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Highly regioselective radical alkylation of 3-substituted pyrroles

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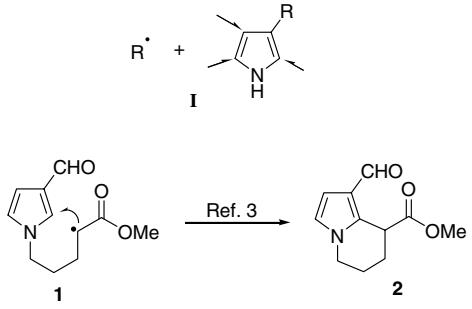
Abstract—It is reported that the intermolecular oxidative radical substitution on 3-substituted pyrroles gives the 2,3-disubstituted pyrroles in a highly regioselective manner. This behavior is explained on the basis of the relative stabilities of the intermediate radicals formed in the process. The methodology reported herein represents a direct entry into 2,3-disubstituted pyrroles, which might be used to construct more complex molecules.

Due to their broad distribution in nature as a constituent of the framework of a number of natural products, and also of synthetic products with significant pharmacological effects, pyrroles are among the most important heterocyclic systems.[1] Therefore, a great deal of attention has been devoted to the development of new and more efficient means of constructing the pyrrole system, and also to the understanding of its reactivity under specific conditions. Without a doubt the nucleophilic nature of the pyrrole aromatic system is mostly responsible for its chemical behavior. Indeed, electrophilic aromatic substitution is one of the main processes employed for introducing new substituents onto the pyrrole nucleus; the reaction mechanisms involved are well established.[1] Alternatively, driven by the need for mild and more versatile methods for the intra and intermolecular substitution of pyrroles, free-radical-based processes have gained increasing importance.[2] For instance, 2-substituted pyrroles are reported to undergo direct alkylation mainly at C-5, under a variety of free-radical conditions. Thus, the reactivity of substituted pyrroles under free-radical conditions has been explained in terms of frontier orbital interactions.[3] In contrast, there are few precedents for the free-radical oxidative alkylation on 3-substituted pyrroles.[2] An important issue in this topic is the regiochemistry of the substitution, given that in principle, three different positions are available for the addition of the free radical (**I** in Scheme 1). For instance, the free-radical cyclization of alkyl[3] and acyl[4] radicals (nucleophilic radicals) is reported to give selectively the product of addition at C-2. In addition, in an earlier study we observed that the main cyclization product of the electrophilic radical **1** was **2**, reflecting the attack of the radical again at C-2; no trace of the product resulting from attack at C-5 was detected (Scheme 1).[5] The observation of this highly regioselective annulation with either nucleophilic or electrophilic radicals, prompted us to examine the intermolecular process (Scheme 2). Herein, preliminary results of our endeavors in this field are described.

It has been recently demonstrated in our group, the effectiveness of xanthate-based free-radical method to achieve intermolecular oxidative radical alkylation of a



Scheme 1.

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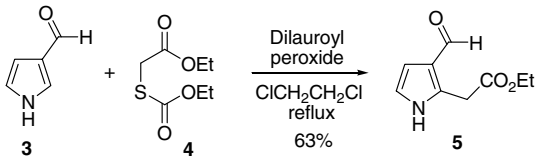


Scheme 2.

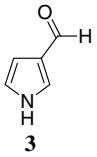
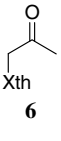
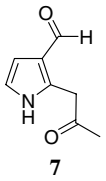
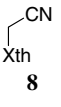
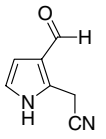
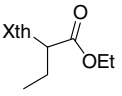
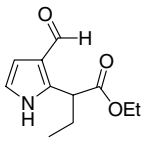
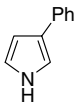
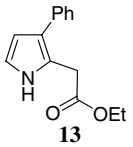
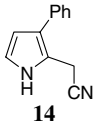
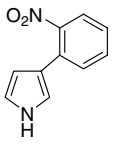
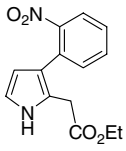
number of heterocyclic aromatic systems.[6] Then, we recognized that this methodology could be useful for the study of intermolecular free-radical aromatic substitution in 3-substituted pyrroles, at least for the addition of electrophilic radicals. We first examined the radical oxidative substitution of xanthate **4** and pyrrole-3-carboxaldehyde **3** (Scheme 2). Surprisingly, 2,3-disubstituted pyrrole **5** was the only product, isolated in moderate yield along with recovered starting material.[7] The position of the new substituent was confirmed with the coupling constants in ^{1}H NMR spectra of the hydrogen atoms at C-4 and C-5 ($J = \sim 2.8$ Hz). Ketone, cyano and butanoate derivatives showed similar behavior (Table 1, entries 1–3). This result is somewhat surprising, given that the reactions at C-2 of pyrrole **3** with these electrophilic radicals are supposed to be a polarity-mismatched process.

