

ARYNIC CONDENSATION OF KETONE ENOLATES—XIV†

CONDENSATION OF AROMATIC α,β -UNSATURATED KETONE ENOLATES ON ARYNES

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Abstract—Benzynes and 1-naphthynes (generated from the corresponding halogeno derivatives and the Complex Base $\text{NaNH}_2\text{-Bu}^t\text{ONa}$) condense with α,β -unsaturated ketone enolates β -substituted by an aromatic ring and only enolisable in the α' -position, to lead to α -tetralones and/or indanones. The reaction path depends upon the nature of the ketone enolate and, less strongly, on the solvent. The reaction mechanism is discussed. These reactions constitute new simple and efficient syntheses of numerous α -tetralones and indanones.

It is well known that condensations of saturated ketone enolates with aromatic halides by means of SR_N1^2 or arynic³ reactions, provide a wide variety of aromatic ketones.

On the other hand, unsaturated ketones have been studied less, although these substrates possess some interesting properties. Thus, depending on their structure and the conditions, they may yield enolates 1 or 2 (Scheme 1).

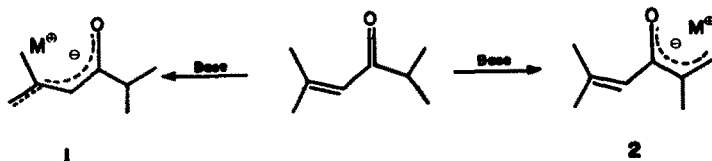
Sammes⁴ and ourselves⁵ showed that arynic condensations performed on type 1 enolates, lead to aromatic ketones and chiefly to naphthalene derivatives⁶.

On the contrary, we reported in a previous short publication⁷ that enolates 2 condense with benzyne to give tetralones and/or indanones. In the present paper we wish to report a more complete description of these partially unexpected reactions and a discussion of their mechanism.

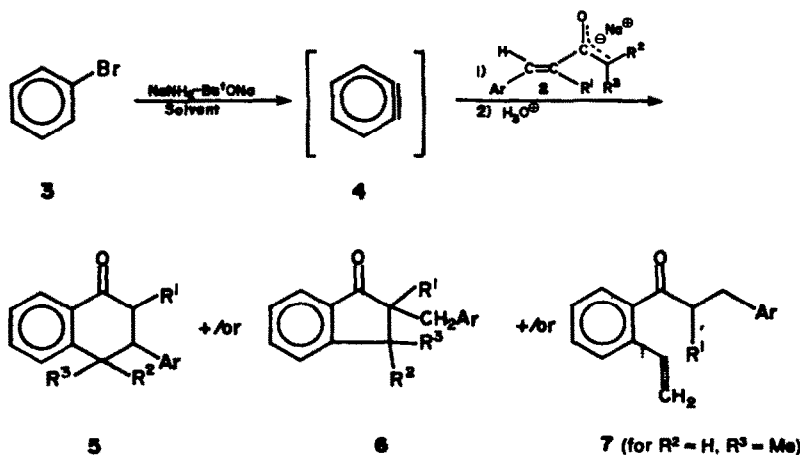
RESULTS

Enolates 2 generally do not yield with NaNH_2 , a complex base³ able to generate the benzyne from haloaromatic derivatives. Thus, these condensations need the presence of the complex base $\text{NaNH}_2\text{-Bu}^t\text{ONa}$.

General reactions observed are shown in Scheme 2 and quantitative results are summarized in the Table 1.



Scheme 1.



Scheme 2.

