# Synthesis of 2-Substituted 3,4-Dihydro-1,2-diazepines by the Reactions of Unsaturated Ketones with Hydrazides

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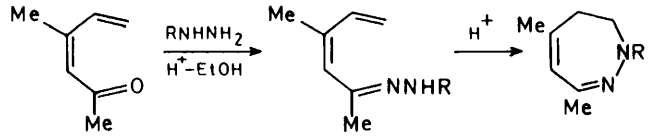
The previously reported synthesis of 3,4-dihydro-2-tosyl-1,2-diazepines by the acid-catalysed reactions of *p*-toluenesulphonylhydrazide with $\alpha\beta,\gamma\delta$-unsaturated ketones has been extended to other 2-substituted analogues (3) by the use of a variety of hydrazine derivatives. A new acid-catalysed ring contraction, the conversion of 2-benzoyl-3,4-dihydro-1,2-diazepine (3d) into 1-benzoyl-3-methylpyrazol-2-ine (4), is also reported.

We recently reported that the reactions of some substituted 2,4-dienones with *p*-toluenesulphonylhydrazine in the presence of an acid catalyst gave 3,4-dihydro-2-toluenesulphonyl-1,2-diazepines [*e.g.* (3a)] *via* tosylhydrazone intermediates.[1] This reaction provides an easy and convenient entry to the 1,2-diazepine system although its utility is somewhat limited by the fact that the ring-closure step is inhibited by certain combinations of substituents on the dienone.

The work described here was undertaken to probe the general applicability of the reaction to the synthesis of diazepines analogous to (3a) but with different *N*-substituents. Thus we examined the reactions of the dienone (1) with a variety of hydrazides. The reactions were carried out at room temperature in ethanol in the presence of hydrochloric or sulphuric acid as catalyst and, for the hydrazides listed in Scheme 1, moderate to good



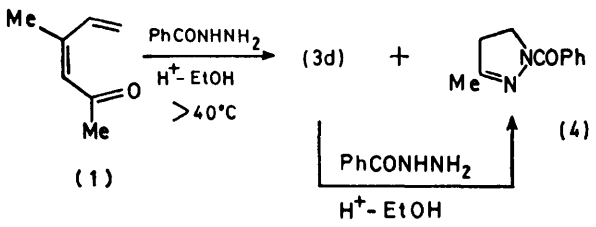

(1) ($E/Z$ = 2·2) (2) (3)

| R | Yield (%) |
|---|---|
| a; *p*-$MeC_6H_4SO_2$ | a; 77 |
| b; $PhSO_2$ | b; 65 |
| c; $MeSO_2$ | c; 60 |
| d; PhCO | d; 44 |
| e; MeCO | e; 46 |
| f; $EtO_2C$ | f; 43 |
| g; Ph | g; 21 |

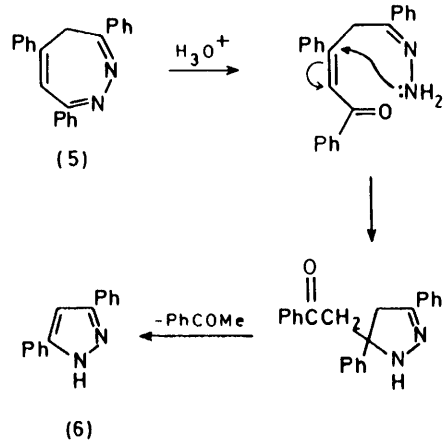
SCHEME 1

yields of diazepines (3b—g) were obtained. Their structures were confirmed by comparison of their i.r. and n.m.r. spectra with those of (3a).[1]

As previously observed for *p*-toluenesulphonylhydrazide, the reaction of (1) with benzoylhydrazide in the absence of acid gave predominantly the hydrazone (2d) and some diazepine (3d). Treatment of the hydrazone with sulphuric acid in ethanol gave the diazepine (3d) in 60% yield. It was found to be important in this and in some other cases to keep the reaction temperature low (<40 °C) both during the reaction and the work-up

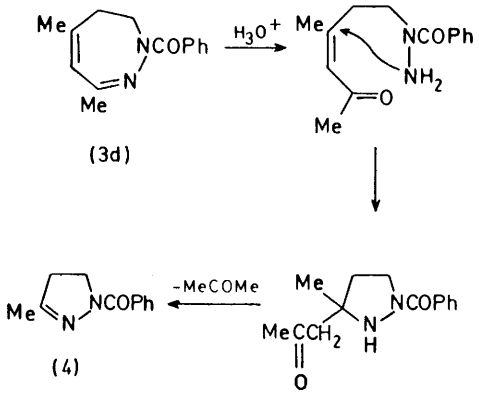



procedure; failure to do this resulted in the formation of pyrazolines, *e.g.* (4). Monitoring by t.l.c. and control experiments showed that the pyrazoline is a secondary product which is formed when the diazepine is heated in ethanol in the presence of acid and benzoylhydrazide. This diazepine ⟶ pyrazoline conversion is similar in some respects to the known acid-catalysed conversion of the fully unsaturated 4*H*-1,2-diazepine (5) into the



