2-Bromo-3-methoxycyclohex-2-enone, a New Reagent for the α-Arylation of Lactams

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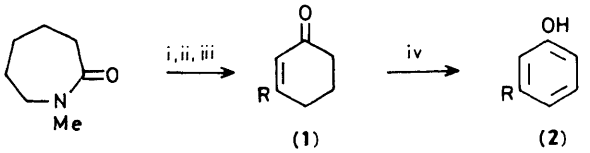
We report efficient syntheses of 2-bromo- and 2-chloro-3-methoxycyclohex-2-enone and their use as *m*-hydroxyphenyl cation synthons for the α-arylation of lactams. The sequence has been used to synthesize the analgesic drug meptazinol.

We have previously reported a synthesis of α-aryl lactams by condensation of the lithium anion of the parent lactam with 3-methoxycyclohex-2-enone to give a 3-substituted cyclohexenone (**1**) which was oxidised to the corresponding phenol (**2**) by bromine (Scheme 1).[1]



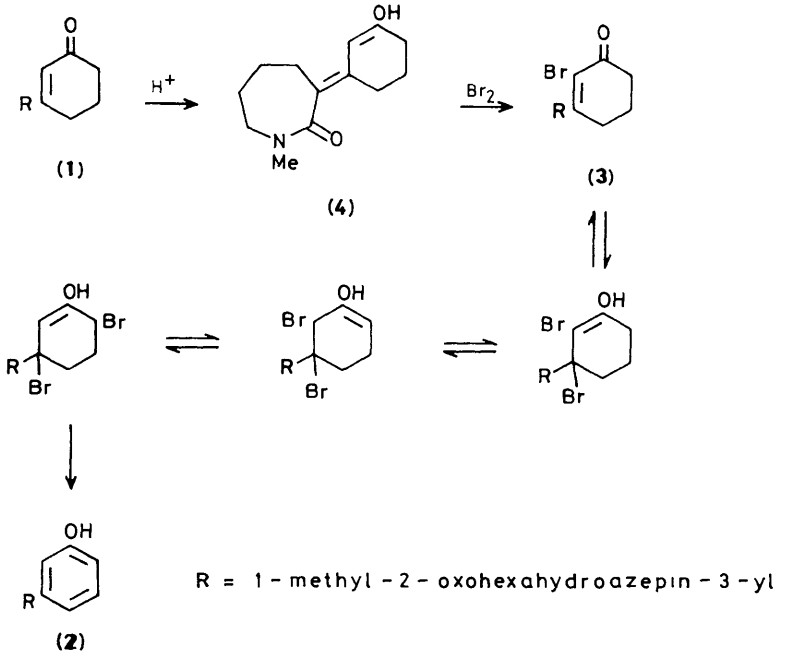
R = 1-methyl-2-oxohexahydroazepin-3-yl

Scheme 1. *Reagents:* i, LDA; ii, 3-methoxycyclohexenone; iii, H_2O–H^+; iv, Br_2–CH_2Cl_2

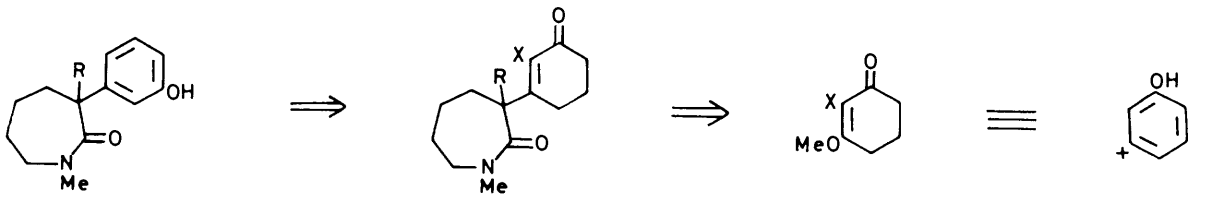
When the bromination was carried out in dichloromethane or acetic acid, the phenol (**2**) was formed rapidly and no intermediates could be isolated; however, using water as the solvent and potassium bromate–hydrobromic acid as an *in situ* source of bromine, the major product (67% isolated yield) was the bromo enone (**3**) rather than the expected phenol (**2**). In the presence of a large excess of hydrobromic acid a mixture of the bromo enone (**3**) and the phenol (**2**) was formed. Clean conversion of the bromo enone into the phenol is difficult under aqueous conditions but is readily achieved under anhydrous conditions with acid catalysis. Bromination of the enone (**1**) under these conditions presumably occurs *via* the extended enol (**4**) to give the bromo enone (**3**). Rearrangement and dehydrobromination of (**3**) would be expected to occur readily under anhydrous conditions[2] but with difficulty in the presence of water[3] *via* a series of equilibria as in Scheme 2.