Table 1. Condensation of 2 with bromobenzene in THF^a

Run	Ar	R ¹	R ²	R ³	Yield (b)	$\bar{5}$ (c)	$\bar{6}$ (c)	$\bar{7}$ (c)
1	C ₆ H ₅	H	H	H	70	86	14	-
2	4-MeO-C ₆ H ₄	H	H	H	45	100	-	-
3	3,4-(MeO) ₂ C ₆ H ₃	H	H	H	50	100	-	-
4	2,4,6-(MeO) ₃ C ₆ H ₂	H	H	H	60	100	-	-
5	2-furyl	H	H	H	45	100	-	-
6	C ₆ H ₅	H	CH ₃	H	60	-	100	-
7	4-MeO-C ₆ H ₄	H	CH ₃	H	70	29(d)	58	13
8	3,4-(MeO) ₂ C ₆ H ₃	H	CH ₃	H	50	-	100	-
9	4-F-C ₆ H ₄	H	CH ₃	H	50	-	100	-
10	C ₆ H ₅	CH ₃	H	H	70	100(e)	-	-
11	C ₆ H ₅	CH ₃	CH ₃	H	45	-	-	100
12	C ₆ H ₅	-(CH ₂) ₃ -	H	H	85	-	100	-
13	C ₆ H ₅	-(CH ₂) ₃ -	CH ₃	H	65	-	100	-
14	C ₆ H ₅	-(CH ₂) ₄ -	H	H	70	-	100	-
15	4-MeO-C ₆ H ₄	-(CH ₂) ₄ -	H	H	50	-	100	-
16	C ₆ H ₅	-(CH ₂) ₅ -	H	H	45	-	100	-

(a) 4 hours at 30°C for R² and/or R³ ≠ H and 45°C for R² = R³ = H.

Ratio enolate/bromobenzene = 2

(b) Relative to bromobenzene

(c) Relative percentage

(d) Isomeric mixture

(e) Cis:trans = 66:34

The yields of these reactions were generally fair to excellent and these condensations provided a wide range of tetralones and indanones. Ketones 7 were rather unexpected, and their formation will be discussed later.

From the synthetic view point, these reactions are applied to 1-naphthyl. As previously shown, saturated ketone enolates essentially condense on the position 2 of 1-naphthyl.⁸ The same regioselectivity occurs with unsaturated ketone enolates. Thus condensation of 1-bromonaphthalene with cyclic unsaturated ketone enolates 8 lead to polycyclic ketones 10 (Scheme 3 and Table 2).

DISCUSSION

From the numerous examples previously studied,³ we can say that the first steps of the reactions are those given in Scheme 4 using benzyne as an example.

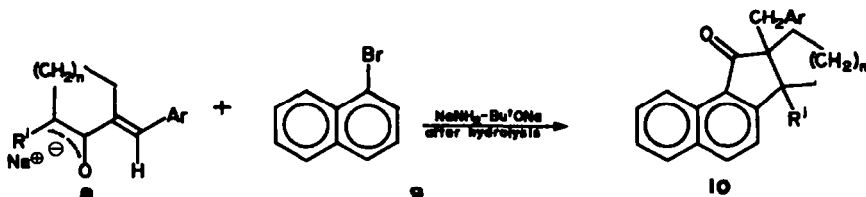
Normally a Michael type reaction, leading to tetralones is expected from 13. However, this was not always the case (*vide supra*). The explanation of the evolution of 13, when 2 is an acyclic ketone enolate, requires the examination of the following points:

Table 2. Condensation of 8 on 1-bromonaphthalene in THF (4 h at 30°)

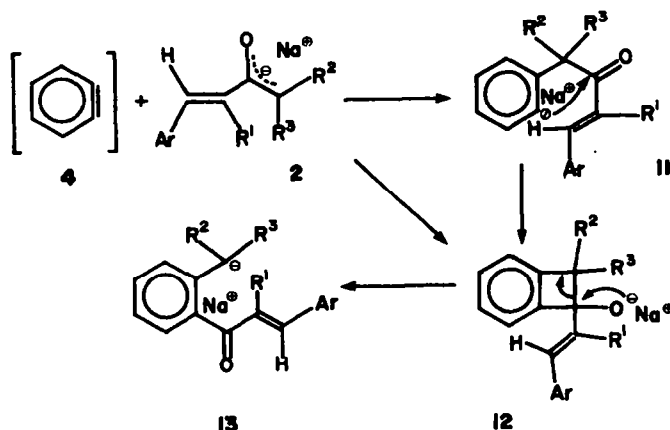
Run	n	Ar	R ¹	10 (a)
17	2	C ₆ H ₅	H	60
18	2	C ₆ H ₅	CH ₃	60
19	3	C ₆ H ₅	H	50
20	3	4-MeO-C ₆ H ₄	H	50

