

# Interaction between fixed geometry $\alpha$ , $\beta$ -unsaturated ketones with phenylhydrazine

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The condensation reaction between benzaldehyde and bicyclo[3.3.1]nonanones in the presence of solid NaOH performed upon grinding without any solvent resulted in the corresponding  $\alpha$ ,  $\beta$ -unsaturated derivatives. These compounds were used as precursors for fused pyrazole and bicyclo[3.3.1]nonane derivatives.

**Key words:** bicyclo[3.3.1]nonane, Claisen-Schmidt reaction, pyrazole

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## INTRODUCTION

Substituted pyrazoles are widely found as the core structures in a large variety of compounds and they can be used as very versatile ligands for bioinorganic and coordination chemistry as well as for organometallics [1], or in OLED technology [2]. They also exhibit a broad spectrum of biological properties such as antimicrobial, antiviral, anticancer activities [3–5]. On the other hand, bicyclo[3.3.1]nonane derivatives have V-shape geometry. This peculiarity can be employed to form supramolecular structures [6], may be used in drug research [7, 8], and these compounds represent one of the most versatile type of ligands, that can coordinate to a wide variety of elements [9]. Classical methods for the synthesis of substituted pyrazoles involve approaches based on the condensations of hydrazines with either 1,3-dicarbonyl or

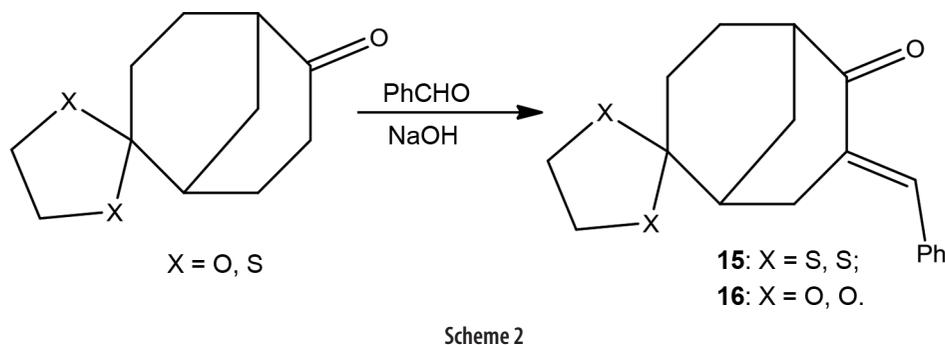
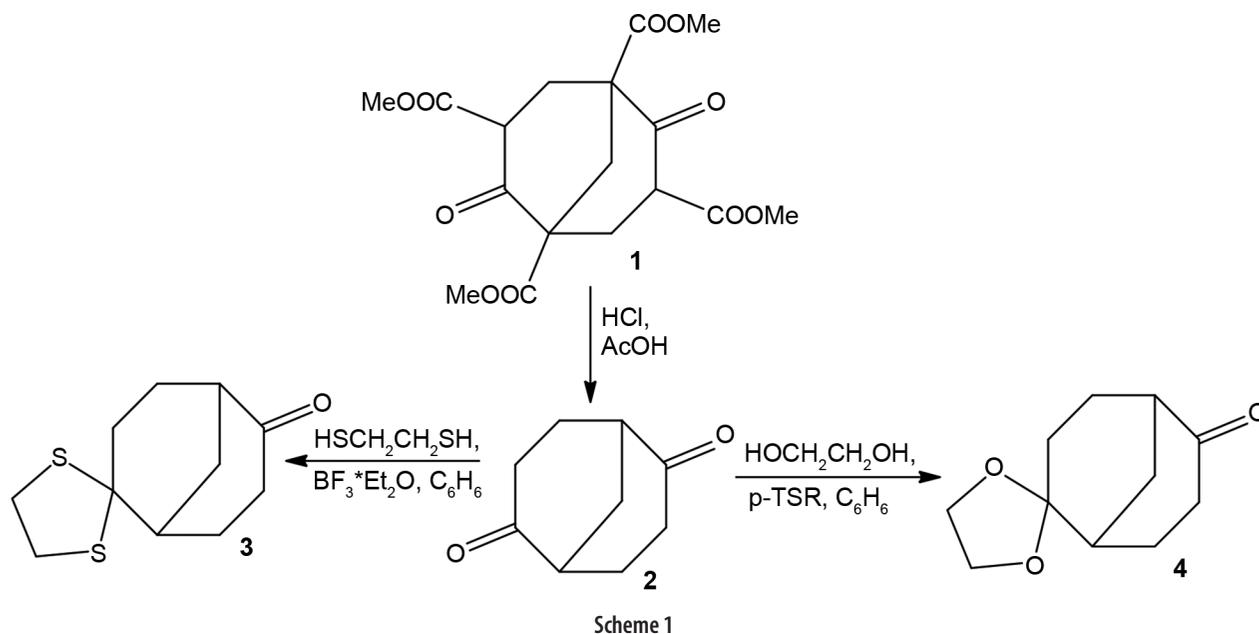
$\alpha$ ,  $\beta$ -unsaturated compounds [10–13]. Despite the fact that the amount of literature to this problem is huge, some synthetic aspects remain to be studied. For example, there is rather little known about the synthesis of pyrazole derivatives containing fused bicyclic or carcass structures. Hence, we employed the  $\alpha$ ,  $\beta$ -unsaturated bicyclodiketones and Meerwein's ester as a useful precursor for synthesis of pyrazoles.