A continuing interest in α-aryl lactams as precursors to the analgesic, meptazinol, and the observation of the clean conversion of the bromo enone (**3**) into the phenol (**2**) prompted us to investigate the use of 2-bromo-3-methoxycyclohex-2-enone (**5**) as a *m*-hydroxyphenyl cation equivalent (Scheme 3).

Synthesis of 2-Bromo-3-methoxycyclohex-2-enone (**5**).—Synthesis of compound (**5**) has been reported by *N*-bromosuccinimide (NBS) bromination of 3-methoxycyclohex-2-enone in carbon tetrachloride,[4] but other authors have reported 4- or 6-substituted derivatives from this reaction.[5,6] A reinvestigation of this reaction demonstrated that compound (**5**) was indeed the major product (*ca.* 70% by n.m.r. analysis) but that a large number of by-products were formed including other monobrominated, dibrominated, and phenolic materials. With dichloroethane rather than carbon tetrachloride as solvent and in the absence of light, the reaction was faster and much more selective, the required product being obtained in >90% yield.



Scheme 2.



(2) R = H
(10) R = Et

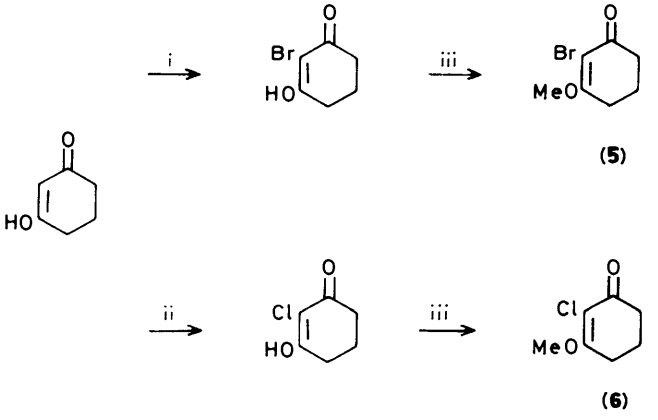
(3) R = H, X = Br
(7) R = H, X = Cl
(8) R = Et, X = Br
(9) R = Et, X = Cl

(5) X = Br
(6) X = Cl

Scheme 3.

Presumably substitution at the 2-position proceeds *via* an ionic mechanism and is thus favoured by a more polar solvent, whereas substitution at the 4- and 6-position occurs *via* a free radical process and is promoted in a non-polar solvent.[7]

Although the bromination reaction is efficient, complete removal of succinimide is difficult since compound (**5**) is hydrolytically unstable, and the best synthesis of compound (**5**) involves bromination of cyclohexane-1,3-dione in aqueous solution using potassium bromate–hydrobromic acid and conversion of the resulting 2-bromo-1,3-dione into (**5**). Although conventional procedures for this etherification (alcohol–acid catalyst,[8] alcohol–azeotropic removal of water,[9] or alcohol–trialkyl orthoformate–acid[10]) result in low yields of compound (**5**) contaminated with aromatised materials, we have found that use of methanol–trimethyl orthoformate in the presece of a strongly acid ion-exchange resin, *e.g.* Amberlite IR120 H^+, results in clean and rapid conversion of the bromo dione into compound (**5**) at room temperature and without the necessity of an aqueous work-up. The chloro analogue (**6**) may be prepared in a similar manner (Scheme 4).



