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SYNTHETIC APPLICATIONS OF LITHIATION REACTIONS—V*

NOVEL SYNTHESIS OF METHOXY ISOCOUMARINS. SYNTHESIS OF (±) MELLEIN†

N. S. NARASIMHAN and B. H. BHIDE
Department of Chemistry, University of Poona, Poona-7, India

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Abstract—A general method for the synthesis of 5,6, and 8-methoxy isocoumarins is described. The novel approach is used to synthesise mellein, a metabolite occurring in *Aspergillus mellus.*

COMPOUNDS incorporating the isocoumarin ring system abound in nature. In view of this, several syntheses of this ring system have been developed and the subject has been comprehensively reviewed by Barry.[1]

Lithiation of N-methyl benzamide, at the *ortho* position, has been reported by Hauser *et al.*,[2] who have further developed it into a new isocoumarin synthesis. The simplicity of the reaction prompted us to investigate the possibility of extending the method to obtain the hitherto not reported 5 and 8 methoxy isocoumarins and also mellein, a naturally occurring 8-hydroxy dihydro isocoumarin.

The starting compounds for the synthesis of the methoxy isocoumarins are the corresponding methoxy N-methyl benzamides. These compounds have two groups, the amide and the OMe, both of which are capable of controlling the position of entry of the Li atom in a metalation reaction. Thus it was first necessary to ascertain where the lithiation reaction would occur; the isocoumarin synthesis would succeed only if it occurred *ortho* to the amide group.

The lithiation of the methoxy N-methyl benzamides was carried out with n-BuLi in refluxing THF. The position of lithiation was determined by treating the lithio derivative with an electrophilic reagent like benzophenone and studying the nature of the benzhydrols obtained.

The reaction with *o*- and *p*- methoxy N-methyl benzamides gave, in high yield, single compounds with m.p. 171° and 154° respectively, with molecular formula $C_{21}H_{16}O_3$ and IR absorption at 1760 cm^{-1}; (C=O of lactone). The molecular formula of the benzhydrols further indicated that the compounds had structures II and III respectively.

The reaction with *m*-methoxy N-methyl benzamide also gave a single compound $C_{21}H_{16}O_3$, m.p. 226°, (yield 91%). The molecular formula and the IR band at 1750 cm^{-1} were consistent with two structures IV and V for the compound.

A choice between them could not be readily made. Its NMR had a complex pattern in the aromatic region, which could not be interpreted unambiguously. The compound

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also could not be converted to derivatives of known structure. However, in analogy with another experiment (*vide infra*) where 5 methoxy dihydroisocoumarin was obtained on treatment of the organolithium intermediate with ethylene oxide, the compound would have structure IV.

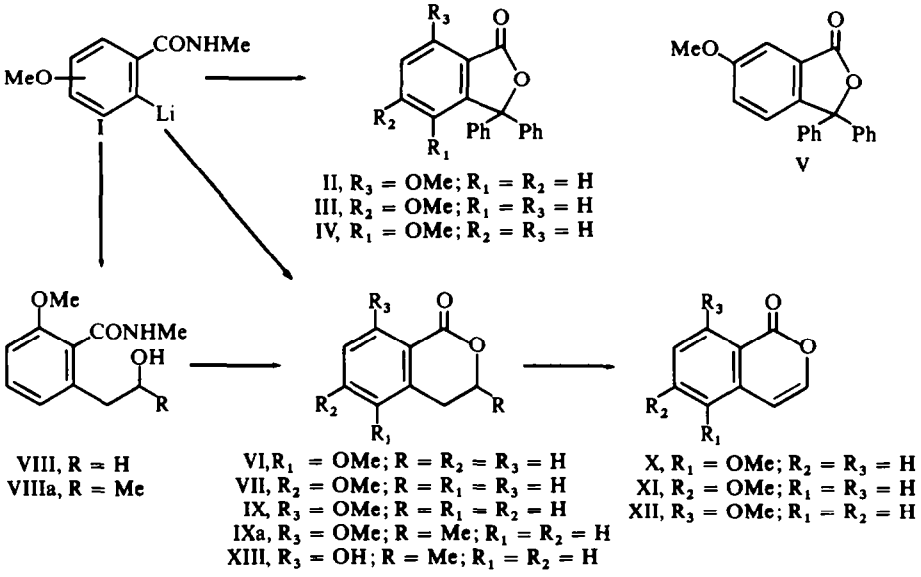


FIG 1.