Muchowski et al.[3] have shown that nucleophilic radical addition at C-2 is particularly favorable on 3-acylated pyrroles, due to a large LUMO coefficient at this site. However, it was also shown that the system has significant and approximately equal HOMO coefficients at C-2 and C-5. On the basis of a favorable SOMO/HOMO interaction attack at both sites, a mixture of products was expected. In contrast, a highly regioselective transformation was observed in the present study (Table 1). It is obvious that additional effects must control radical attack on the pyrrole system, besides frontier orbital interactions. It seems to be that the energy of the transition state of the addition process might be strongly influenced by the stability of the formed radical intermediates (**A**, **B** or **C** depending on the site of radical attack, Fig. 1). Therefore, results might be explained on the basis that radical **A** is more stabilized (allylic and α- to a carbonyl group) than **B** (only allylic) and **C** (α to the nitrogen atom). According to resonance theory **A** is more stable since more Lewis structures could be depicted, than for **B** or **C**. This qualitative speculation was supported by the theoretical calculation of their energies (Table 2).[8] According to the computation, radical **A** is ~5.5 and ~8 kcal/mol more stable than radicals **B** and **C**, respectively.

We then examined the generality of the concept, and submitted pyrrole **12**, bearing a weak electron-withdrawing phenyl group, to the same oxidative free-radical alkylation conditions with xanthates **4** and **8**. As expected, 2,3-disubstituted pyrroles **13** and **14** were obtained in good yields. A similar result was observed for the substituted pyrrole **15** bearing the strong electron-withdrawing nitro group on the aryl moiety. It seems that the electronegativity of the group at C-3 has no influence in the regiochemistry of this radical addition. Furthermore, it is worth pointing out that the substitution takes place at the most sterically hindered carbon C-2.

In closing, a highly regioselective intermolecular oxidative free-radical substitution on 3-aryl and 3-formyl pyrroles, to give 2,3-disubtituted pyrroles, has been described. This behavior might be explained on the basis of the relative stabilities of the intermediate radicals formed in the process. From the synthetic point of view, the methodology reported herein represents a direct

Table 1.

Entry	Pyrrole	Xanthate	Yield (%)
1	 **3**	 **6**	 **7**	38
2	**3**	 **8**	 **9**	35
3	**3**	 **10**	 **11**	60
4	 **12**	**4**	 **13**	62
5	**12**	**8**	 **14**	87
6	 **15**	**4**	 **16**	85

Xth = S(C)SOEt.

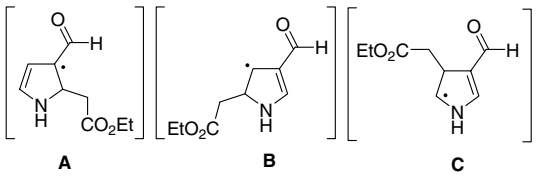


Figure 1. Possible radical intermediates in the radical addition process.

Table 2. Relative gas-phase energies (ΔE), enthalpies (ΔH^0), and free energies (ΔG^0) values for the radicals **A**, **B** and **C** (charge = 0, multiplicity = 2, $T = 298.15$ K) computed at the UB3LYP level using the 6-311G(d,p) basis set (all values are in kcal/mol)

Radical	ΔE[a]	ΔE[b]	ΔH^0[c]	ΔG^0[d]
A	0.0	0.0	0.0	0.0
B	6.4	5.5	5.7	5.3
C	8.2	7.7	7.8	8.0

[a] Electronic energies.
[b] Electronic energies with zero-point corrections.
[c] Enthalpies.
[d] Free energies.

entry into 2,3-disubstituted pyrroles, whose utility as synthetic intermediates in the construction of more complex molecules has been largely documented.[1]