(a) Relative to 1-bromonaphthalene

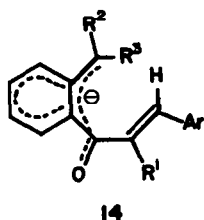
(1) The negative charge on the benzylic carbon of 13 may be more or less delocalized towards the CO function through the aromatic ring. This delocalization is favoured by electrodonating groups R², R³, by a counter cation of low complexing ability and by a dissociating cationic solvating solvent. For a large delocalization, the structure of 13 looks like 14. In other words, the enone system is disrupted and the Michael cyclisation is hardly possible. Thus, if Ar is sufficiently electroattracting, the



Scheme 3.



Scheme 4.



addition on the activated double bond is possible as in styrene compounds.

(2) For R², R³ given, Z electrodonating groups on the aromatic ring (Scheme 5) do not favour 14 as it may be seen from the resonance formula.

This electrodonating effect must favour the attack of the negative charge on the benzylic position relative to the ring bearing the Z group, thus producing tetralone.

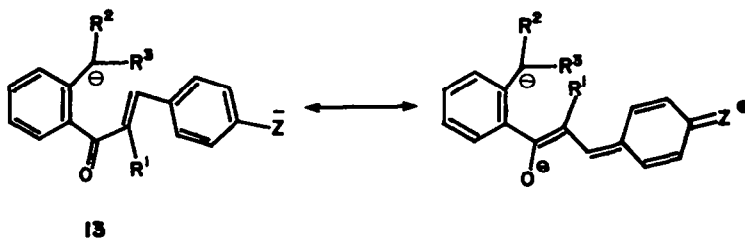
A comparison of runs 1 and 6, 2 and 7, 3 and 8 shows that the replacement of R² = R³ = H by R² = Me, R³ = H (which destabilizes the negative charge on the benzylic position) increases the formation of indanones 6.

The effect of donating group Z on the aromatic ring is shown by a comparison of runs 1 and 2, 6 and 7.

The solvent effects on the complexation of the negative charge by the cation Na⁺ were shown by the reactions summarized in the Table 3.

Comparison of runs 1 and 21 show that HMPA (a strong cation complexing solvent), favours the delocalization of the negative charge resulting in the formation of the indanone.

Comparison of runs 22, 7 and 23 is still more revealing. Passing from THF to a less polar solvent THF-benzene (1:1), promotes the localization of the negative charge on the benzylic position and gives an increased yield of tetralone. On the contrary, the more polar solvent THF-HMPA (1:1) favours indanone formation.



Scheme 5.

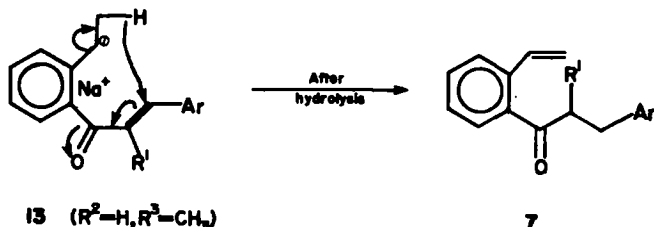
Table 3. Solvent effect on arylc condensations of 2

Run	Ar	R ¹	R ²	R ³	Solvent	t (hrs)	T°C	Yield(a)	5(b)	6(b)	7(b)
1	C ₆ H ₅	H	H	H	THF	4	45	70	86	14	-
21	C ₆ H ₅	H	H	H	THF+HMPA (1:1)	4	0	40	-	100	-
22	4-MeO-C ₆ H ₄	H	CH ₃	H	THF+C ₆ H ₆ (1:1)	6	45	50	64(c)	26	10
7	4-MeO-C ₆ H ₄	H	CH ₃	H	THF	4	30	70	29(c)	58	13
23	4-MeO-C ₆ H ₄	H	CH ₃	H	THF+HMPA (1:1)	5	0	40	-	100	-

(a) Relative to bromobenzene

(b) Relative percentage

(c) Isomeric mixture



Scheme 6.

