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DECARBOXYLATIVE RADICAL ADDITION ONTO PROTONATED HETEROAROMATIC SYSTEMS INCLUDING PURINE BASES

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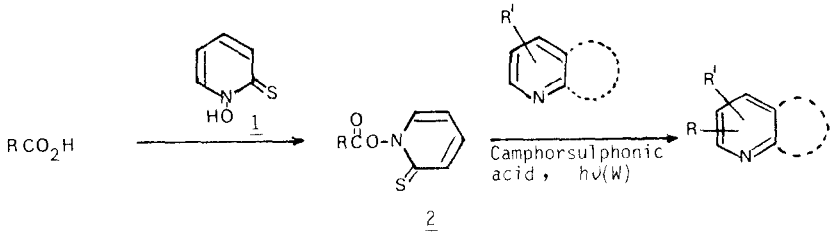
Abstract - *Irradiation of esters 2 derived from carboxylic acids and N-hydroxypyridine-2-thione 1 in the presence of anhydrous camphorsulphonic acid and various heteroaromatic systems including purines affords the corresponding adducts in moderate to good yield.*

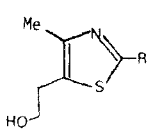
We have recently reported that the radical decarboxylation[1] of carboxylic acids *via* their esters 2 derived from *N*-hydroxypyridine-2-thione 1 can be performed in the presence of a strong anhydrous acid. This finding has allowed us to accomplish clean radical additions onto highly base sensitive olefins such as nitroalkenes[2] and vinyl phosphonium salts.[3] In a further, and potentially more important, application we have shown that under these conditions a highly efficient addition to pyridines and quinolines takes place[4] to give *ortho* and/or *para* substituted (with respect to the ring nitrogen) derivatives (Scheme). We have now found that this latter reaction is, in fact, of a more general scope and may be applied to a variety of heteroaromatic systems, some of which are of considerable biological importance.



2a R = 1-adamantyl
2b R = cyclohexyl

Scheme

Thus, irradiation with visible light (tungsten lamp; all irradiations at 0°C) of a solution of derivative 2a, anhydrous camphorsulphonic acid and thiazole 3a (a precursor of thiamine) in dichloromethane afforded adduct 3b (m.p. 90-92°C) in 64% yield. A similar addition of adamantyl radicals to triazole 4a proceeded less efficiently (30%). The yield of 4b (m.p. 228-230°C) could nevertheless be increased to 52% by using a vast excess of the triazole. In this case DMF (dimethylformamide) had to be employed because of solubility problems. This new solvent for our radical chemistry is worthy of note.



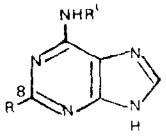
3a R = H

3b R = adamantyl

4a R = H

4b R = 1-adamantyl

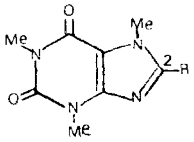
A more important application of this reaction lies in the modification of purine bases. For example, an adamantyl group could be appended on position-8 of benzoyl adenine[6] 5a in good yield (66%). In this case as well DMF had to be used instead of dichloromethane. Exposure of 5b (m.p. 264°C) to methanolic sodium hydroxide gave 8-adamantyladenine 5c (m.p. >300°C) in excellent yield (97%). Caffeine 6a underwent a similar reaction providing 6b[5] (m.p. 261°C) in good yield (76%). Addition of cyclohexyl radicals however was much less efficient and only a modest yield (25%) of 6c (m.p. 205-207°C) could be obtained.



5a R = H; R'= -COPh

5b R = 1-adamantyl; R'= COPh

5c R = 1-adamantyl; R'= H



6a R = H

6b R = 1-adamantyl

6c R = cyclohexyl

Although radical additions to adenine and caffeine have previously been reported,[7] the present approach employs comparatively mild non-oxidative conditions. This should allow ready access to otherwise unavailable derivatives and the method may be applicable to nucleotides.

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