Scheme 4. *Reagents:* i, $KBrO_3$–HBr–H_2O; ii, Chloramine T aq.; iii, $(MeO)_3CH$–MeOH–IR120 H^+

α-Arylation of Lactams with Reagents (**5**) and (**6**).—Metallation of *N*-methylcaprolactam[1] with lithium di-isopropylamide (LDA) in tetrahydrofuran–hexane followed by reaction with either reagent (**5**) or (**6**) gave the expected halogeno enone (**3**) or (**7**), respectively, in good yield after aqueous acidic work-up. Both (**3**) and (**7**) were smoothly converted into the phenol (**2**) by treatment with hydrogen bromide in either dichloromethane or acetic acid at room temperature. Application of the same sequence to 2-ethyl-*N*-methylcaprolactam[1] failed to produce any of the required halogeno enones (**8**) or (**9**), unfunctionalised lactam and reagent being recovered on aqueous acidic work-up.

We have previously demonstrated that the products of the reaction between lithiated 2-ethyl-*N*-methylcaprolactam and 3-methoxycyclohexenone are time-dependent; at short contact times (<60 s) the required functionalised lactam can be obtained but at longer reaction times the initial adduct undergoes 'reverse-aldol' reaction as a consequence of steric compression (2 adjacent quaternary carbons), leading to recovery of starting materials.[1] With the halogenated reagents (**5**) and (**6**), the 'reverse aldol' reaction is faster and the required products are not obtained even at short contact times.

Metallation of 2-ethyl-*N*-methylcaprolactam with bromomagnesium di-isopropylamide[1] followed by treatment with either (**5**) or (**6**) did, however, provide the required halogeno enones (**8**) or (**9**) in good yield after aqueous acidic work-up and both (**8**) and (**9**) were smoothly converted into the phenol (**10**) by hydrogen bromide in dichloromethane. Since reduction of the lactam function of (**10**) yields the analgesic drug, meptazinol,[1] this sequence offers a very short, efficient synthesis of this drug.

Experimental

General procedures are as described previously,[1] yields are of isolated, pure material but are not optimised. ^1H N.m.r. spectra were determined in deuteriochloroform solution at 60 MHz.

3-(2-Bromo-3-oxycyclohex-1-enyl)hexahydro-1-methylazepin-2-one (**3**).—A mixture of hexahydro-1-methyl-3-(3-oxocyclohex-1-enyl)azepin-2-one (**1**)[1] (22.1 g, 0.1 mol), 48% hydrobromic acid (30 ml, *ca.* 0.2 mol), and water (300 ml) was treated with a solution of potassium bromate (5.7 g, 33 mmol) in warm water (100 ml). After 1 h the mixture was extracted with dichloromethane (2 × 200 ml) and the extracts were washed with water (200 ml), dried, and evaporated. Recrystallisation of the residue from ethyl acetate gave the *bromo enone* (**3**) (20 g, 67%), m.p. 120—121 °C (Found: C, 51.7; H, 6.2; N, 4.7. $C_{13}H_{18}BrNO_2$ requires C, 52.0; H, 6.0; N, 4.7%); $\nu_{max.}$ 1 680 (α,β-unsaturated C=O) and 1 630 cm^{-1} (amide); δ 4.3 (1 H, m, allylic CH), 3.0—4.0 (2 H, m, NCH_2), 3.0 (3 H, s, NMe), 2.4—3.0 (4 H, m, $COCH_2$ and allylic CH_2), and 1.4—2.4 (8 H, m, 4 × ring CH_2).

