman@mail.biu.ac.il (A. Nudelman).
‡ X-ray crystallographic analysis

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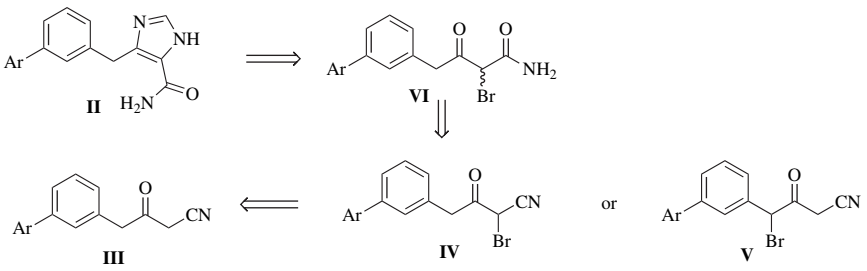


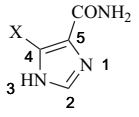
Figure 2. Retrosynthesis of **II**.

2. Results and discussion

Extension of the Bredereck reaction to the synthesis of compounds of Formula **II** required initial bromination of the corresponding 4-aryl-3-oxobutanenitrile precursors **III**. An expected problem in the course of such a bromination was the possibility that the reaction could take place at either of the methylene groups. Actually, the bromination proceeded solely at the undesired benzylic position to give **V** (Fig. 2), and therefore an alternative approach for the synthesis of the carboxamido-substituted imidazoles **II** was sought.

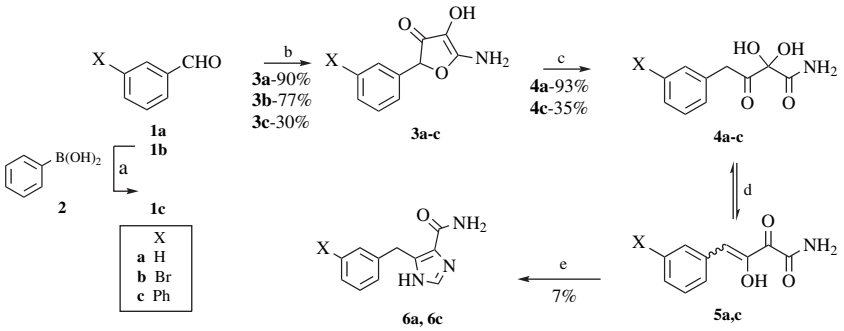
The desired products **II**, were prepared[3] from 1,2,3-tricarbonyl derivatives **4**,[4,5] hexamethylenetetramine and ammonium acetate in acetic acid under microwave irradiation conditions[6] (Scheme 1). Although the final cyclization step gave the desired benzyl-substituted imidazole, the low reaction yields (~ 10%), preclude this approach from being of general use for the synthesis of imidazoles.

Table 1
^1H and ^{13}C chemical shifts (ppm) and coupling constants (Hz) of carboxamido-substituted imidazoles



Compound	X	C-2	C-4	C-5	$CONH_2$	H-2	$^1J_{C2-H}$
6a	Bn	133.5	139.6	133.7	165.6	7.5	210
7[a]	Ph	149.9	143.7	124.9	159.5	8.3	250
Δ		16	4.1	9	6	0.8	40

[a] As shown later, **7** was found to be an oxazole and not an imidazole as assigned previously.[1]



a) $PdCl_2$, K_2CO_3, EtOH, Bu_4NBr; b) KCN, Na_2CO_3, glyoxal bis(sodium hydrogen sulfite), dioxane, AcOH; c) Amberlite IR 120 (H^+-form), H_2O; d) H_2O; e) hexamethylenetetramine/NH_4OAc, AcOH, microwave irradiation or165 °C

Scheme 1. Synthesis of carboxamido-substituted imidazoles.

2.1. Structure elucidation based on NMR studies and theoretical calculations

Comparison of the products such as compound **7** (a derivative of Formula **I**) obtained under the Bredereck reaction conditions, to those isolated from the 1,2,3-tricarbonyl derivatives, such as compound **6** (a derivative of Formula **II**), revealed several discrepancies: (a) The Bredereck products did not form hydrochloride salts when exposed to aqueous 3 M HCl; (b) they had much higher R_f elution values on silica gel than the products of the 1,2,3-tricarbonyl derivatives; (c) in the NMR spectra the ^{13}C chemical shift of the C-2 carbon (found between the heteroatoms) showed a shift of ~15 ppm downfield in the Bredereck products compared to those of the 1,2,3-tricarbonyl derivatives or other imidazoles; (d) other changes were also found in the ^1H chemical shift of the proton at position 2 and the ^{13}C chemical shifts of the carbon at position 5. The major differences are presented in Table 1; and (e) most surprisingly, the $^1J_{CH}$ coupling constants for C_2-H were found to be between 35 and 45 Hz greater for the Bredereck products, and were confirmed using HMBC spectra (see Supplementary data).