## RESULTS AND DISCUSSION

The starting compounds (2–4), several derivatives of bicyclo[3.3.1]nonanone were synthesized from Meerwein's ester (1) using standard procedures [14] (Scheme 1).

There are several ways to form  $\alpha$ ,  $\beta$ -unsaturated ketones [15–19], but for our purposes the most promising way was the condensation reaction since it can be easily adapted to the solid phase format. The crossed-aldol reaction of ketone with benzaldehyde (5) in the presence of an equimolar amount

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of solid NaOH upon grinding without any solvent afforded the corresponding  $\alpha$ ,  $\beta$ -unsaturated ketones (15–21, 24, 25) (Schemes 2 and 3) in moderate to good yields (Table).

The basic conditions of the reaction mixture did not alter the blocking groups. This may be confirmed by NMR data of condensation products (15, 16). As expected, in  $^1\text{H}$  NMR spectra of 15 and 16 the blocking groups signals appear as multiplets at 3.30–3.39 ppm and 3.94–4.06 ppm, respectively,

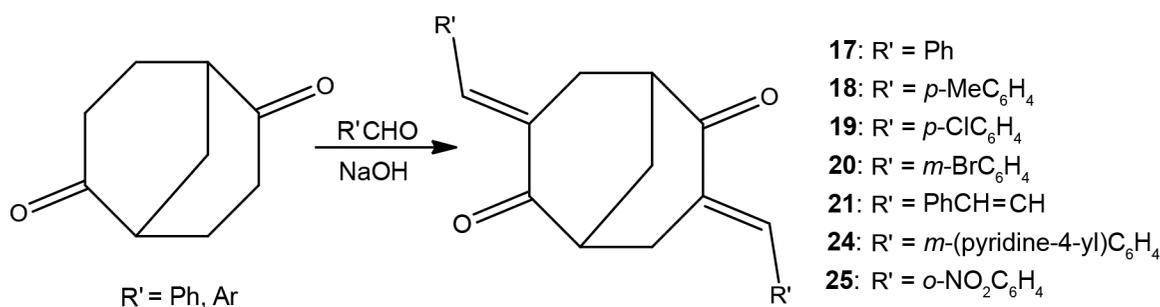
and the singlet of proton ( $\text{Ph}-\text{CH}=\text{C}$ ) was observed at 7.60 ppm and 7.63 ppm, respectively. The presence of a carbonyl group in compounds 15 and 16 was confirmed by IR spectral data (absorption band at  $1674\text{ cm}^{-1}$  in both cases).

Further we examined the limitations of Claisen-Schmidt condensation reactions without any solvent by using different benzaldehydes 5–14 (Table). *Bis*-aryldenes 17–21, 24 and 25 were formed in different yields (Table).

Table. Solventless NaOH catalyzed synthesis of  $\alpha$ ,  $\beta$ -unsaturated ketones

Comp. No.	Aldehyde No.	Aldehyde, m. p., °C	Ketone No.	Time, min	Yield <sup>a</sup> , %	Product, m. p., °C
15	PhCHO (5)	–26	3	6	78	156–158
16	PhCHO (5)	–26	4	6	54	149–150
17	PhCHO (5)	–26	2	5	92	194–196 <sup>b,c</sup>
18	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CHO (6)	–6	2	6	68	172–175
19	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO (7)	45–50	2	10	31	208–211
20	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CHO (8)	18–21	2	10	49	133–136 <sup>c</sup>
21	PhCH=CHCHO (9)	–7.5	2	5	90	245–246 <sup>b,d</sup>
22	<i>p</i> -(Me) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CHO (10)	74	2	20	–	–
23	PhC≡CCHO (11)	75 <sup>e</sup>	2	20	–	–
24	<i>m</i> -(pyridine-4-yl)C <sub>6</sub> H <sub>4</sub> CHO (12)	163	2	15	14	200–201
25	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO (13)	43	2	15	19	92–93
26	8-nitroquinolin-7-carbaldehyde (14)	168–171	2	20	–	–