The above results showed that lithiation of the methoxy N-methyl benzamides was occurring exclusively *ortho* to the amide group. This was presumably due to the fact that BuLi was complexing better with the amide function (after replacement of the acidic hydrogen on nitrogen by Li) than with the OMe group. This would lead to transition state (A)[2] (Fig. 2) which in further stages could give the *ortho* lithiated intermediate (I).

The exceptionally good yield obtained in the lithiation of *m*-methoxy N-methyl benzamide would suggest that the complex (A) was losing the hydrogen *ortho* to the Bu group of the reagent as a proton. In this complex the hydrogen, which is *ortho* both to the amide and the OMe group, would be more acidic than the one which is *ortho* to the amide but *para* to the OMe group. The former would be then more reactive in a lithiation reaction.

In the above reactions, it may be noted that the lithiation, in effect was occurring at positions which were less reactive in acid catalysed electrophilic substitution reactions. Since organolithium derivatives have superior reactivity with electrophilic reagents, these could provide methods to effect substitution at positions not favoured by the usual acid catalysed reactions. This feature was then used to synthesise the 5, 6 and 8 methoxy isocoumarins. The 6 methoxy isocoumarin was the only known compound of this series, and had been obtained by earlier workers by acid catalysed methods,[3] while the 5 and 8 methoxy isocoumarins were novel.

The procedure for the synthesis of the methoxy isocoumarins is briefly as follows. The metalation mixture obtained as in the previous case, was treated with ethylene oxide

TABLE I. NMR SPECTRA OF THE DIHYDRO ISOCOUMARINS AND THE ISOCOUMARINS CHEMICAL SHIFT IN δ, MULTIPLICITY (COUPLING CONSTANT IN HZ)

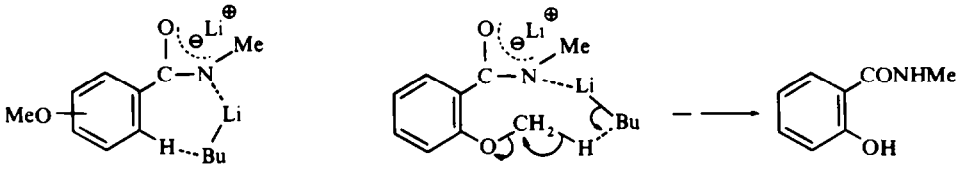
Compound	C_3	C_4	C_5	C_6	C_7	C_8
VI	4·52, t (6)	3·01, t (6)	—	7·1 , q (8 and 2)	7·37, t (8)	7·73, q (8 and 2)
VII	4·5, t (6)	3·1, t (6)	6·75, d (2)	—	6·9 , q (8 and 2)	8·03, d (8)
IX	4·41, t (6)	3·0, t (6)	6·92, q (7·5 and 2) or 6·82, q (7 and 2)	7·47, q (7·5 and 7)	6·82, q (7 and 2) or 6·92, q (7·5 and 2)	—
X	7·19. d (6)	6·7. d (6)	—	7·05, q (8 and 2)	7·35, t (8)	7·76, q (8 and 2)
XI	7·2, d (6)	6·3, d (6)	6·71, d (2)	—	6·95, q (8 and 2)	8·09, d (8)
XII	7·2, d (6)	6·37, d (6)	6·97, q (7·5 and 2) or 6·96, q (7 and 2)	7·63, q (7·5 and 7)	6·96, q (7 and 2) or 6·97, q (7·5 and 2)	—
IXa	4·55, m	2·87, d (7)	6·95, q (7·5 and 2) or 6·81, q (7 and 2)	7·47, q (7·5 and 7)	6·81, q (7 and 2) or 6·95, q (7·5 and 2)	—