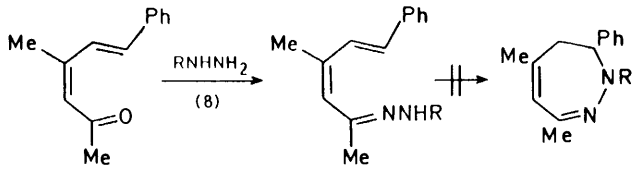

pyrazole (6).[2] It has been suggested that this reaction involves hydrolytic ring opening followed by an intramolecular Michael addition and a retro-aldol cleavage. The formation of the pyrazoline (4) from (3d) can be rationalised by a similar mechanism (Scheme 2). A low yield of an analogous pyrazoline was also isolated from the reaction of (1) with ethyl carbazate. These diazepine ⟶ pyrazoline conversions have not been investi-

gated in any depth; their study is complicated by the fact that the pyrazolines are also quite readily susceptible to acid-catalysed decomposition so their isolation is strongly dependent on the reaction conditions. For example, although both (3a) and (3d) are rapidly decomposed by 5% v/v hydrochloric acid in ethanol, only the latter gives any isolable pyrazoline.



SCHEME 2

We also examined the reactions of 4-methyl-6-phenylhexa-3,5-dien-2-one (7) with acetyl- and methanesulphonyl-hydrazides. This dienone when reacted with *p*-toluenesulphonylhydrazide gave a tosylhydrazone (9a) which could not be cyclised to a diazepine.[1] It was suggested that this might be due to steric inhibition of cyclisation by the phenyl group since it is known that Michael reactions are sensitive to steric effects. Thus it seemed worthwhile to react (7) with these less bulky



R

a; *p*-$MeC_6H_4SO_2$

b; $MeSO_2$

c; MeCO

hydrazides (8b and c) to see if the hydrazones (9b and c) were equally resistant to cyclisation. In the event they were, so it is still not clear whether it is the bulk of the phenyl group or its electronic effect which prevents ring closure. Attempts to prepare the 6-cyclohexyl analogue of (7) were not fruitful.

This work has shown that the reaction in Scheme 1 provides a route to a variety of 3,4-dihydro-1,2-diazepines with differing 2-substituents; the yields in some cases are moderate but the disadvantage of this is offset by the ready availability of the starting materials and the ease of carrying out the reaction.

## EXPERIMENTAL

N.m.r. spectra were run in deuteriochloroform and chemical shifts are recorded in δ from $SiMe_4$. All cyclisation reactions were carried out under nitrogen and in the dark. The unsaturated aldehydes and ketones were prepared as described earlier.[1]

*Reactions of 4-Methylhexa-3,5-dien-2-one* (1) *with Hydrazides.*—(i) *Benzenesulphonylhydrazide.* 4-Methylhexa-3,5-dien-2-one (0.50 g, 4.55 mmol), benzenesulphonylhydrazide (0.78 g, 4.54 mmol), and concentrated hydrochloric acid (0.25 ml) in ethanol (8 ml) were stirred overnight at room temperature. The white precipitate (0.78 g, 65%) was filtered off and recrystallised from ethanol to give *2-benzenesulphonyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine* (0.65 g, 54%) m.p. 132—133 °C (Found: C, 59.2; H, 6.2; N, 10.6. $C_{13}H_{16}N_2O_2S$ requires C, 59.1; H, 6.1; N, 10.6%); $\delta_H$ 1.88 (s, 5-Me), 2.00 (s, 7-Me), 2.60 (t, *J* 6 Hz, 4-$H_2$), 3.39 (t, *J* 6 Hz, 3-$H_2$), 5.65 (br s, 6-H), and 7.35—8.1 (m, aromatic, 4 H).

(ii) *Methanesulphonylhydrazide.* 4-Methylhexa-3,5-dien-2-one (1.00 g, 9.10 mmol), methanesulphonylhydrazide (1.00 g, 9.10 mmol), and concentrated hydrochloric acid (0.5 ml) in ethanol (15 ml) were stirred for 2 h at room temperature. Removal of the solvent by evaporation under reduced pressure gave an oil (1.95 g) which was chromatographed to give *2-methanesulphonyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine* (1.1 g, 60%), m.p. 73—73.5 °C (from ethanol–hexane) (Found: C, 47.2; H, 6.9; N, 13.7. $C_8H_{14}N_2O_2S$ requires C, 47.5; H, 6.7; N, 13.8%); $\delta_H$ 1.90 (s, 5-Me), 2.06 (s, 7-Me), 2.62 (t, *J* 7 Hz, 4-$H_2$), 2.98 (s, $SO_2Me$), 3.58 (t, *J* 7 Hz, 3-$H_2$), and 5.70 (s, 6-H).