The use of $^1J_{CH}$ values in structure elucidation is well known but, in our opinion, underutilized, probably because the average chemist doesn't bother to extract such parameters from the spectra. Figure 3 illustrates, for 3-carbomethoxyimidazole (in CD_3OD solution, at 16.4 Tesla), three techniques for the measurement of the one bond carbon-proton coupling, $^1J_{CH}$: (a) the observation of ^{13}C satellites in the ^1H spectrum (the unmarked small peaks originate from impurities, even the low-field 'B' peak is superimposed to an impurity peak); (b) the direct measurement of CH multiplets in a gated-decoupled ^{13}C spectrum and (c) the measurement of the doublet splittings in an HMBC (long-range $^{13}C\times^1H$ correlation, low pass *J*-filter turned off) spectrum. In every case the AA and BB distances correspond to $^1J_{CH}$ for C-2 and C-4, and their values are 210.7±0.3 and 193.9±0.3 Hz, respectively. Of course, each technique has its advantages: for accuracy of measurement (i.e., digital resolution), a>b>c; for sensitivity, a>c>b; for robustness (small amounts of impurities don't matter) c>b>a.

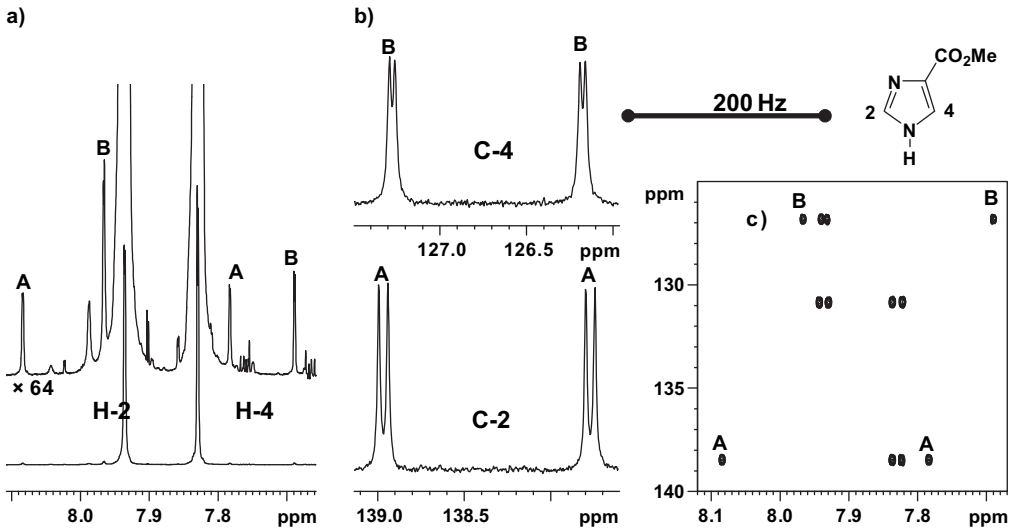
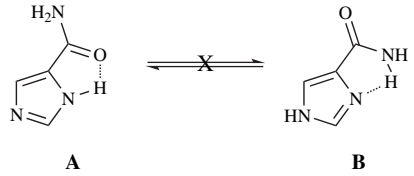


Figure 3. $^{1}J_{CH}$ measurement, for 3-carbomethoxyimidazole, using three different NMR techniques (see text). In every case the AA and BB distances correspond to $^{1}J_{CH}$ for C-2 and C-4, respectively.

To elucidate the source of these discrepancies various theoretical and experimental approaches were undertaken.

2.2. Structure assignment based on theoretical calculations

(a) *Exploration of the possibility of the presence of equilibrating tautomeric forms*[7] where in one case the imidazole is the H-bond donor and in the second case it is the H-bond acceptor to the carboxamido moiety. In the spectra of our imidazoles the N–CH–NH proton appeared as a sharp singlet (both in acetone-d_6 and in $CDCl_3$). This fact could be attributed to: (a) either two rapidly equilibrating tautomeric forms; or (b) to a situation in which only one of the possible tautomers is significantly populated. To determine which of these two possibilities prevailed, theoretical calculations based on DFT/GIAO methods were conducted, which revealed that the molecules existed in a single non-equilibrating form for **6a** (Scheme 2). For compound **7** the CH proton also appeared as a sharp singlet, because this compound was found to be an oxazole rather than an imidazole, as will be shown in the conclusion of these studies. In the following discussion, it will be assumed that **7** is an imidazole, as was initially thought.

