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Efficient, intermolecular, oxidative radical alkylation of heteroaromatic systems under "tin-free" conditions

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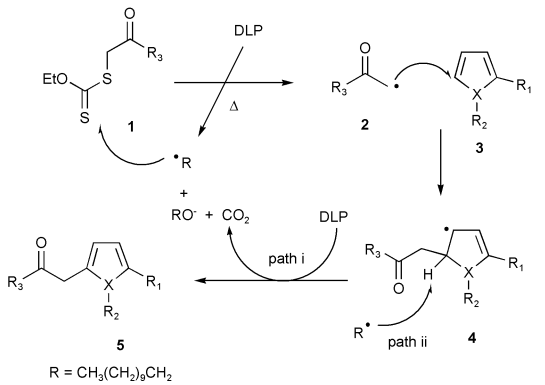
Novel and efficient radical alkylation of several heterocyclic systems including pyrroles, indoles, furan and thiophenes is described using xanthate based radical chemistry. The present methodology could be used to provide rapid access to various nonsteroidal antiinflammatory drugs.

The alkylation of aromatic systems is an important carbon–carbon bond formation process that is used to provide access to diverse synthetically and pharmacologically important molecules. Electrophilic alkylation, which can be used for such purposes, is often associated with the generation of undesired rearranged products. This is generally not the case with oxidative radical alkylation.[1–4] Whereas the intramolecular oxidative radical alkylation of homocyclic and heterocyclic aromatic systems has been quite intensively studied, and is frequently of preparative value,[1,2] much less information exists regarding the intermolecular process.[3–4] In part, this is because product yields are often low, unless a large excess (15–20 equiv.) of the aromatic substrate is used.[3a] Recently Zard and coworkers[2] have annelated five, six, and seven-membered rings to an aromatic nucleus, exploiting the xanthate based radical chemistry. These reactions not only can be conducted in the absence of heavy metals, and under tin-free conditions, but also the premature reduction of the intermediate radicals is easily avoided.[5] Indeed, free radicals generated from xanthates have a comparatively long lifetime and can add to unactivated olefins, reactions which are inefficient otherwise.[5] In this report we demonstrate that under xanthate-mediated radical conditions the intermolecular oxidative radical alkylation of various heteroaromatic systems can be effected in preparatively useful yields even when the aromatic substrate is not used in excess.

The proposed mechanism to the reaction is depicted in Scheme 1. α-Acetyl or α-acetonyl radical **2** generated by the action of dilauroyl peroxide (DLP) on xanthate **1**, adds to the heteroaromatic system **3** producing the conjugated radical **4**. Aromatized derivative **5** could then be produced either by a DLP-mediated oxidative pathway in a chain reaction (Scheme 1, path i)[2] or by a direct abstraction of the hydrogen by the alkyl radical derived from fragmentation of the peroxide in a non-chain process (path ii). According to both mechanisms a stoichiometric amount of the peroxide would be required to



Scheme 1 Proposed mechanism for homolytic alkylation.

Table 1 Radical alkylation of different heteroaromatic systems[a]

Entry	Substrate	Xanthate	Product
1	**6**	**7**	**8** 69%
2	**6**	**9**	**10** 74% (81%)
3	**11**	**9**	**12** 65% (79%)
4	**13**	**7**	**14** 86%
5	**15**	**7**	**16** 46%; **17** 18%
6	**18**	**7**	**19** 65%
7	**20**	**9**	**21** 60%
8	**22**	**9**	**23** 44% (71%)

[a] Yields in parentheses are based on recovered starting material.

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complete the reaction. At the present time we do not have evidence to strongly support or eliminate either mechanism.

