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Synthesis and nitration of ibuprofen 1-monoglyceride

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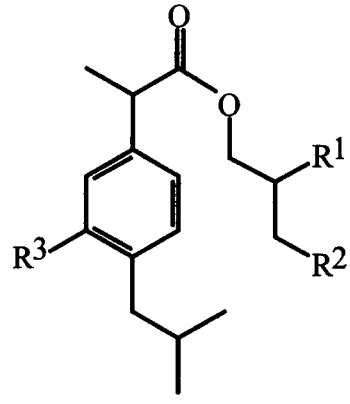
Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics which are associated with gastrointestinal side effects. NSAID pro-drugs with nitric oxide releasing properties have been reported as compounds which retain the activity of the parent NSAIDs while providing local, nitric oxide-induced, gastroprotective effects Cirino et al (1996). We have investigated the synthesis and subsequent nitration reactions of glycerides of ibuprofen, with the aim of obtaining general routes to pro-drugs of NSAIDs and well established nitrovasodilators.

Ibuprofen 1-monoglyceride (1) has been obtained by three routes. These are: (i) esterification and subsequent selective hydrolysis of 1,2-isopropylidine glycerol, (ii) by direct, selective esterification of ibuprofen and glycerol in the presence of phenol Hilditch & Rigg (1935), and (iii) by lipase catalysed esterification. Route (ii) was found to be the highest yielding and most convenient. Subjection of (1) to classical O-nitration conditions (Ac_2O, HNO_3) resulted in both O-nitration and C-nitration of the aryl ring, giving compound (2). Ibuprofen and its n-propyl ester (3) also gave ring-nitrated products, e.g. (4), under these conditions.



(1) R^1, R^2 = OH; R^3 = H

(2) R^1, R^2 = ONO_2; R^3 = NO_2

(3) R^1, R^2, R^3 = H

(4) R^1, R^2 = H; R^3 = NO_2

Cirino, G., Wheeler-Jones, C. P. D., Wallace, J. L., Del Soldato, P., Baydoun, A. R. (1996) Br. J. Pharmacol. 117: 1421-1426

Hilditch, T. P., Rigg, J. G. (1935) J. Chem. Soc. 1774-1778