Finally, the formation of ketones 7 should be explained (Scheme 6) by an hydride transfer as encountered with saturated ketones.⁹

Concerning the results observed with cyclic ketone enolates, it is clear that they may only allow indanone formation. Indeed, evolution of the corresponding anion 13 toward bicyclic tetralone should pass by an energetic unfavorable anti Bredt like intermediate.

CONCLUSION

Condensations of unsaturated ketone enolates with arynes provide various tetralones or indanones. The reactions are easily performed and the path taken by the condensation may be partially monitored by adequate choice of solvent.

EXPERIMENTAL

M.p.s (Kofler) are uncorrected. The NMR spectra were recorded with a Perkin-Elmer R 12 B spectrometer or CAMECA (250 MHz) using TMS as internal standard. The IR spectra were obtained on a Perkin-Elmer 457 instrument. The UV spectra were recorded with a Beckmann DK 2A spectrometer, using EtOH as solvent. The starting unsaturated ketones were prepared by condensation of ArCHO on $R^2R^3CH-CO-CH_2R^1$ in basic or acid medium, and had physical properties in accord with those described in the literature.

General procedure. A soln of Bu^tOH (25 mM) in THF (10 ml) was added to sodamide (100 mM) in THF (20 ml), and stirred for 1.5 hr at 40–45° under dry N₂; then the ketone (25 mM) in THF (20 ml) was added dropwise during 15 min at 25–30°. The mixture was stirred at this temp. for 5–10 min, and bromobenzene (12.5 mM) in THF (10 ml) was added. The reaction was continued during 4 hr at 30° for R² and/or R³ ≠ H and at 40–45° for R² = R³ = H, whatever nature of Ar and R¹.

After cooling to room temp., the mixture was poured onto ice, acidified with 20% HCl, extracted with ether (3 × 100 ml) and dried over MgSO₄. The solvent was removed under reduced pressure and the residual oil was chromatographed on a silica gel column using 2–5% ether–petroleum ether as eluent, except for runs 3, 4 and 8 (10–30%).

Run 1, 5¹⁰ and 6^{11,12} have physical properties in accord with those described in literature.

Run 2, 5: m.p. 94–95°; ν (KBr) 1680 cm⁻¹ (C=O); λ_{max} (log ϵ) 293 sh (3.39), 285 (3.52), 279 (3.51), 248 (4.13); δ (CCl₄) 2.45–3.50 (5 H, m, aliph), 3.71 (3 H, s, OMe), 6.66–7.60 (7 H, m, arom), 7.85–8.12 (1 H, m, arom). (Found: C, 81.22; H, 6.55. C₁₇H₁₆O₂ requires: C, 80.92; H, 6.39%).

Run 3, 5: m.p. 124°; ν (KBr) 1680 cm⁻¹ (C=O); λ_{max} (log ϵ) 294 sh (3.51), 283 (3.71), 245 (4.11); δ (CDCl₃) 2.60–3.62 (5 H, m, aliph), 3.86 (6 H, s, OMe), 6.82 (3 H, br.s, arom), 7.13–7.65 (3 H, m, arom), 7.97–8.21 (1 H, m, arom). (Found: C, 76.46; H, 6.59. C₁₈H₁₈O₂ requires: C, 76.57; H, 6.43%).

Run 4, 5: m.p. 139°; ν (CCl₄) 1680 cm⁻¹ (C=O); λ_{max} (log ϵ) 293 (3.48), 250 (4.15), 241 (4.23); δ (CDCl₃) 2.40–4.40 (14 H, m with two s at 3.74 and 3.78, OMe), 6.15 (2 H, s, arom), 7.05–7.60 (3 H, m, arom), 8.00–8.22 (1 H, m, arom). (Found: C, 73.03; H, 6.26. C₁₉H₂₀O₄ requires: C, 73.06; H, 6.45%).