2-Bromo-3-methoxycyclohex-2-enone (**5**).—(a) *From 3-methoxycyclohex-2-enone.* A solution of 3-methoxycyclohex-2-enone[1] (22.6 g, 0.18 mol) in dichloroethane (100 ml), maintained between 5 and 10 °C was treated with NBS (32.0 g, 0.18 mol) in portions over 0.5 h (exothermic). After 0.5 h the mixture was filtered and the filtrate evaporated. The residue was

dissolved in toluene (500 ml) and rapidly washed with cold water (2 × 200 ml). The organic layer was dried and evaporated to *ca.* 100 ml, cooled to 0 °C and the bromo compound (**5**) was filtered off (33.2 g, 90%), m.p. 92—94 °C (lit.,[4] 94—95 °C) (Found: C, 41.0; H, 4.7. Calc. for $C_7H_9BrO_2$: C, 41.0; H, 4.4%); $\nu_{max.}$ 1 640 cm^{-1} (C=O); δ 3.9 (3 H, s, MeO) and 1.9—2.9 (6 H, m, 3 × ring CH_2).

(b) *From cyclohexane-1,3-dione.* A mixture of cyclohexane-1,3-dione (11.2 g, 0.1 mol), 48% hydrobromic acid (15 ml, 0.1 mmol), and water (50 ml) was treated dropwise with a solution of potassium bromate (5.7 g, 33 mmol) in warm water (50 ml). After the addition was complete, the resulting precipitate was filtered off, washed with water (3 × 20 ml), and dried *in vacuo* to yield 2-bromocyclohexane-1,3-dione (17 g, 89%). A mixture of the crude bromo dione (17 g, 89 mmol), trimethyl orthoformate (11 ml, 0.1 mol), and methanol (100 ml) was stirred in the presence of IR120H ion-exchange resin (1 g, pre-washed with methanol). After 4 h the mixture was filtered and the filtrate evaporated. Recrystallisation of the residue from ethyl acetate gave the methoxy compund (**5**) (16.4 g, 80% overall) identical with material prepared by method (a).

2-Chloro-3-methoxycyclohex-2-enone (**6**).—A solution of cyclohexane-1,3-dione (112 g, 1 mol) in water (1 l), maintained at 5—10 °C was treated dropwise with a solution of chloramine T (281 g, 1 mol) in water (2 l). After 0.5 h the mixture was filtered and the precipitate washed with cold water (200 ml). The combined filtrate and washings were acidified to pH 2 with 36% hydrochloric acid (80 ml) and the resulting precipitate was filtered off, washed with a small volume of cold water, and dried *in vacuo*. A second crop of the chloro dione was obtained by saturating the mother liquors with sodium chloride (total yield: 117 g, 80%). A solution of the crude chloro dione (117 g, 0.8 mol) and trimethyl orthoformate (96 ml, 0.88 mol) in methanol (600 ml) was stirred in the presence of IR120H ion-exchange resin (4 g, pre-washed with methanol). After 4 h the mixture was filtered off and the filtrate evaporated under reduced pressure. Recrystallisation of the residue from ethyl acetate gave the methoxy compound (**6**) (115 g, 72% overall), m.p. 90—92 °C (lit.,[11] not reported) (Found: C, 52.5; H, 5.5. Calc. for $C_7H_9ClO_2$: C, 52.3; H, 5.6%); $\nu_{max.}$ 1 645 cm^{-1} (C=O); δ 3.0 (3 H, s, MeO) and 1.9—2.9 (6 H, m, 3 × ring CH_2).

3-(2-Bromo-3-oxocyclohex-1-enyl)hexahydro-1-methylazepine-2-one (**3**) *from* (**5**).—A solution of LDA [from 1.55M butyl-lithium in hexane (12.9 ml, 20 mmol), di-isopropylamine (2.8 ml, 20 mmol), and THF (13 ml)] was treated with *N*-methylcaprolactam [1] (2.5 ml, 20 mmol) at 5—10 °C. After 5 min a solution of (**5**) (4.1 g, 20 mmol) in THF (15 ml) was added and after a further 5 min the mixture was poured onto a mixture of 5M hydrochloric acid (8 ml) and water (100 ml). The mixture was extracted with ether (100 ml) and the extract was dried and evaporated. Recrystallisation of the residue from ethyl acetate gave the *bromo enone* (**3**) (4.9 g, 82%) identical with material made by bromination of (**1**).