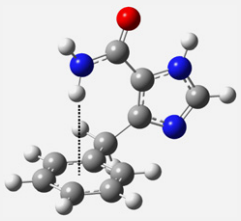
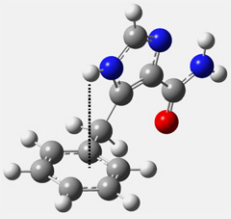
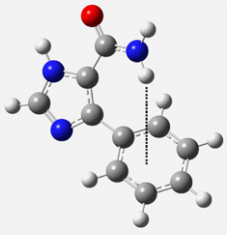
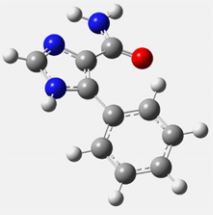


A **B**

Scheme 2. Non-equilibrating tautomeric forms carboxamido-substituted imidazoles.

To explore the possibility that compounds **6a** and **7** have different non-equilibrating tautomeric forms with different NMR spectra, density functional theory calculations at the mPW1PW91/6-311++G(3df,2p) level, were conducted. Structures **A** and **B** were computed to be close in potential energy. For **6a** the potential energy difference is 1.6 kcal/mol in favor of the **B** tautomer (Table 2). This is likely due to a more favorable intramolecular H-bond for tautomer **B** than for tautomer **A**. In the **A** and **B** tautomers there are possible favorable intramolecular dipole–π interactions between the amide group and the aromatic phenyl ring. Such dipole–π interactions have recently been studied.[8,9] For **7** the **A** tautomer is favored by 0.3 kcal/mol (Table 2). In the case of the **A** tautomer of **7**, intramolecular dipole–π interaction between the amide group and the

Table 2
Relative tautomerization potential energy, enthalpy, and free energy (kcal/mol) for compounds **6a** and **7**, and their optimized structures

Compounds	Optimized structures	ΔE_p [a]	ΔH	ΔG
6a tautomer **A**		1.6	1.5	2.8
6a tautomer **B**		0.0	0.0	0.0
7 tautomer **A**		0.0	0.0	0.0
7 tautomer **B**		0.3	0.3	0.1

[a] ΔE_p corresponds to the potential energy from mPW1PW91/6-311+G(3df,2p)//mPW1PW91/6-31G(d) electronic structure calculation. ΔH and ΔG were obtained by adding zero-point energy and thermal effects as described in the Computational Methods.

aromatic phenyl ring is possible, while in the **B** tautomer there is steric hindrance between the imidazole NH moiety and a phenyl hydrogen and no possible dipole–π interaction, shifting the tautomeric equilibrium in favor of the **A** tautomer. These potential energy differences are near the expected error-bar for the theoretical method employed.[10] Inclusion of zero-point energy and thermal enthalpy effects gives nearly identical results, while adding entropy effects changes these values only slightly. The free energy difference between the two tautomers of **6a** is slightly greater at 2.8 kcal/mol in favor of tautomer **B**, while for **7** the difference is a negligible 0.1 kcal/mol in favor of tautomer **A**.[11] Thus, the computations suggest that for **6a** only a single tautomer exists in accord with experimental data, while for **7** two co-existing tautomers are predicted.

In an attempt to elucidate the differences in chemical shifts and coupling constants between **6a** and **7**, the GIAO method was employed in conjunction with DFT electronic structure calculations at the mPW1PW91/6-311+G(2d,p) level. The use of computed shielding constants has become an increasingly useful tool in elucidating NMR spectra.[12,13] The chemical shifts of imidazole were initially computed to serve as benchmarks for the substituted imidazoles. Inspection of the data in Table 3 suggests that the computed chemical shifts are in good accord with the experimental values shown in Table 1. Turning to the computed NMR data for compounds **6a** and **7**, it is interesting that the chemical shifts of the tautomer **B** of **6a** are in better overall agreement with experiment than those for the tautomer **A**. This is clear from the chemical shifts at positions C-2, C-4, C-5, and $CONH_2$ that support the above predicted tautomerization equilibrium. In the case of **7**, the computed NMR data are similar to those of **6a**, but differ considerably from the experimentally determined values (Table 1). In summary, the computed properties of compound **6a** are in accord with the experimental data. However, the computations cannot rationalize the existence of only a single tautomer for **7** or its NMR spectra.

