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Et_3B-Mediated radical alkylation of pyrroles and indoles

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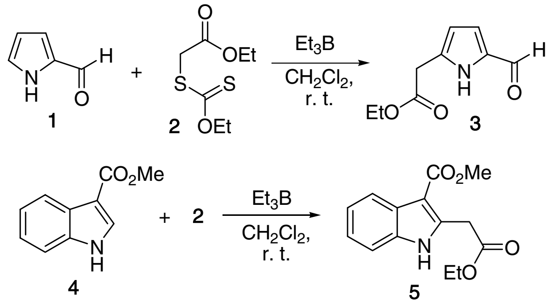
Abstract—An efficient Et_3B-mediated oxidative radical substitution of substituted pyrroles and indoles using xanthate based radical chemistry in the presence of iron(II) sulfate is described. Unsubstituted indole gave only low yield or failed in the process. 2-Cyanofuran and 2-benzoylthiophene did not afford the corresponding alkylated products under these conditions.

The use of triethylborane in air as an initiator of radical based processes has become increasingly popular in recent years.[1] Because radical reactions can be initiated by this reagent at ambient or subambient temperatures, it has found widespread application, particularly in the stereoselective addition of alkyl radicals to double bonds.[1c] In contrast, there are very few examples of the use of Et_3B to initiate oxidative radical substitution of aromatic systems,[2] a carbon–carbon bond forming reaction that has considerable preparative value.[3,4] We recently reported an efficient intermolecular oxidative radical alkylation of various heterocyclic aromatic systems which included pyrroles, indoles, furans and thiophenes, using xanthate based radical chemistry, lauroyl peroxide as the initiator in 1,2-dichloroethane at reflux temperature, and near stoichiometric quantities of the heteroaromatic substrate.[5] In order to widen the scope of this latter methodology it was of interest to attempt the reaction at room temperature using triethylborane as an initiator. Herein are described preliminary results of the alkylation reaction of pyrroles and indoles using xanthates as the radical source and Et_3B as initiator at room temperature.

A critically important issue in the oxidative radical alkylation of aromatic systems is the requirement of an agent to effect the oxidation step. It was considered possible that boron peroxides, which are reported to be formed in the reaction of triethylborane with oxygen,[1] might accomplish this oxidation. The initial results using xanthate **2** as the radical source, Et_3B in air as the initiator, and pyrrole-2-carboxaldehyde (**1**) or 3-methoxycarbonylindole (**4**) as the heteroaromatic substrates (3 equiv), generated the expected products **3** and **5** (Scheme 1) in low yields (Table 1, entries 1 and 2).



Scheme 1.

Table 1.

Entry	Substrate	Time (h)	Et_3B (equiv)	Additive	Yield (%)
1	**1**	2	4	—	15
2	**4**	2	4	—	10
3	**1**	6	4	—	35
4	**1**	14	4	—	62
5	**4**	14	4	—	43
6	**1**	14	2	$FeSO_4$	65
7	**1**	14	2	$Fe(ClO_4)_2$	—
8	**1**	14	2	$CuCl_2$	—
9	**1**	14	2	$FeSO_4$	44
10	**4**	14	2	$Fe(ClO_4)_2$	—
11	**4**	14	2	$CuCl_2$	—

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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
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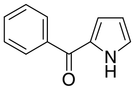
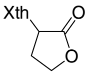
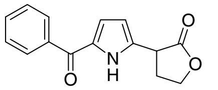
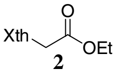
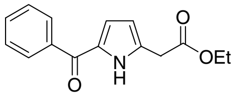
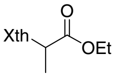
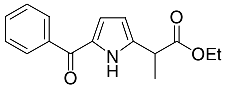
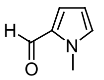
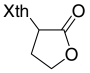
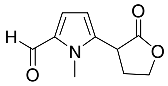
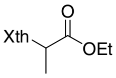
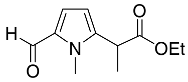
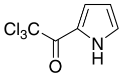
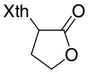
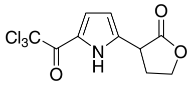
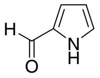
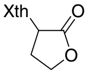
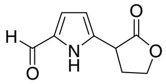
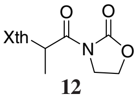
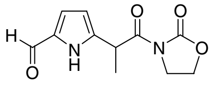
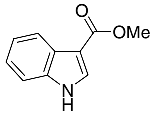
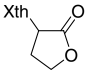
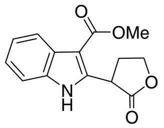
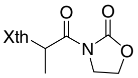
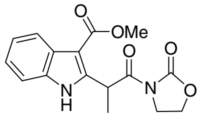
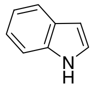
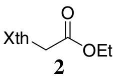
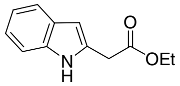
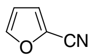
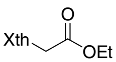
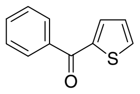
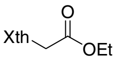
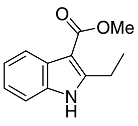
Table 2.