The initial experiments were carried out on 2-acylpyrroles. Thus, portionwise addition of a stoichiometric amount of lauroyl peroxide (over 12 h) to a boiling solution of pyrrole **6** (1 equiv.) and xanthate **7** (1.2 equiv.) in dichloroethane (2 mL $mmol^{-1}$) led to alkylation at C-5 and furnished **8** in good yield.† Under identical reaction conditions, acetonyl radical derived from xanthate **9** efficiently added to pyrroles **6** and **11** to furnish **10** and **12** respectively (Table 1, entries 2 and 3). The regiochemistry of these reactions is in accordance with SOMO–HOMO predictions.[3d] Similarly the 5-benzoylpyrrol-2-yl acetate derivative **14** could be prepared in very high yield (Table 1, entry 4). This molecule contains the basic structural features of the important non-steroidal antiinflammatory agents tolmetin and amtolmetin guacil,[6] both of which should be accessible using the methodology described herein. Thiophene and furan systems can also be alkylated. This is illustrated by the synthesis of **16** and **19**, which were obtained by radical addition of the appropriate xanthate to **15** and **18**, respectively (Table 1, entries 5 and 6). In the case of the thiophene system, a significant quantity of the 2,3-disubstituted derivative **17** was also generated. The reaction of indole **20** and xanthate **9** gave the 2-substituted compound **21** with high regioselectivity, a previously observed phenomenon,[3a] fully consistent with the significant HOMO coefficient at C-2 of indole[3e] (Table 1, entry 7). It is worth noting that electrophilic substitution reactions of indole, including alkylations, occur at C-3.

2-Arylpropionic acids constitute a large class of nonsteroidal antiinflammatory drugs, which are used worldwide. A concise approach to 2-heteroarylpropionic acids consists in simply using the secondary xanthate **25** (Table 2). The tiaprofenic acid ester **26** was thus prepared in good yield from commercially available 2-benzoylthiophene **24**. Likewise the reaction of the xanthate **25** and pyrrole **13** afforded 2-(5-benzoylpyrrol-2-yl)propionic acid ethyl ester **27** in high yield along with small quantities of recovered starting material.

Even though the process has not yet been fully optimised it is clear that the xanthate-mediated intermolecular oxidative radical alkylation of various heteroaromatic systems can be effected in preparatively useful yields. The present radical based, tin-free approach could be used, in principle, to provide rapid access to various medicinally important compounds, such as nonsteroidal antiinflammatory drugs.

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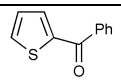
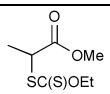
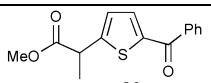
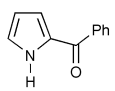
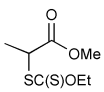
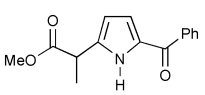
Table 2 Synthesis of 2-heteroarylpropionic acid derivatives[a]

Entry	Substrate	Xanthate	Product
1	 **24**	 **25**	 **26** 75%
2	 **13**	 **25**	 **27** 81% (90%)

[a] Yields in parentheses are based on recovered starting material.

Notes and references

† *Typical experimental procedure*: A solution of the xanthate (1.2 mmol) and the heteroaromatic compound (1 mmol) in degassed 1,2-dichloroethane (2 mL $mmol^{-1}$) was heated at reflux, and a solution of dilauroyl peroxide (1–1.2 mmol) in 1,2-dichloroethane (0.5 mL $mmol^{-1}$) was added dropwise over a 12 h period. The reaction was monitored by TLC. 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 spectroscopic data:* **8** as a white solid m.p. 57–59 °C; IR (KBr cm^{-1}): 2929, 1727, 1659; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 9.48 (s, 1H), 6.86 (d, J = 3.9 Hz, 1H), 6.17 (d, J = 3.9 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 3.67 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 179.3, 168.9, 135.9, 132.4, 124.1, 110.7, 61.4, 32.5, 32.4, 14.1. HRMS FAB (M + 1, m/z) calcd for $C_{10}H_{14}O_3N_1$: 196.0974, found: 196.097. **14** m.p. 156–158 °C (Lit.[7] 158–159 °C); HRMS FAB (M + 1, m/z) calcd for $C_{15}H_{16}O_3N_1$: 258.1130, found: 258.1139. **21** as a white solid m.p. 25–26 °C. (Lit.[8] 24.5–25 °C), HRMS FAB (M + 1, m/z) calcd for $C_{12}H_{14}O_2N_1$: 204.1025, found: 204.1017.

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