(iii) *Benzoylhydrazide.* (a) *In the presence of acid.* 4-Methylhexa-3,5-dien-2-one (0.50 g, 4.55 mmol), benzoylhydrazide (0.62 g, 4.55 mmol), and concentrated hydrochloric acid (0.25 ml) in ethanol (8 ml) were stirred for 4 h at room temperature. The solvent was removed by evaporation under reduced pressure at room temperature and the residual oil was chromatographed on silica to give *2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine* (0.46 g, 44%), m.p. 44—46 °C (from hexane) (Found: C, 73.8; H, 7.2; N, 12.1. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3%); $\delta_H$ 1.95 (s, 5-Me), 2.03 (s, 7-Me), 2.60 (t, *J* 5 Hz, 4-$H_2$), 3.92 (t, *J* 5 Hz, 3-$H_2$), 5.71 (s, 6-H), and 7.1—8.7 (m, aromatic, 5 H); $\nu_{max.}$ (Nujol) 1 645 $cm^{-1}$ (C=O). Further elution gave an intractable tar (0.35 g).

A similar reaction using double the above quantities in which the product mixture was heated (*ca.* 60 °C) during evaporation of the solvent gave 2-benzoyl-3,4-dihydro-5,7-diazepine (37%): 1-benzoyl-3-methyl-2-pyrazoline (15%), m.p. and mixed m.p. 98—99 °C (lit.,[3,4] 98.5—99 °C); $\delta_H$ 2.01 (br s, 3-Me), 2.80 (t, *J* 9 Hz, 4-$H_2$), 4.06 (t, *J* 9 Hz, 5-$H_2$), and 7.1—7.9 (m, aromatic, 5 H); $\nu_{max.}$ (Nujol) 1 620 $cm^{-1}$ (C=O): benzoylhydrazide (8%): and polymeric material (0.88 g). In a control experiment the diazepine (0.20 g, 0.807 mmol), benzoylhydrazide (0.12 g, 0.882 mmol), and concentrated hydrochloric acid (0.2 ml) in ethanol (4 ml) were refluxed for 1 h. Evaporation of the solvent under reduced pressure and chromatography of the residue gave 1-benzoyl-3-methyl-2-pyrazoline (0.092 g, 56%), m.p. and mixed m.p. 98—99 °C. A similar reaction in the absence of benzoylhydrazide did not give the pyrazoline.

(b) *In the absence of acid.* 4-Methylhexa-3,5-dien-2-one (1.00 g, 9.10 mmol) and benzoylhydrazide (1.24 g, 9.11 mmol) in ethanol (15 ml) were stirred overnight at room

temperature. The usual work-up and chromatography on silica gave 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.24 g, 12%), m.p. 44—46 °C: *4-methylhexa-3,5-dien-2-one benzoylhydrazone* (0.54 g, 26%) as yellow needles, m.p. 112 °C (from ethanol) (Found: C, 73.5; H, 7.2; N, 12.3. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3%); $\delta_H$ 1.85—2.15 (2 × Me), 4.7—6.5 (m, olefinic, 4 H), and 7.3—8.0 (m, aromatic, 5 H); $\nu_{max.}$ (Nujol) 3 200 (N–H) and 1 650 $cm^{-1}$ (C=O): and unreacted benzoylhydrazide (0.67 g, 54%). The benzoylhydrazone (0.10 g) and concentrated sulphuric acid (2 μl) in ethanol (0.5 ml) were stirred at room temperature for 4 h. The usual work-up and chromatography gave 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.06 g, 60%).

(iv) *Acetylhydrazide.* A reaction as in (ii) above but using acetylhydrazide (0.68 g, 9.18 mmol) gave *2-acetyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine* (0.70 g, 46%) as a yellow oil (Found: C, 64.8; H, 8.5; N, 17.1. $C_9H_{14}N_2O$ requires C, 65.0; H, 8.5; N, 16.85%); $\delta_H$ 1.88 (s, 5-Me), 2.10 (s, 7-Me), 2.19 (s, COMe), 2.41 (t, *J* 5 Hz, 4-$H_2$), 3.79 (t, *J* 5 Hz, 3-$H_2$), and 5.65 (s, 6-H); $\nu_{max.}$ (film) 1 660 $cm^{-1}$ (C=O): and polymeric material (0.61 g).