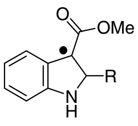
Entry	Substrate	Xanthate	Product
1	 **6**	 **11**	 **14** (62%)
2	**6**	 **2**	 **15** (16%)
3	**6**	 **12**	 **16** (57%)
4	 **1a**	 **11**	 **17** (60%)
5	**1a**	 **12**	 **18** (49%)
6	 **7**	 **11**	 **19** (63%)
7	 **1**	 **11**	 **20** (57%)
8	**1**	 **12**	 **21** (61%)
9	 **4**	 **11**	 **22** (54%)
10	**4**	 **13**	 **23** (56%)
11	 **8**	 **2**	 **24** (30%)
12	 **9**	 **2**	—
13	 **10**	 **2**	—

Xth = SC(S)OEt.

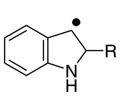
Borane reagent (4 equiv) was required to effect full consumption of the radical source **2,** a phenomenon which has previously been observed.[2a] Further experimentation revealed that the time addition of the borane had a significant effect on the product yield and a 14 h addition period was found to be the optimal for substrates **1** and **4** (Table 1, entries 4 and 5). We then speculated that borane peroxides might not be efficient in the oxidation pathway and decided to test some cooxidants. For instance Fe(III) has been successfully used as an oxidant in similar processes.[2b,6] In this context we hypothesized that Fe(II) might be oxidized to Fe(III) by the action of boron peroxides formed during the autoxidation of triethylborane. Thus, when $FeSO_4{\cdot}7H_2O$ (1 equiv in a 6:3:1 CH_2Cl_2–H_2O–EtOH solvent mixture) was utilized in these reactions, only 2 equiv of the borane were required for complete consumption of the xanthate, although the product yields were not improved (entries 6 and 9). Neither $Fe(ClO_4)_2$ nor $CuCl_2$ functioned as cooxidants, and only decomposition of the substrates was observed (entries 7, 8, 10 and 11). It seems evident that the presence of ferrous sulfate enhances the efficiency of the process, perhaps as expected by acting as a source of Fe(III) which then participates in the oxidative pathway of the rearomatization process.[2b,6] However, the precise role of this salt is currently not known and experiments to better understand it are in progress. It is noteworthy that only 3 equiv of the aromatic substrate were used in these experiments, which represents a distinct advantage in comparison with previously reported methodology where a large excess was used (10–30 equiv),[2b] and approaches the high substrate economy of our lauroyl peroxide initiated xanthate based oxidative radical alkylations.[5] With these optimized reaction conditions in hand, we examined the scope of the process with various xanthates and several different substituted pyrrole and indole substrates (Table 2).[7] Generally good yields of the alkylated pyrroles were obtained with primary and secondary xanthates (Table 2, entries 1–8). Even trichloroacetylpyrrole **7** afforded the expected alkylated product **19** in good yield (entry 6). Even the isoxazolidinone containing xanthate derivative **12** furnished the alkylated pyrrole **21** in quite acceptable yield. Under the same conditions, indole **4** afforded similar yields of the alkylated indoles **23** and **24** along with small quantities of the indole **25** (5–6%), derived from the direct addition of the ethyl radical onto the indole (entries 9 and 10). In contrast, the reaction of indole (**8**) with xanthate **2** gave a low yield of the expected 2-alkylated indole **24** (entry 11). Remarkably, reaction of this latter indole with xanthates **11** and **12** failed to afford the expected products. This is somewhat surprising, given that the reactions of 3-carbomethoxyindole (**4**) with these xanthate derived radicals are supposed to be polarity mismatched processes, yet they are nevertheless much more efficient than the analogous reaction with indole. This result might be better explained on the basis that the radical **26** is more stabilized (benzylic and α- to a carbonyl group) than **27** (only benzylic).



25



26



27

A few experiments were also carried out with 2-cyanofurano and 2-benzoylthiophene, but all of them failed, and only the aromatic substrates were recovered (entries 12 and 13).

In closing it has been demonstrated that the xanthate-mediated intermolecular oxidative radical alkylation of pyrroles and indoles can be effected in moderate to good yields at room temperature using Et_3B as the initiator and $FeSO_4{\cdot}7H_2O$ as a cooxidant. In principle, these are conditions which could be used in the stereoselective radical additions to aromatic systems. Work along these lines is underway.