Run 5, 5: ν (film) 1690 cm⁻¹ (C=O); λ_{max} (log ϵ) 293 (3.43), 248 (4.13); δ (CCl₄) 2.15–3.80 (5 H, m, aliph), 5.89–6.27 (2 H, m, furyl),

6.90–7.77 (4 H, m, furyl+arom), 7.82–8.09 (1 H, m, arom). (Found: C, 79.41; H, 5.58. C₁₄H₁₂O₂ requires: C, 79.22; H, 5.70%).

Run 6, 6: ν (film) 1710 cm⁻¹ (C=O); λ_{max} (log ϵ) 295 (3.71), 288 (3.72), 246 (4.07); δ (CCl₄) 1.10 (3 H, d, J = 7.3 Hz, Me), 2.20–3.50 (4 H, m, aliph), 7.10–7.80 (9 H, m, arom). (Found: C, 86.42; H, 6.76. C₁₇H₁₆O requires: C, 86.40; H, 6.83%). 6 treated by Na–D₂O during 12 hr under reflux gave 6 (R¹ = D): δ (CCl₄) 1.06 (3 H, d, J = 7.3 Hz, Me), 2.20–3.55 (3 H, m, aliph), 7.00–7.75 (1 H, m, arom). The catalytic reduction¹³ of 3-methyl, 2-benzylidene, indan, 1-one¹⁴ gave quantitatively 3-methyl, 2-benzyl, indan, 1-one which had the physical properties (NMR, IR and tic) of 6 formed by arynic condensation.

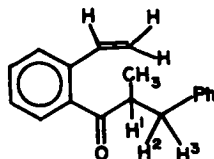
Run 7, 5 (isomeric mixture): ν (CCl₄) 1690 cm⁻¹ (C=O); λ_{max} (log ϵ) 295 sh (3.48), 285 (3.58), 278 (3.56), 248 (4.12); δ (CCl₄) 0.96 (d, J = 6.7 Hz) and 1.19 (d, J = 6 Hz) (3 H, two Me of the two isomers), 2.50–3.50 (4 H, m, aliph), 3.64 (3 H, br. s, OMe), 6.55–7.62 (7 H, m, arom), 7.80–8.10 (1 H, m, arom). (Found: C, 81.22; H, 6.75. C₁₈H₁₈O₂ requires: C, 81.17; H, 6.81%). 6: ν (film) 1710 cm⁻¹ (C=O); λ_{max} (log ϵ) 292 sh (3.50), 286 (3.63), 279 sh (3.62), 246 (4.13), 225 (4.16); δ (CCl₄) 1.10 (3 H, d, J = 7.3 Hz, Me), 2.14–3.36 (4 H, m, aliph), 3.64 (3 H, br. s, OMe), 6.57–7.60 (8 H, m, arom), (Found: C, 80.98; H, 6.92. C₁₈H₁₈O₂ requires: C, 81.17; H, 6.81%). 6 treated with Na–D₂O during 12 hr under reflux gave 6 (R¹ = D): δ (CCl₄) 1.10 (3 H, d, J = 7.3 Hz, Me), 2.5–3.3 (3 H, m, aliph), 3.64 (3 H, br.s, OMe), 6.57–7.75 (8 H, m, arom). 7: ν (film) 1690 cm⁻¹ (C=O); δ (CCl₄) 2.82–3.08 (4 H, m, (CH₂)₂), 3.64 (3 H, br. s, OMe), 5.07–5.68 (2 H, m, C=CH₂), 6.50–7.58 (9 H, m, arom + Ar–CH=C). (Found: C, 81.25; H, 6.53. C₁₈H₁₈O₂ requires: C, 81.17; H, 6.81%).