Table 3
Computed ^{1}H and ^{13}C chemical shifts (ppm) and $^{1}J_{CH}$ coupling (Hz) for **6a** and **7**[a]

Compound	C-2	C-4	C-5	$CONH_2$	H-2	$^{1}J_{C2-H}$
6a tautomer **A**	135.9	147.8	126.4	163.5	7.57	188.8
6a tautomer **B**	133.2	138.2	134.7	166.2	7.21	190.4
6a experimental values	133.5	139.6	133.7	165.6	7.50	210
7 tautomer **A**	137.3	147.5	124.2	162.5	7.64	189.1
7 tautomer **B**	133.1	137.6	136.2	165.8	7.46	190.4
7 experimental values	149.9	143.7	124.9	159.5	8.3	250

[a] Chemical shifts and coupling constants were obtained by the GIAO method at the mPW1PW91/6-311+G(2d, p)//mPW1PW91/6-31G(d) level.

(b) *Influence of the degree of conjugation of the heterocyclic ring on the chemical shift of C-2 and the corresponding coupling constant* $^{1}J_{CH}$. As seen in Table 1 there is a major difference in the chemical shifts and coupling constants of the CH at position 2 in compounds **6**a and **7**. Therefore, it was considered possible that the degree of conjugation in these compounds would have an effect on these parameters. For this purpose several model imidazoles (**8**–**15**), unsubstituted or substituted with ester or amido groups were examined by NMR (Table 4). In all cases the ^{13}C chemical shifts of the C-2 and the $^{1}J_{CH}$ coupling constants corresponded to those of the compounds obtained from the 1,2,3-tricarbonyls and not to the Bredereck products.

Since approaches (a) and (b) did not provide a convincing explanation for the indicated discrepancies, an X-ray crystallogram (Fig. 4) of one of the Bredereck products, obtained upon treatment of methyl 2-bromo-3-(3-iodophenyl)-3-oxopropanoate with formamide, to which an imidazole (**15**) had been assigned, was obtained revealing that the structure of this compound corresponded to that of oxazole **16**; moreover, the computed NMR data of oxazole is similar to that of compound **16**. The computed chemical shifts for oxazole are: H-2 (7.86 ppm), C-2 (154.50 ppm), C-4 (141.38 ppm), C-5 (131.97 ppm), and the $^{1}J_{CH}$ coupling constant is 209.93 Hz.

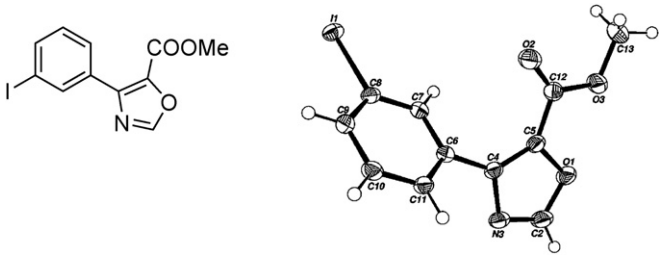


Figure 4. ORTEP drawing of **16**. The thermal ellipsoids are scaled to enclose 50% probability.

Bredereck reported that under similar reaction conditions imidazoles as well as oxazoles could be prepared.[2c] For instance when Theilig reacted α-haloketones in the presence of equimolar amounts of formamide at 130 °C, oxazoles were isolated, whereas in the presence of an excess formamide at 180 °C the obtained products were imidazoles. Furthermore, upon heating the oxazoles in formamide at reflux they underwent conversion into imidazoles.

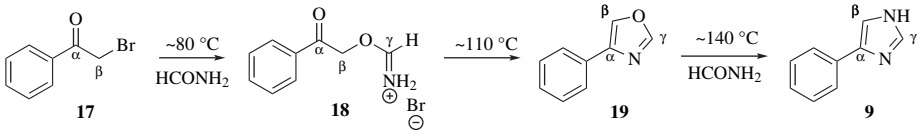
Table 4
Substituent effects on the ^{1}H and ^{13}C chemical shifts (ppm) and $^{1}J_{CH}$ coupling constants (Hz) of imidazoles