3-(2-Chloro-3-oxocyclohex-1-enyl)hexahydro-1-methylazepin-2-one (**7**).—This compound was prepared in a manner similar to (**2**), using the chloro compound (**6**) in place of the bromo compound (**5**); yield 75%, m.p. 118—120 °C (Found: C, 61.4; H, 7.3; N, 5.3. $C_{13}H_{18}ClNO_2$ requires C, 61.6; H, 7.1; N, 5.5%); $\nu_{max.}$ 1 680 (α,β-unsaturated C=O) and 1 635 cm^{-1} (amide); δ 4.2 (1 H, m, allylic CH), 3.2—4.0 (2 H, m, NCH_2), 3.0 (3 H, s, NMe), 2.3—2.9 (4 H, m, CH_2CO and allylic CH_2), and 1.5—2.3 (8 H, m, 4 × ring CH_2).

Hexahydro-3-(3-hydroxyphenyl)-1-methylazepin-2-one (**2**).—A solution of the bromo enone (**3**) (1.48 g) in dichloromethane (10 ml) was treated with 48% hydrogen bromide in acetic acid (0.2 ml). After 3 h water (20 ml) was added and the dichloromethane evaporated off. The crystalline product was filtered off, washed with water, and dried *in vacuo* to yield the phenol (**2**) (844 mg, 77%), m.p. 190—192 °C (lit.,[1] 192—192 °C). This material was also produced in similar yield from the chloro enone (**7**).

3-(2-Chloro-3-oxocyclohex-1-enyl)-3-ethylhexahydro-1-methylazepin-2-one and 3-(2-Bromo-3-oxocyclohex-1-enyl)-3-ethylhexahydro-1-methylazepin-2-one.—Both these compounds were prepared from the bromomagnesium enolate of 2-ethyl-*N*-methylcaprolactam [1] and the chloro (**6**) or bromo compound (**5**), respectively. The *chloro compound* (**9**) had m.p. 115—116 °C (from di-isopropyl ether) (Found: C, 63.7; H, 7.9; N, 4.85. $C_{15}H_{22}ClNO_2$ requires C, 63.5; H, 7.8; N, 4.9%); $\nu_{max.}$ 1 690 (α,β-unsaturated C=O) and 1 635 cm^{-1} (amide); δ 3.2 (2 H, m, NCH_2), 3.0 (3 H, m, NMe), 2.3—2.8 (4 H, m, CH_2CO and allylic CH_2), 1.3—2.3 (10 H, m, 5 × CH_2), and 1.0 (3 H, t, *J* 7 Hz; $MeCH_2$). The *bromo compound* (**8**) had m.p. 106—107 °C (from ethyl acetate) (Found: C, 54.7; H, 6.8; N, 4.2. $C_{15}H_{22}BrNO_2$ requires C, 54.9; H, 6.8; N, 4.3%); $\nu_{max.}$ 1 680 (α,β-unsaturated C=O) and 1 635 cm^{-1} (amide); δ 3.2 (2 H, m, NCH_2), 3.0 (3 H, s, NMe), 2.5—2.8 (4 H, m, CH_2CO and allylic CH_2), 1.5—2.3 (10 H, m, 5 × CH_2), and 1.1 (3 H, t, *J* 7 Hz, $MeCH_2$).

3-Ethylhexahydro-3-(3-hydroxyphenyl)-1-methylazepin-2-one (**10**).—This compound was prepared from either the bromo (**8**) or chloro compound (**9**) in a manner similar to the preparation of (**3**). The phenol had m.p. 178—180 °C (ethyl acetate) (lit.,[1] 178—180 °C).

Acknowledgements

We thank Dr. K. Heatherington and the staff of the Physical Chemical Laboratory for analytical and spectral determinations.

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Received 1*st August* 1986; *Paper* 6/1566