Run 8, 6: ν (film): 1710 cm⁻¹ (C=O); λ_{max} (log ϵ) 284 (3.72), 244 sh (4.13), 237 (4.16); δ (CCl₄) 1.15 (3 H, d, J = 7.3 Hz, Me), 2.18–3.35 (4 H, m; aliph), 3.71 (6 H, s, OMe), 6.60–6.80 (3 H, m, arom), 7.10–7.79 (4 H, m, arom). (Found: C, 70.06; H, 6.66. C₁₅H₂₀O₃ requires: C, 70.00; H, 6.66%). 6 treated by Na–D₂O during 12 hr under reflux gave 6 (R¹ = D): δ (CCl₄) 1.15 (3 H, d, J = 7.3 Hz, Me), 2.4–3.4 (3 H, m, aliph), 3.72 (6 H, s, OMe), 6.63–6.80 (3 H, m, arom), 7.10–7.79 (4 H, m, arom).

Run 9, 6: m.p. 58°; ν (KBr) 1715 cm⁻¹ (C=O); δ (CCl₄) 1.13 (3 H, d, J = 7.3 Hz, Me), 2.05–3.60 (4 H, m, aliph), 6.70–7.80 (8 H, m, arom). (Found: C, 81.35; H, 4.45; F, 7.15. C₁₇H₁₅FO requires: C, 81.58; H, 4.45; F, 7.59%).

Run 10, Arynic condensation gave an isomeric mixture of 5. At the end of the reaction, EtOH (100 ml) was added. After stirring 3 hr epimerisation occurs and after hydrolysis, one isomer only was isolated (55–60%). m.p. 62°. It should be the *trans* isomer and had physical properties in accord with that described in the literature.¹⁵

Run 11, 7: ν (film) 1695 cm⁻¹ (C=O), δ (CCl₄) 1.05 (3 H, d, J = 6.7 Hz, Me), 2.28–3.58 (3 H, m, H¹ + H² + H³), 5.03–5.70 (2 H, m, C=CH₂), 6.62–7.62 (10 H, m, arom + Ar–CH=C). (Found: C, 86.17; H, 7.23. C₁₈H₁₈O requires: C, 86.26; H, 7.25). 7 treated with Na–D₂O during 12 hr under reflux gave 7 (H¹=D): δ



(CCl₄) 1.06 (3 H, s, Me), 2.5 and 3.06 (2 H, AB system, $J = 13.5$ Hz, H², H³), 5.05–5.70 (2 H, m, C=CH₂), 6.62–7.62 (10 H, m, arom + Ar-CH=C).

Run 12, 6: ν (film) 1710 cm⁻¹ (C=O); λ_{\max} (log ϵ) 2.96 (3.43), 288 (3.42), 248 (4.09); δ (CCl₄) 0.80–2.26 (6 H, m, cyclic CH₂), 2.6–3.8 (3 H, m, benzylic protons), 7.00–7.68 (9 H, m, arom). (Found: C, 86.98; H, 6.91. C₂₀H₁₈O requires: C, 86.49; H, 6.88%).

Run 13, 6: ν (film) 1710 cm⁻¹ (C=O); λ_{\max} (log ϵ) 292 (3.44), 247 (4.13); δ (CCl₄) 0.80–2.25 (9 H, m with s at 1.40, cyclic CH₂ + Me), 2.7–3.0 (2 H, AB system, $J = 13.9$ Hz, Ph-CH₂), 7.00–7.72 (9 H, m, arom). (Found: C, 86.86; H, 7.12. C₂₀H₂₀O requires: C, 86.92; H, 7.29%).

Run 14, After elimination of the starting ketone by liquid chromatography, the crude product contained some impurities. It was purified by reduction with LAH to two alcohols easily isolated by liquid chromatography. Oxidation of these alcohols by Jones reagent gave 6: m.p. 60–61°; ν (KBr) 1710 cm⁻¹ (C=O); λ_{\max} (log ϵ) 297 (3.57), 290 (3.56), 246 (4.13); δ (CCl₄) 0.80–2.13 (8 H, two m, cyclic CH₂), 2.67–3.4 (3 H, m, benzylic protons), 6.95–7.82 (9 H, m, arom). (Found: C, 86.70; H, 7.39. C₂₀H₂₀O requires: C, 86.92; H, 7.29%). Alkylation of 1,2,3,4,4a,9a-hexahydrofluoren, 9 - one by Ph-CH₂Cl gave 9a - benzyl, 1,2,3,4,4a,9a - hexahydrofluoren, 9 - one (yield: 84%) which had the physical properties (m.p., NMR, IR and tic) of 6 formed by arynic condensation.