Acknowledgements

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Angew. Chem., Int. Ed. **2004**, *43*, 95; (l) Bennasar, M.-Ll.; Roca, T.; Ferrando, F. *Tetrahedron Lett.* **2004**, *45*, 5605; Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Osornio, Y. M.; Muchowski, J. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001.

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7. *Typical experimental procedure*: A solution of Et_3B (1.0 M in THF) was added dropwise (2 equiv/14 h) to a stirred solution of the xanthate (1 equiv), the aromatic compound (3 equiv) and $FeSO_4$ (1 equiv) in $CH_2Cl_2/EtOH/H_2O$ (6:3:1, 4 ml/mmol of the xanthate). The organic solvent was removed under reduced pressure and the crude residue extracted with EtOAc. The organic layer was dried with Na_2SO_4, and solvent removed under reduced pressure. The product was purified by chromatography on a silica gel column (ethyl acetate/hexane 8:2) to furnish the desired product. *Selected spectral data.* Compound **14**: ^1H NMR (200 MHz, CD_3COCD_3) δ ppm: 7.87–7.85 (m, 2H), 7.61–7.47 (m, 3H), 6.81 (dd, $J = 3.9$, 2.7 Hz, 1H), 6.28 (dd, $J = 3.9$, 2.7 Hz, 1H), 4.56–4.33 (m, 2H), 4.20 (dd, $J = 11.0$, 9.0 MHz, 1H), 2.9–2.55 (m, 2H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm: 184.3, 176.2, 139.7, 136.5, 132.4, 132.0, 129.5, 129.1, 119.9, 109.8, 67.5, 39.6, 30.4; IR (neat, cm^{-1}) ν 3273, 1767, 1612; MS (EI) (*m/z*), M^+ 255 (90%), 77 (100%). Compound **15**: ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 10.41 (br s, 1H), 7.89 (dd, $J = 8.5$, 1.8 Hz, 2H), 7.57–7.43 (m, 3H), 6.81 (dd, $J = 3.8$, 2.5 Hz, 1H), 6.18 (dd, $J = 3.8$, 2.5 Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.77 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 184.2, 169.4, 138.6, 131.9, 131.6, 131.2, 128.9, 128.2, 119.8, 110.6, 61.4, 33.6, 14.1; IR (neat, cm^{-1}) ν 3286, 2922, 1737, 1606; HRMS FAB+ (M^{+1}, *m/z*) calcd for $C_{15}H_{16}O_3N$: 258.1130, found: 258.1130. Compound **16**. White solid mp 72–74 °C. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 10.12 (br s, 1H, NH), 7.86–7.89 (m, 2H), 7.44–7.57 (m, 3H), 6.80 (dd, $J = 3.6$ Hz, 2.4 Hz, 1H), 6.18 (dd, $J = 3.6$ Hz, 2.4 Hz, 1H), 3.91 (q, $J = 7.2$ Hz, 1H), 3.71 (s, 3H), 1.59 (d, $J = 7.2$ Hz, 3H); HRMS FAB+ (M^{+1}, *m/z*) calcd for $C_{15}H_{16}O_3N_1$: 258.1130, found: 258.1125. Compound **17**. ^1H NMR (300 MHz, CD_3COCD_3) δ ppm: 9.51 (s, 1H), 6.94 (d, $J = 4.2$ Hz, 1H), 6.25 (dd, $J = 3.9$, 0.4 Hz, 1H), 4.55–4.37 (m, 2H), 4.27 (dd, $J = 10.8$, 9.0 Hz, 1H), 4.00 (s, 3H), 2.81–2.73 (m, 1H), 2.66–2.52 (m, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm: 179.83, 175.6, 139.9, 133.7, 124.3, 108.9, 67.5, 38.1, 32.9, 29.6; IR (neat, cm^{-1}) ν 1768, 1659; EM (EI) $m/z = M^+$ 193 (100%). Compound **18**: ^1H NMR (300 MHz, CD_3COCD_3) δ ppm: 9.49 (s, 1H), 6.92 (d, $J = 4.2$ Hz, 1H), 6.19 (d, $J = 4.2$ Hz, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 3.98 (q, $J = 13.5$ Hz, 1H), 