* All the compounds had their —OMe signal between 3·9 and 3·92

† Mellein methyl ether (IXa) had the C_3-Me signal at 1·45. d (7)

at 0°. Work up gave the dihydro isocoumarin directly in the case of *m* and *p* methoxy N-methyl benzamides. In the case of *o*-methoxy N-methyl benzamide the dihydro isocoumarin itself was obtained only in small yield. The chief product was the alcohol (VIII). which however, on hydrolysis with alkali, yielded quantitatively the dihydro isocoumarin. The structures of the dihydro isocoumarins were established by their NMR spectra (Table I).

In the case of *o*-methoxy N-methyl benzamide it was observed that a side reaction also occurred leading to N-methyl salicylamide. This could have formed by the following sequence (Fig. 2). The side reaction was considerably reduced and the yield of the



(A)

FIG 2.

dihydro isocoumarin increased when 5 molar excess of BuLi was used for the metalation.

Finally the dihydro isocoumarins were converted to the isocoumarins by the conventional sequence. i.e. by treatment with N-bromo succinimide followed by Et_3N.[4]

Synthesis of mellein

The success in the synthesis of the 8-methoxy isocoumarin prompted us to undertake the synthesis of mellein, a naturally occurring dihydro isocoumarin, which has been isolated from the metabolite of *Aspergillus mellus*.[5] Mellein has been synthesised by two groups of workers.[6,7] The methods however involve a large number of steps. Thus one starting with *m*-hydroxy benzoic acid involves eleven steps, while the other with *p*-bromophenol as the starting compound requires fourteen. In sharp contrast to these methods, the synthesis of mellein. with *o*-methoxy benzoic acid as the starting compound, was achieved by the above method in only three steps.

The lithiation of *o*-methoxy N-methyl benzamide was effected as earlier with a 5 molar excess of BuLi. The metalation mixture was then treated with propylene oxide. Work up gave the alcohol. $C_{12}H_{17}O_3N$, m.p. 127° (VIIIa), which on hydrolysis furnished a compound. m.p. 68°, whose NMR spectrum (Table I) showed it to be (±) mellein methyl ether $C_{11}H_{12}O_3$ (IXa). Demethylation with HBr then yielded (±) mellein, (XIII). m.p. 39°, in quantitative yield, identical in all respects (m.m.p., TLC. superimposable IR) with an authentic sample.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were recorded as Nujol mulls. All NMR spectra were taken in 10% solution in $CDCl_3$ with TMS as internal standard on a Varian Associates. A-60 spectrometer. signals are recorded in δ (ppm) relative to TMS as zero.

o. m. p-*Methoxy* N-*methyl benzamides.* These were prepared by slowly adding the corresponding acid chlorides to 33% $MeNH_2$ solution.

o-Methoxy N-methyl benzamide, b.p. 148°/2 mm; ($C_9H_{11}O_2N$ requires: C, 65·44; H. 6·71; N, 8·48. Found: C, 65·1; H, 6·9; N, 8·6%).

m-Methoxy N-methyl benzamide, m.p. 65° (EtOAc–hexane): ($C_9H_{11}O_2N$ requires: C, 65·44; H, 6·71; N, 8·48. Found: C, 65·39; H, 6·85; N, 8·2%).

p-Methoxy N-methyl benzamide, m.p. 120° (EtOAc–hexane): ($C_9H_{11}O_2N$ requires: C, 65·44; H. 6·71; N, 8·48. Found: C, 65·3; H, 6·8; N, 8·6%).

Lithiation of the N-methyl benzamides. The following general procedure was used. To a well stirred refluxing solution of the N-methyl benzamide (0·025 mole, 4·125 g) in 50 ml THF (freshly distilled over LAH) was added n-BuLi (0·0625 moles in case of *m*- and *p*-methoxy and 0·125 moles in case of *o*-methoxy derivative) in ether under N_2 during 10 min. The metalation mixture which turned red was then further refluxed for 45 min.