Run 15, 6: m.p. 87–88°; ν (CCl₄) 1710 cm⁻¹ (C=O); λ_{\max} (log ϵ) 292 (3.61), 286 (3.63), 225 (4.14); δ (CDCl₃) 0.85–2.15 (8 H, m, cyclic CH₂), 2.55–3.45 (3 H, m, benzylic protons), 3.62 (3 H, s, OMe), 6.55–7.87 (8 H, m, arom). (Found: C, 82.25; H, 7.25. C₂₁H₂₂O₂ requires: C, 82.32; H, 7.24%).

Run 16, 6: m.p. 89–90°; ν (KBr) 1710 cm⁻¹ (C=O); λ_{\max} (log ϵ) 295 (3.43), 248 (4.11); δ (250 MHz) (CDCl₃) 0.96–2.14 (10 H, four m, cyclic CH₂), 2.75 and 2.9 (2 H, AB system, $J = 14$ Hz, Ph-CH₂), 3.52 (1 H, m, benzylic proton), 7.0–7.8 (9 H, four m, arom). (Found: C, 86.88; H, 7.70. C₂₁H₂₂O requires: C, 86.85; H, 7.64%).

Run 17, 6: m.p. 90°; ν (KBr) 1685 cm⁻¹ (C=O); λ_{\max} (log ϵ) 333 sh (3.69), 317 sh (3.86), 309 (3.95), 300 sh (3.85), 233 (4.40); δ (CDCl₃) 0.80–2.35 (6 H, m, cyclic CH₂), 2.8–3.3 (2 H, AB system, $J = 13.3$ Hz, Ph-CH₂), 3.6 (1 H, m, benzylic H), 6.90–7.95 (10 H, m, arom), 9.10–9.30 (1 H, m, arom). (Found: C, 88.21; H, 6.67. C₂₃H₂₆O requires: C, 88.42; H, 6.45%).

Run 18, 6: m.p. 79°; ν (KBr) 1690 cm⁻¹ (C=O); λ_{\max} (log ϵ) 333 sh (3.69), 316 sh (3.85), 309 (3.94), 296 sh (3.83), 233 (4.36); δ

(CCl₄) 0.8–2.3 (9 H, m with s at 1.43, cyclic CH₂ + Me), 2.7 and 3.1 (2 H, AB system, $J = 14$ Hz, Ph-CH₂), 6.9–8.05 (10 H, m, arom), 9.1–9.3 (1 H, m, arom). (Found: C, 88.28; H, 6.82. C₂₄H₂₂O requires: C, 88.31; H, 6.79%).

Run 19, 6: m.p. 132°; ν (KBr) 1685 cm⁻¹ (C=O); λ_{\max} 333 sh (3.73), 310 (3.98), 300 sh (3.87), 233 (4.65); δ (CDCl₃) 0.9–2.2 (8 H, m, cyclic CH₂), 2.8–3.5 (3 H, m, benzylic protons), 6.95–8.05 (10 H, m, arom), 9.05–9.2 (1 H, m, arom). (Found: C, 88.48; H, 6.90. C₂₄H₂₂O requires: C, 88.31; H, 6.79%).

Run 20, 6: ν (film) 1695 cm⁻¹ (C=O); λ_{\max} (log ϵ) 332 sh (3.67), 310 (3.93), 300 sh (3.84), 287 (3.68); δ (CDCl₃) 0.7–2.1 (8 H, m, cyclic CH₂), 2.5–3.6 (6 H, m with s at 3.45, benzylic protons + OMe), 6.49–7.97 (9 H, m, arom), 9.1–9.3 (1 H, m, arom). (Found: C, 84.28; H, 6.98. C₂₅H₂₄O₂ requires: C, 84.24; H, 6.79%).

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