	X	Y	C-2	C-4	C-5	CO	H-2	$^{1}J_{C2-H}$
8	H	H	135.0	122.0	—	—	7.6	205
9	Ph	H	135.9	133.9	115.9	—	7.7	[f]
10	Me	H	134.4	118.4	118.6	—	7.6	208
11	Me	$CONH_2$	135.0[b]	138.2[b]	126.4[b]	165.9[b]	7.8[b]	208
12	H	$CONH_2$	135.8[c]	134.5[c]	121.2[c]	162.8[c]	7.7[c]	210
13	Me	COOEt	136.5[b]	124.9[b]	140.6[b]	163.9[b]	7.6[b]	209
14	H	COOMe	137.0[d]	129.6[d]	126.0[d]	162.8[d]	7.7[d]	210
15[a]	*m*-I-Ph	COOMe	153.8[e]	144.5[e]	139.2[e]	159.4[e]	8.45[e]	234

[a] As shown later, **15** was found to be an oxazole and not an imidazole as assigned here.
[b] $CDCl_3$–CD_3OD.
[c] DMSO-d_6.
[d] CD_3OD.
[e] Acetone-d_6.
[f] Not reported.

Two alternative mechanisms for the conversion were proposed,[2b] and using virtually analogous conditions, other reports[14–17] describe the synthesis of either oxazoles or imidazoles and one article[16] illustrates the isolation of mixtures of both heterocyclic compounds.

In an attempt to clarify the sequence of events in the reaction of α-haloketones with formamide, we followed the NMR spectra (^{1}H and ^{13}C) of a solution of α-bromoacetophenone in formamide, as a function of time and temperature. (a) At room temperature (ca. 30 °C) the peaks of the starting materials could be seen. As soon as the probe equilibrated at ca. 45 °C the appearance of a new methylene peak at δ 6.17 was detected, which was attributed to the methylene protons of compound **18** (Scheme 3); the presence of a carbonyl at 194.9 and the CH_2O moiety at 67.0 ppm supports the proposed structure. Within 30 min all the starting material had disappeared. (b) Since the mixture at ca. 45 °C seemed to have reached equilibrium, the NMR tube was further heated to ca. 110 °C. Immediately the formation of oxazole **19**[18] was noticed, but the reaction proceeded relatively slowly, and after 30 min, roughly equal amounts of **18** and **19** were present. (c) Some 15 min later when the temperature was raised to ca. 140 °C, **18** had completely disappeared and **19** dominated, but some 25% of a new species-**9**-



Scheme 3. Synthesis of imidazole **9** via oxazole **19**.

was present; and 2 h later, the latter compound had completely replaced **19**. The mechanism for the thermal conversion of an oxazole to an imidazole in the presence of formamide has been discussed by Theilig.[2b]

Although the signals of the *ortho* hydrogens of the phenyl ring were primarily monitored, the ^{13}C signals of the heterocycle were diagnostic in defining each product. (d) The reaction was repeated in the laboratory under roughly the same conditions as those described in a–c, and the intermediates were isolated. Their NMR chemical shifts are presented in Table 5. The assignments for **18** and **19** were confirmed by 2D spectra (COSY, and HMBC).

While this reaction sequence had been postulated in the literature[2] we believe that we have been the first to directly observe the intermediates. Based on the NMR data of the compounds synthesized earlier[1] by the Bredereck procedure, it is obvious that the reported products were oxazoles and not imidazoles.

imidazoles it is found at ca. 135 ppm, with a $^1J_{C\text{-}H}$ of ca. 250 Hz for the oxazoles and ca. 210 Hz for the imidazoles ($^1J_{C\text{-}H}$ values can be easily obtained from a gated-decoupled ^{13}C spectrum, but, even more trivially, from the separation of the H-2 ^{13}C satellites in the ^{1}H spectra).

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained on 200, 300 or 600 MHz spectrometers. Chemical shifts are expressed in parts per million downfield from Me_4Si used as internal standard. For some compounds the NMR data assignment was aided by several two-dimensional spectra including COSY, HMQC and HMBC analyses. Mass spectra and HRMS were obtained on CI=chemical ionization/CH_4 mode. Progress of the reactions was monitored by TLC on silica gel or alumina plates. Flash chromatography was carried out on silica gel. The microwave experiments were carried out at a maximum power of 300 W/frequency 2450 MHz. Commercially available compounds were used without further purification.

*4.1.1. 5-Amino-4-hydroxy-2-phenylfuran-3(2H)-one, (**3a**)*[4,5]. ^{1}H NMR (300 MHz, DMSO-d_6): δ=5.37 (1H, s, *H*C–CO), 7.34 (5H, m, *H*-aromatic), 7.8 (2H, br s, NH_2). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ=82.6 (*C*H–O), 111.5 (*C*–OH), 126.35 (C-*o*), 128.1 (C-*p*), 128.2 (C-*m*), 138.2 (C-*ipso*), 172.5 ($CONH_2$), 182.5 (*C*O ketone).