3.93 (s, 3H), 1.51 (d, $J = 13.5$ Hz, 3H), 1.19 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm: 179.8, 172.8, 143.3, 133.2, 124.5, 108.7, 61.6, 37.5, 32.6, 16.7, 14.3. IR (neat, cm^{-1}) ν 1734, 1661, 1468; EM (EI) $m/z = M^+$ (%). Compound **19**: ^1H NMR (200 MHz, CD_3COCD_3) δ ppm: 11.4 (br s, 1H), 7.36–7.34 (m, 1H), 6.39–6.37 (m, 1H), 4.54–4.36 (m, 2H), 4.23 (dd, $J = 11.5$, 8.8 Hz, 1H), 2.89–2.78 (m, 1H) 2.68–2.56 (m, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm: 175.8, 172.9, 139.5, 123.3, 120.3, 96.19, 122.4, 110.9, 67.5, 39.7; IR (neat, cm^{-1}) ν 3409, 1770, 1668, 1167; EM (IE), $m/z = (M^+)$ 295 (5%), (M^++1) 296, 178 (100%). Compound **20**: ^1H NMR (300 MHz, CD_3COCD_3) δ ppm: 11.05 (br s, 1H), 9.46 (s, 1H), 6.93 (dd, $J = 3.81$, 2.34 Hz, 1H), 6.27 (dd, $J = 3.81$, 2.34 Hz, 1H), 4.50–4.33 (m, 2H), 4.13 (dd, $J = 11.13$, 9.09 Hz, 1H), 2.65–2.52 (m, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm: 179.1, 176.0, 137.2, 134.3, 121.3, 110.0, 67.4, 39.7, 30.3; IR (neat, cm^{-1}) ν 3259, 1767, 1647; EM (EI), *m/z* (M^+): 179 (100%). Compound **21**: ^1H NMR (300 MHz, CD_3COCD_3) δ ppm: 10.75 (br s, 1H), 9.43 (s, 1H), 6.88 (dd, 1 = 3.81, 2.34 Hz, 1H), 6.17 (dd, $J = 3.8$, 2.34 Hz, 1H), 5.20 (q, $J = 7.02$ Hz, 1H) 4.52–4.40 (m, 2H), 4.11–3.96 (m, 2H), 1.51 (d, $J = 7.02$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 178.9, 173.3, 154.5, 14.6, 133.8, 121.1, 109.6, 63.2, 43.8, 37.5, 17.8; IR (neat, cm^{-1}) ν 3297, 1776, 1698, 1649; EM (EI), *m/z* (M^+): 236 (15%), 149 (100%). Compound **22**: ^1H NMR (300 MHz, CD_3COCD_3) δ ppm: 11.75 (br, 1H), 8.07–8.02 (m, 1H), 7.48–7.42 (m, 1H), 7.25–7.13 (m, 2H), 4.92 (dd, $J = 12.0$, 9.3 Hz, 1H), 4.58 (td, $J = 8.6$, 2.3 Hz, 1H), 4.45 (ddd, $J = 11.3$, 9.8, 6.8 Hz, 1H), 3.87 (s, 3H), 2.79–2.61 (m, 2H). ^{13}C NMR (300 MHz, CD_3COCD_3) δ ppm: 176.0, 166.5, 143.8, 136.6, 127.83, 123.5, 122.3, 122.2, 112.4, 105.6, 67.4, 51.0, 40.3, 30.8; IR (neat, cm^{-1}) ν 3452, 2925, 1736, 1624; EM (EI), *m/z* (M^+): 259 (30%), 227 (100%). Compound **23**: ^1H NMR (300 MHz, CD_3COCD_3) δ ppm: 10.95 (br s 1H) 8.07–8.00 (m, 1H), 7.50–7.45 (m, 1H), 7.18–7.12 (m, 2H), 6.13 (q, $J = 7.0$ Hz, 1H), 4.49 (t, $J = 7.9$ Hz, 2H), 4.08–4.032 (m, 2H), 3.8 (s, 3H), 1.64 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm: 174.3, 166.2, 154.0, 146.0, 136.4, 127.7, 123.0, 122.1, 121.9, 112.5, 104.5, 63.1, 50.8, 43.7, 37.5, 17.2; IR (neat, cm^{-1}) ν 3338, 2951, 1779, 1693; EM (EI), *m/z* (M^+): 316 (10%), 71 (100%). Compound **24**: ^1H NMR (200 MHz, CD_3COCD_3) δ ppm: 10.08 (br s, 1H), 7.47 (d, $J = 7.5$Hz, 1H), 7.37 (d, $J = 7.5$ Hz, 1H), 7.10–6.91 (m, 2H), 6.33 (dd, $J = 2.0$, 1.0 Hz, 1H), 4.14 (q, $J = 7$ Hz, 2H), 3.84 (d, $J = 1$ Hz, 2H), 1.22 (t, $J = 7$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm: 170.6, 137.7, 132.6, 129.5, 121.8, 120.5, 119.9, 111.7, 101.9, 61.3, 34.6, 14.4; IR (neat, cm^{-1}) ν 3397, 2926, 1728; HMRS calcd for $C_{12}H_{13}NO_2 = 204.1025$, found 204.1017.