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References and notes

1. For reviews on pyrrole, see: (a) Sundberg, R. J.. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 119–206; (b) Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. L. *Chem. Rev.* **2004**, *104*, 2481; (c) Furstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582, and references cited therein.
2. (a) Byers, J. H.; DeWitt, A.; Nasveschuk, C. G.; Swigor, J. E. *Tetrahedron Lett.* **2004**, *45*, 6587; (b) Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Osornio, Y. M.; Muchowski, J. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001; (c) Byers, J. H.; Duff, M. P.; Woo, G. W. *Tetrahedron Lett.* **2003**, *44*, 6853; (d) Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 145; (e) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *43*, 4191; (f) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951; (g) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181; (h) Miranda, L. D.; Cruz-Almanza, R.; Alvarez-García, A.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 3035; (i) Byers, J. H.; Campbell, J. E.; Knapp, F. H.; Thissell, J. G. *Tetrahedron Lett.* **1999**, *40*, 2677; (j) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153; (k) Aldabbagh, F. W.; Bowman, R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111; (l) Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937; (m) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083; (n) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287; (o) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639; (p) Dobbs, P. A.; Jones, K.; Veal, K. T. *Tetrahedron* **1997**, *53*, 8287; (q) Aboutayab, K.; Caddick, S.; Jenkins, K.; Joshi, S.; Khan, S. *Tetrahedron* **1996**, *52*, 11329; (r) Tim, C. T.; Jones, K.; Wilkinson, J. *Tetrahedron Lett.* **1995**, *36*, 6743; (s) Antonio, Y.; De la Cruz, E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhuouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15.
3. Muchowski, J. M.; Cho, I. S.; Jaime-Figueroa, S.; Artis, R. D. *J. Org. Chem.* **1994**, *59*, 2456.
4. Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887.
5. Miranda, L. D.; Cruz-Almanza, R.; Pavon, M. *ARKIVOC* **2002**, 15–22.
6. (a) Osornio, Y. M.; Cruz-Almanza, R.; Jiménez-Montaño, V.; Miranda, L. D. *Chem. Commun.* **2003**, 2316; (b) Guerrero, M. A.; Miranda, L. D. *Tetrahedron Lett.* **2006**, *47*, 2517.
7. *Typical experimental procedure:* A deaerated solution of the 3-phenyl or pyrrole-3-carboxaldehyde (0.5 mmol) and the appropriate xanthate derivative (1 mmol, 2 equiv) in 1 ml of dichloroethane, was heated at reflux, and 2 mmol of dilauroyl peroxide were added portionwise (0.25 mmol/h). Then the solvent was removed under reduced pressure and the crude residue was purified by chromatography on a silica gel column (ethyl acetate/hexane) to furnish the desired product. *Selected spectral data* **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.3 (3H, t, $J = 7$), 4.09 (2H, s), 6.59 (1H, dd, $J = 3.0$, 2.9), 6.74 (1H, dd, $J = 3.0$, 2.9), 9.86 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 31.19, 61.55, 110.22, 118.42, 122.0, 131.1, 170.8, 186.3. IR (film) cm^{-1}: 1521.7, 1668.8, 1727.1, 2857.2, 2930.7. EM (EI) $m/z = M^+$ (%): 181 (50), 108 (100). Compound **7**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.31 (3H, s), 4.25 (2H, s), 6.58 (1H, dd, $J = 3.0$, 2.8), 6.74 (1H, dd, $J = 3.0$, 2.8), 9.854 (1H, br), 9.85 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 32.13, 39.66, 110.86, 118.2, 125.0, 135.2, 186.9, 206.3. IR (film) cm^{-1}: 1561.4, 1657.1, 1711.3, 2958.7, 3281.2. EM (EI) $m/z = M^+$ (%): 151 (30), 108 (100). Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.24 (2H, s), 6.63 (1H, dd, $J = 3.0$, 2.8), 6.8 (1H, dd, $J = 3.0$, 2.8), 9.58 (1H, br), 9.88 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 16.2, 111.95, 116.2, 119.24, 121.8, 124.85, 187.29. IR (film) cm^{-1}: 1656.28, 2256.7, 2853.77, 3022.41, 3293.2. EM (EI) $m/z = M^+$ (%): 134 (100). Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.91 (3H, t, $J = 7.5$), 1.29 (3H, t, $J = 7.2$), 1.82–2.08 (2H, m), 4.12–4.3 (2H, m), 4.40 (1H, t, $J = 7.5$), 6.59 (1H, dd, $J = 3.0$, 2.7), 6.73 (1H, dd, $J = 3.0$, 2.7), 9.72 (1H, br), 9.85 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.43, 14.06, 28.47, 43.37, 61.41, 109.58, 118.5, 121.9, 136.2, 174.0, 185.82, IR (film) cm^{-1}: 1460, 1562, 1651, 1730, 2877, 3308. EM (EI) $m/z = M^+$ (%): 209, 136 (100). Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (3H, t, $J = 7.2$), 3.79 (2H, s), 4.20 (2H, q, $J = 7.5$), 6.32 (1H, dd, $J = 3.0$, 2.8), 6.80 (1H, dd, $J = 3.0$, 2.8), 7.18–7.39 (5H, m), 8.96 (1H, br). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.13, 31.82, 61.2, 108.8, 117.3, 120.0, 121.5, 125.6, 128.0, 128.4, 136.3, 171.3. IR (film) cm^{-1}: 1604, 1724, 2855, 2926, 3297. EM (EI) $m/z = M^+$ (%): 229, 156 (100). Compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.86 (2H, s), 6.33 (1H, dd, $J = 3.0$, 2.8), 6.82 (1H, dd, $J = 3.0$, 2.8), 7.22–7.45 (5H, m), 8.51 (1H, br). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.9, 109.2, 114.6, 117.2, 118.4, 124.0, 126.3, 127.9, 128.7, 135.2. IR (film) cm^{-1}: 1604, 2252, 2853, 2920, 3339. Compound **16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (3H, t, $J = 7.2$), 3.56 (2H, s), 4.18 (2H, q, $J = 7.5$), 6.14 (1H, dd, $J = 3.0$, 2.8), 6.79 (1H, dd, $J = 3.0$, 2.8), 7.35–7.44 (3H, m), 7.51–7.59 (2H, m), 9.0 (1H, br). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1, 31.4, 61.3, 109.3, 117.2, 121.0, 123.7, 127.1, 130.4, 131.7, 132.7, 170.9. IR (film) cm^{-1}: 1445, 1517, 1604, 1715, 2854, 2925, 3347.
8. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi,

M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. GAUSSIAN 98, revision A.7; gaussian, Inc., Pittsburgh, PA, 1998.