Condensation of the organo-lithium derivative with benzophenone. To the above metalation mixture was added, during 10 min. a solution of benzophenone (0·04 mole in case of *m*- and *p*-methoxy and 0·08 mole in case of *o*-methoxy derivative) in ether. The resulting blue solution was refluxed for 3 hr, when it turned clear green. The mixture was hydrolysed with 50 ml water, the organic layer washed with water, saturated NaCl solution and dried (Na_2SO_4). Evaporation of solvent furnished the lactones II, III and IV.

Lactone (II), $C_{21}H_{16}O_3$, m.p. 171° (EtOH–hexane), 4·74 g, (60%); IR: 1,760, 810, 790, 780 cm^{-1}; ($C_{21}H_{16}O_3$ requires: C, 79·73; H, 5·1. Found: C, 79·87; H, 5·22%).

Lactone (III), $C_{21}H_{16}O_3$, m.p. 154° (EtOAc–hexane), 5·0 g, (63%); IR: 1,760, 900, 820, 800 cm^{-1}; ($C_{21}H_{16}O_3$ requires: C, 79·73; H, 5·1. Found: C, 80·0; H, 5·0%).

Lactone (IV), $C_{21}H_{16}O_3$, m.p. 226° (EtOAc–hexane), 7·2 g, (91%); IR: 1,750, 800, 790, 770 cm^{-1}; ($C_{21}H_{16}O_3$ requires: C, 79·73; H, 5·1. Found: C. 79·6; H, 5·16%).

Condensation of the organo-lithium derivative with ethylene oxide. To the metalation mixture obtained above (cooled to 0°) a solution of ethylene oxide (0·05 mole in case of *m*- and *p*-methoxy and 0·1 mole in case of *o*-methoxy derivative) in 50 ml ether was added with stirring during 30 min. The resulting solution containing a white precipitate was stirred for two hr at 0° and for an additional 1 hr at room temp, then hydrolysed with water.

The workup of the reactions, case a (the *m*- and *p*-methoxy) and b (the *o*-methoxy) derivative was different and they are described separately.

(a) The ether layer did not furnish any useful compound. The alkaline layer was acidified with conc HCl (without cooling) to give the respective dihydro isocoumarins. 5-Methoxy dihydro isocoumarin. (VI). m.p. 82° (colourless needles from ether), 3g (67%), IR: 1,720 cm^{-1}; ($C_{10}H_{10}O_3$ requires: C, 67·4; H, 5·66. Found: C, 67·33; H, 5·75%). 6-Methoxy dihydro isocoumarin, (VII), m.p. 68° (EtOAc–hexane, lit.[3] m.p. 67–68°), 2 g (50%), IR: 1,710 cm^{-1}; ($C_{10}H_{10}O_3$ requires: C, 67·4; H, 5·66. Found: C, 67·76; H, 5·71%).

(b) On evaporation of the ether extract a neutral residue was obtained. This was chromatographed over silica gel in C_6H_6. Elution with C_6H_6 gave a white solid, which was crystallized from EtOH–hexane to furnish white plates of the alcohol, (VIII), m.p. 130°, 2·6 g (50%), IR: 3,400, 3,300, 1,640, 800, 770, 750 cm^{-1}; ($C_{11}H_{15}O_3N$ requires: C, 63·14; H, 7·23, N, 6·90. Found: C, 63·43; H, 6·91; N, 6·95%).

After acidification an amber coloured liquid was obtained from the alkaline aqueous extract (700 mg). It was chromatographed over silica gel. Elution with C_6H_6 gave N-methyl salicyl amide (160 mg), m.p. 91° (m.m.p. undepressed). Further elution with C_6H_6–$CHCl_3$ (1 : 1) gave 8-methoxy dihydro isocoumarin. (IX), m.p. 118° (200 mg). identical with sample obtained below.