*4.1.2. 5-Amino-2-(3-bromophenyl)-4-hydroxyfuran-3(2H)-one (**3b**).* Compound **3b** was obtained as a white solid in 77% yield from compound **1b** as described:[4,5] mp 176–178 °C. The NMR data assignment was aided by several two-dimensional spectra including COSY, HMQC, and HMBC analysis. ^{1}H NMR (600 MHz, DMSO-d_6): δ=5.44 (1H, s, *H*C–CO), 7.27 (1H, s, O*H*), 7.28 (1H, d, *J*=7.8 Hz, *H*-6), 7.36 (1H, t, *J*=7.8 Hz, *H*-5), 7.43 (1H, s, *H*-2), 7.54 (1H, d, *J*=7.8 Hz, *H*-4), 7.82 (2H, br s, NH_2). ^{13}C NMR (150.9 MHz, DMSO-d_6): δ=81.9 (*C*H–O), 111.2 (*C*-OH), 121.5 (*C*Br), 125.2 (*C*-6), 128.6 (C-2), 130.7 (C-5), 130.9 (C-4), 138.9 (*C*–CH–O), 172.7 (CNH_2) 182.0 (*C*O ketone).

Table 5
^{13}C NMR data for products and intermediates of the reaction shown in Scheme 3

Compd.	^{1}H NMR, δ (ppm) chemical shifts					^{13}C NMR, δ (ppm) chemical shifts						
	ortho	*meta*	*para*	H-β	H-γ	*ipso*	*ortho*	*meta*	*para*	C-α	C-β	C-γ
17[a]	7.95	7.46	7.58	4.45	—	134.1	128.8	128.8	133.8	191.0	31.3	—
18[b]	7.87	7.43	7.56	5.39	8.21	139.14	127.70	128.83	134.00	191.13	65.30	160.06
19[c]	7.73	7.38	7.29	7.92	7.91	130.62	125.51	128.72	128.12	140.25	133.72	151.32
9[a]	7.72	7.37	7.24	7.35	7.71	133.89	124.14	128.37	125.97	138.06	114.89	135.88

[a] $CDCl_3$, 300 MHz, data from the Aldrich library of ^{13}C and ^{1}H FT NMR spectra (1993).
[b] Reaction was conducted in formamide. NMR was carried out in $CDCl_3$ 600 MHz, 80 °C.
[c] Formamide, 600 MHz, 110 °C.

3. Conclusions

From the above discussion it can be concluded that it is difficult to predict whether the products of the Bredereck reaction will be oxazoles or imidazoles. Experimental NMR data provide a facile method for identification of the products where the C-2 in the oxazoles has a chemical shift of ca. 150 ppm whereas in the

MS (CI$^+$) *m*/*z* (%) 270.97 (M^+, 31.6), 268.97 (M^+, 32.5), 197.96 (M^+–CO, 66.9), 195.08 (M^+–CO, 66.8), 170.97 ($BrBn^+$, 37.2), 168.97 ($BrBn^+$, 39.6). HRMS calcd for $C_{10}H_8NO_3Br$ 270.963; found 270.967.

*4.1.3. 5-Amino-2-(biphenyl-3-yl)-4-hydroxyfuran-3(2H)-one (**3c**).* Compound **3c** was obtained in 30% yield from **1c**, as described:[4,5] mp 164–166 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=5.47

(1H, s, *H*C–CO), 7.40 (1H, m, H-*p*), 7.48 (3H, m, H-*m*, H-5), 7.54 (1-H, s, H-2), 7.64 (3H, m, H-*o*, H-4), 7.86 (2H, br s NH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=82.5 (*C*H–O), 111.5 (*C*–OH), 124.8, 125.3, 126.5, 126.7, 127.6, 129.05, 129.09, (*C*H-aromatic), 138.0 (C-*ipso* CH), 139.9, 140.3 (C-*ipso* biphenyl, C-*ipso* biphenyl) 172.7 ($CONH_2$), 182.5 (*C*O ketone). MS (CI^+) *m*/*z* (%) 267.09 (MH^+, 0.63), 250.08 (MH^+-H_2O, 0.42). HRMS calcd for $C_{16}H_{13}NO_3$ 267.0900; found 267.092.