(v) *Ethyl carbazate.* A similar reaction using ethyl carbazate (0.95 g, 9.13 mmol) and cold work-up gave *ethyl 3,4-dihydro-5,7-dimethyl-1,2-diazepine-2-carboxylate* (0.76 g, 43%) as a yellow oil (Found: C, 61.1; H, 8.0; N, 14.2. $C_{10}H_{16}N_2O_2$ requires C, 61.2; H, 8.2; N, 14.3%); $\delta_H$ 1.28 (t, *J* 6 Hz, $CH_2Me$), 1.89 (s, 5-Me), 2.12 (s, 7-Me), 2.50 (t, *J* 5 Hz, 4-$H_2$), 3.75 (t, *J* 5 Hz, 3-$H_2$), 4.20 (q, *J* 6 Hz, $CH_2Me$), and 5.70 (s, 6-H); $\nu_{max.}$ (film) 1 700 $cm^{-1}$ (C=O): *ethyl 3-methyl-2-pyrazoline-1-carboxylate* (0.09 g, 6%) as an oil (Found: $M^+$, 156.089 620. $C_7H_{12}N_2O_2$ requires *M*, 156.089 872); $\delta_H$ 1.30 (t, *J* 9 Hz, $CH_2Me$), 2.04 (d, *J* 0.5 Hz, 3-Me), 2.80 (t, *J* 9 Hz, 4-$H_2$), 3.85 (t, *J* 9 Hz, 5-$H_2$), and 4.25 (q, *J* 9 Hz, $CH_2Me$); $\nu_{max.}$ (film) 1 690 $cm^{-1}$ (C=O): and polymeric material (0.75 g).

*Reaction of 4-Methylhexa-3,5-dien-2-one with Phenylhydrazine.*—The ketone (0.20 g, 1.82 mmol) was added to a solution of phenylhydrazine hydrochloride (0.524 g, 3.64 mmol) and sodium acetate (0.79 g) in water (10 ml) and the mixture was stirred for 12 h at room temperature. The mixture was extracted with ether (3 × 10 ml), the ether solution was dried and evaporated under reduced pressure, and the residue was chromatographed on alumina to give *3,4-dihydro-5,7-dimethyl-2-phenyl-1,2-diazepine* (0.078 g, 21%) as a colourless oil (Found: $M^+$, 200.131 290. $C_{13}H_{16}N_2$ requires *M*, 200.131 342); $\delta_H$ 1.91 (s, 5-Me), 2.14 (s, 7-Me), 2.61 (t, *J* 6 Hz, 4-$H_2$), 3.68 (t, *J* 6 Hz, 3-$H_2$), 5.74 (m, 6-H), and 6.65—7.35 (m, aromatic, 5 H); and *4-methylhexa-3,5-dien-2-one phenylhydrazone* (0.166 g, 46%) as a colourless oil, readily oxidised in air (Found: $M^+$, 200.130 162. $C_{13}H_{16}N_2$ requires *M*, 200.131 342); $\delta_H$ 1.99 (s, Me), 2.23 (s, Me), 5.13 (br d, *J* 11 Hz, 6-H), 5.32 (br d, *J* 17 Hz, 6-H), 5.95 (br s, 3-H), 6.49 (dd, *J* 17 and 11 Hz, 5-H), and 6.75—7.5 (m, aromatic, 5 H).

*Reactions of other Unsaturated Ketones with Hydrazides.*—*4-Methyl-6-phenylhexa-3,5-dien-2-one.* Reactions with methanesulphonylhydrazide and acetylhydrazide under the conditions of (ii) above gave only the hydrazones in 86 and 85% yields respectively. The *methanesulphonylhydrazone* had m.p. 137—138 °C (from ethanol) (Found: C, 60.3; H, 6.5; N, 10.1. $C_{14}H_8N_2O_2S$ requires C, 60.4; H, 6.5; N, 10.1%); $\delta_H$ 1.99 (s, 2-Me), 2.20 (d, *J* 0.5 Hz, 4-Me), 3.11 (s, $SO_2Me$), 5.99 (d, *J* 0.5 Hz, 3-H), and 6.73 (br s, 3-H); $\nu_{max.}$ (Nujol) 3 210 $cm^{-1}$ (N–H). The *acetylhydrazone* had m.p. 147—148.5 °C (from ethanol) (Found: C, 74.2; H, 7.5; N, 11.6. $C_{15}H_{18}N_2O$ requires C, 74.35; H, 7.5; N, 11.6%); $\delta_H$ 2.00 (s, 2-Me), 2.25 (d, *J* 0.5 Hz, 5-Me), 2.30 (s, COMe), 5.97 (d, *J* 0.5 Hz, 4-H), and 6.75 (br s, 3-H); $\nu_{max.}$ (Nujol) 3160 (N–H), 1660 $cm^{-1}$ (C=O).

Attempts to cyclise these hydrazones using hydrochloric acid, *p*-toluenesulphonic acid, boron trifluoride, and DBU in a variety of solvents were not successful.

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