Cyclization of VIII *to 8-methoxy dihydro isocoumarin* (IX). A solution of the alcohol VIII (1 g) in ethanolic NaOH (10%, 25 ml) was refluxed for 10 hr. The alcohol was removed by distillation. To the remaining mixture 25 ml water was added and it was ether extracted to remove any alkali insoluble impurity. The alkaline layer upon acidification and usual workup gave 8-methoxy dihydro isocoumarin, (IX), m.p. 118° (colourless needles from EtOAc–hexane), 500 mg (60%), IR: 1,720 cm^{-1}; ($C_{10}H_{10}O_3$ requires: C, 67·4; H, 5·66. Found: C, 67·61; H, 5·79%).

Conversion of dihydro isocoumarins into isocoumarins. The following general procedure was followed:

A mixture of the dihydro isocoumarin (250 mg), N-bromo succinimide (450 mg), benzoyl peroxide (5 mg), and CCl_4 (7 ml) was refluxed for 1 hr by irradiating with a 60 watt lamp. An additional quantity of the benzoyl peroxide (5 mg) was added and refluxed for a further hr. The precipitate formed was filtered off and washed with CCl_4. Evaporation of the CCl_4 layer gave the yellow bromo derivative which was mixed with Et_3N (15 ml) and refluxed for 15 hr. The base was removed by distillation *in vacuo*, and the residue repeatedly triturated with conc HCl and water. The solid obtained was extracted with ether, the ether extract washed

with NaCl aq and dried (Na_2SO_4). Removal of solvent furnished the methoxy isocoumarins. *5-Methoxy isocoumarin*, (X), m.p. 107–108° (hexane), (60%), IR: 1,720 cm^{-1}; ($C_{10}H_8O_3$ requires: C, 68·18; H, 4·58. Found: C, 67·9; H. 4·8%). *6-Methoxy isocoumarin*. (XI), m.p. 96° (colourless needles from EtOAc–hexane, lit.[3] m.p. 97–98°), (30%), IR: 1,730 cm^{-1}; ($C_{10}H_8O_3$ requires: C, 68·18; H, 4·58. Found: C, 68·0; H, 4·58%). *8-Methoxy isocoumarin*, (XII). m.p. 114° (hexane), (30%), IR: 1,720 cm^{-1}; ($C_{10}H_8O_3$ requires: C, 68·18; H. 4·58. Found: C. 68·3; H. 4·7%).

Synthesis of (±) *Mellein*. *o*-Methoxy N-methyl benzamide (0·025 moles, 4·125 g) was lithiated with excess n-BuLi (0·125 moles) as above. The metalation mixture was treated with a solution of propylene oxide (0·125 moles, 9 ml), in ether. Work up gave a white solid, which was crystallized from EtOH–hexane to yield white crystals of the alcohol, (VIIIa), m.p. 127°, 3·4 g (60%), IR: 3,400, 1,640, 800, 790, 760 cm^{-1}; ($C_{12}H_{17}O_3N$ requires: C, 64·55; H, 7·68; N, 6·27. Found: C, 64·52; H, 7·42; N, 6·5%).

The alcohol VIIIa on hydrolysis with 10% alcoholic NaOH followed by usual workup gave white prisms of (±) mellein methyl ether. (IXa), m.p. 68° (hexane, lit.[5] m.p. 67–68°), overall yield 60%, IR: 1,720 cm^{-1}; ($C_{11}H_{12}O_3$ requires: C, 68·73; H, 6·29. Found: C, 68·8; H, 6·1%).

(±) Mellein methyl ether, (IXa). (100 mg) was demethylated by refluxing with HBr/AcOH (5 ml, 47%) for 4 hr. The solid obtained after usual work up was crystallized from ether–hexane to furnish white prisms of (±) mellein, (XIII), m.p. 39° (lit.[7] m.p. 39°), 90 mg (98%), identical in all respects (m.p., m.m.p., TLC, superimposable IR) with an authentic sample of (±) mellein. ($C_{10}H_{10}O_3$ requires: C, 67·4; H, 5·66. Found: C, 67·76; H, 5·5%).

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