*4.1.4. 2,2-Dihydroxy-3-oxo-4-phenylbutanamide (**4a**)*[4,5]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=42.7 (*C*H_2), 95.4 (*C*$(OH)_2$), 127.4 (C-*p*), 128.9 (C-*m*), 130.7 (C-*o*), 135.3 (C-*ipso*), 172.1 ($CONH_2$), 204.3 (*C*O ketone). MS (CI^+) (%) 192.067 (MH^+, 15), 174.06 (M^+-NH_3, 7.5) 147.048 (M^+-$CONH_2^+$, 100), 119.06 ($BnCO^+$, 16.3). HRMS calcd for $C_{10}H_{10}NO_3$ 192.066; found 192.067.

*4.1.5. 4-(3-Bromophenyl)-2,2-dihydroxy-3-oxobutanamide (**4b**)*[4,5]. Compound **4b** was obtained as a pale white solid yield from compound **3b** as described and was found to be mixed with residual unreacted **3b**. The diagnostic ^{1}H NMR peak for **3b** is the *H*C–CO found at 5.72 ppm, whereas that of the product **4b** is the CH_2 found at 4.08 ppm.

*4.1.6. 4-(Biphenyl-3-yl)-2,2-dihydroxy-3-oxobutanamide (**4c**)*[4,5]. Compound **4c** was obtained as a pale yellow solid in 35% yield from compound **3c** as described:[4,5] mp 90–92 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ=4.11 (2H, s, CH_2), 6.15 (1H, br s, OH) 7.2 (1H, br s, NH), 7.34 (9H, m, *H*-aromatic, NH). ^{13}C NMR (75.5 MHz, CD_3OD): δ=41.4 (*C*H_2), 97.3 (*C*$(OH)_2$), 123.8, 125.4, 125.7, 127.0, 127.12, 127.15, 127.27 (*C*H-aromatic),133.3 (C-*ipso* to the methylene), 139.7, 137.9 (C-*ipso* to the biphenyl), 169.8 ($CONH_2$), 202.1 (*C*O ketone). MS (CI^+) *m*/*z* (%) 267.09 ($M-H_2O$, 7.4), 212.06 (Ph–Bn–COOH, 40.6). HRMS calcd for $C_{16}H_{13}NO_3$ 267.090; found 267.093.

*4.1.7. 3-Hydroxy-2-oxo-4-phenylbut-3-enamide (**5a**)*[4,5]. Compound **5a** was obtained as a pale yellow solid, mp 165–167 °C, in 93% yield upon evaporation of a solution of **4a** in acetone. ^{1}H NMR (300 MHz, acetone-d_6): δ=7.06 (1H, s, enol), 7.36 (3H, m, H-*m*, H-*p*), 7.93 (2H, m, *o*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=118.8 (*C*H enolic), 128.5 (C-*m*), 128.8 (C-*p*), 130.7 (C-*o*), 134.6 (C-*ipso*), 146.9 (*C*OH enolic), 165.3 ($CONH_2$), 184.6 (*C*O ketone).

*4.1.8. 4-Benzyl-1H-imidazole-5-carboxamide (**6a**).* A solution of **4a** (0.1 g, 0.34 mmol) hexamethylenetetramine (0.1 g, 0.69 mmol), NH_4OAc (26 mg, 0.34 mmol) in acetic acid (1.5 mL) was heated with stirring at 165 °C for 5 min under microwave irradiation conditions. The mixture was poured into a saturated aqueous NH_4OH solution cooled to 0 °C. The brown precipitate formed was filtered and the filtrate was extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a brown residual oil, which was purified by flash chromatography (EtOAc). Compound **6a** was isolated as white needles (crystallized from acetone) in 4% yield (microwave irradiation) or 7% yield (thermal conditions, 1 h at 165 °C, using the same workup). ^{1}H NMR (600 MHz, acetone-d_6): δ=4.48 (2H, s, CH_2), 6.28 (1H, br s, N*H*), 7.15 (1H, br s, NH), 7.16 (1H, t, *J*=7.2 Hz, H-*p*), 7.25 (2H, t, *J*=7.2 Hz, H-*m*), 7.3 (2H, d, *J*=7.2 Hz, H-*o*), 7.50 (1H, s, C*H*-imidazole). ^{13}C NMR (150.9 MHz, acetone-d_6): δ=30.3 (*C*H_2), 126.0 (*C*-*p*), 128.2 (C-*m*), 128.5 (C-*o*), 130.4 (C-*m*), 138.2 (C-*ipso*), 133.5 (*C*H-imidazole), 133.7 (*C*$CONH_2$) 139.6 (Bn-*C*), 165.2 ($CONH_2$). MS (CI^+) *m*/*z* (%) 202.10 (MH^+, 4), 185.068 (MH^+-NH_3, 2), 159.10 (MH^+-CONH_3, 0.81). HRMS (MH^+) calcd for $C_{11}H_{12}N_3O$ 202.098; found 202.097.

*4.1.9. 4-(Biphenyl-3-ylmethyl)-1H-imidazole-5-carboxamide (**6c**).* Compound **6c** prepared from **4c** was isolated as described for **6a**, as a yellow oil in 7% yield (microwave irradiation or thermal conditions). ^{1}H NMR (300 MHz, acetone-d_6): δ=4.50 (2H, s, CH_2), 6.2 (1H, br s, N*H*), 7.11 (1H, br s, NH), 7.34 (3H, m, H-aromatic), 7.42 (3H, m, H-aromatic), 7.51 (1H, s, C*H*-imidazole), 7.62 (3H, m, H-aromatic). ^{13}C NMR (75.5 MHz, acetone-d_6): δ=31.3 (*C*H_2), 125.6, 127.7, 128.10, 128.16, 128.56, 129.63, 129.77 (*C*H-aromatic) 134.33, 134.55 (*C*$CONH_2$, CH-imidazole). At the concentration of the sample, the quaternary (*C*$CONH_2$ and *C*CH_2) were not observed.

*4.1.10. Methyl 4-(3-iodophenyl)oxazole-5-carboxylate (**16**).* A solution of methyl 2-bromo-3-(3-iodophenyl)-3-oxopropanoate (2.61 mmol) in formamide (1 mL) to which 0.1 mL of water was added was heated at 140 °C for 5 h. Na_2CO_3 1 M and $CHCl_3$ were then added and the organic phase was separated, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (hexane/EtOAc 20:1) to provide **16** as a white solid in 2.3% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.46 (1H, t, *J*=1.73 Hz), 8.08 (1H, ddd, *J*=8.14; 1.73; 1 Hz, *H*), 8 (1H s,), 7.76 (1H, ddd, *J*=8.14; 1.73; 1 Hz), 7.19 (1H, t, *J*=8.2 Hz), 3.94 (3H s,). ^{13}C NMR (150.9 MHz, $CDCl_3$/acetone-d_6): δ=159.3, 153.8, 144.56, 139.26, 138.65, 138, 133.16, 130.9, 129.32, 94.03, 52.67.

4.2. Computational methods

The structures of compounds **6a** (tautomers A and B), **7** (tautomers A and B), **12**, and oxazole were optimized with the mPW1PW91 density functional[19] in conjunction with the 6-31G(d) basis set.[20–22] Frequency calculations were performed to analyze the nature of the stationary points, and local minima were verified. Thermal corrections were added employing standard statistical mechanics equations.[23] The frequencies were scaled by 0.9547.[24] Single-point energies were calculated at the mPW1PW91/6-311++G(3df,2p) level.[25,26] To obtain tautomerization free energies, the mPW1PW91/6-311++G(3df,2p) level energies were combined with the mPW1PW91/6-31G(d) level zero-point energy and thermal corrections. To verify the reliability of the mPW1PW91 functional, test calculations on compound **12** (tautomers A and B) with the above functional as well as the B1B95[27] and BB1K[28] functionals and second-order perturbation theory calculations (MP2) were conducted with the 6-31+G(d,p) basis set. All four methods favored tautomer **B** by a 1.4–1.6 kcal/mol potential energy difference (see Supplementary data).

To obtain the computational shielding data, the GIAO method was employed. In this method, the nuclear shielding is computed as the second derivative of the energy with respect to the applied magnetic field and the nuclear moment using field dependent atomic orbitals.[29,30] The mPW1PW91 density functional was employed as it has been shown to give good accord with experimental spectra.[31] The 6-311+G(2d,p) basis set was chosen as it was found suitable for nuclear shielding calculations.[32]

The quantity computed by the DFT-GIAO calculations is the shielding of the nuclei by the electrons. The experimentally observed chemical shift for carbon atoms, δ_C, is related to the computed shielding σ_C by σ_C=186.4−δ_C where the experimentally determined shielding of tetramethylsilane (TMS) has been employed.[33] The experimentally observed chemical shift for hydrogens, δ_H, is related to the computed shielding σ_H by σ_H=196.1−δ_H where the computed shielding of TMS has been employed. All calculations employed the Gaussian 03 program.[34]

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Supplementary data

Tables of geometries and potential energies for molecules **6**, **7**, **12**, and oxazole. Table of tautomerization energies for compound **12**

at various theoretical levels. Complete citation for Ref. 34. Crystallographic data for compound **16**. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.12.019.

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