<sup>a</sup> Isolated yields; <sup>b</sup> [15]; <sup>c</sup> [18]; <sup>d</sup> isolated analytical sample for  $^1\text{H}$  NMR spectra; <sup>e</sup> b. p. (°C)/20 mmHg



Scheme 3

Using this modified method 3,7-dibenzylidenbicyclo[3.3.1]nonane-2,6-dione (17) and 3,7-dicinamilidenbicyclo[3.3.1]nonane-2,6-dione (21) were obtained in 92% and 90% yields, respectively, that are comparable or even better than the ones obtained in classical methods [15].

The yield of the product depends on the state of starting compounds. The condensation reaction between bicyclo[3.3.1]nonanone and liquid aldehydes (5–6, 8, 9) afforded products in a higher yield than between bicyclo[3.3.1]nonanone and solid aldehydes (7, 12, 13). Such drop of the yield may be caused by several factors. Despite the differences in reactivity by itself, grinding the mixture of three solid components might not ensure optimal reaction media and prolonged grinding is required. Moreover, due to the heterogeneity of the reaction mixture the self condensation and Cannizzaro reactions may occur in elevated ratio. This may explain the formation of side products such as *bis*(2-nitrobenzyl)ether (25a) (Scheme 4).

The synthesis of *bis*-benzylidene derivatives 22, 23 from 4-dimethylaminobenzaldehyde (10) and 3-phenyl-2-propenal (11) was less consistent. The complex mixtures of products were formed, and due to very low solubility in the most of the solvents individual compounds were not separated.

Even light oxidative properties bearing nitro compounds – 2-nitrobenzaldehyde (13) and 8-nitro-7-quinolin-

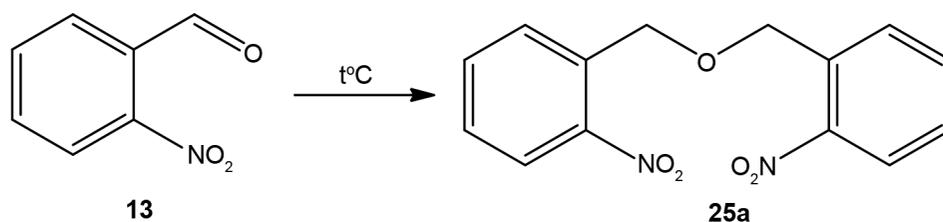
carbaldehyde (14) caused deflagration of the reaction mixture and target compounds were formed in very low yield or have not been formed at all.

In the <sup>1</sup>H NMR spectra shifts of the proton (Ph-CH=) of all the bis(arylidene)bicyclo[3.3.1]nonane-2-ones (15–21, 24 and 25) fall into the 7.44–7.81 ppm interval [18, 20]. The IR spectra of these compounds displayed absorption bands at 1683 cm<sup>-1</sup> which are typical for  $\alpha$ ,  $\beta$ -unsaturated ketones.

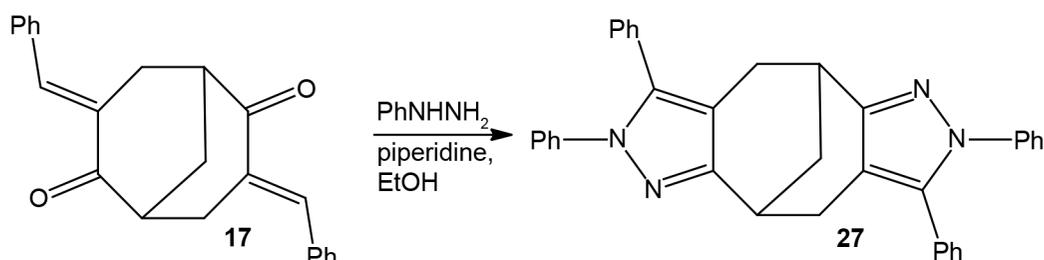
Attempts to synthesize pyrazoles from 3,7-dibenzylidenbicyclo[3.3.1]nonane-2,6-dione (17) and phenylhydrazine under acidic or neutral conditions were unsuccessful. The reaction proceeded only in the presence of piperidine (Scheme 5).

The prolonged reflux time was needed to obtain cyclization. Product 27 was formed in 23% yield. Such a low yield can be explained by low reactivity of  $\alpha$ ,  $\beta$ -unsaturated ketone and oxidation of phenylhydrazine.

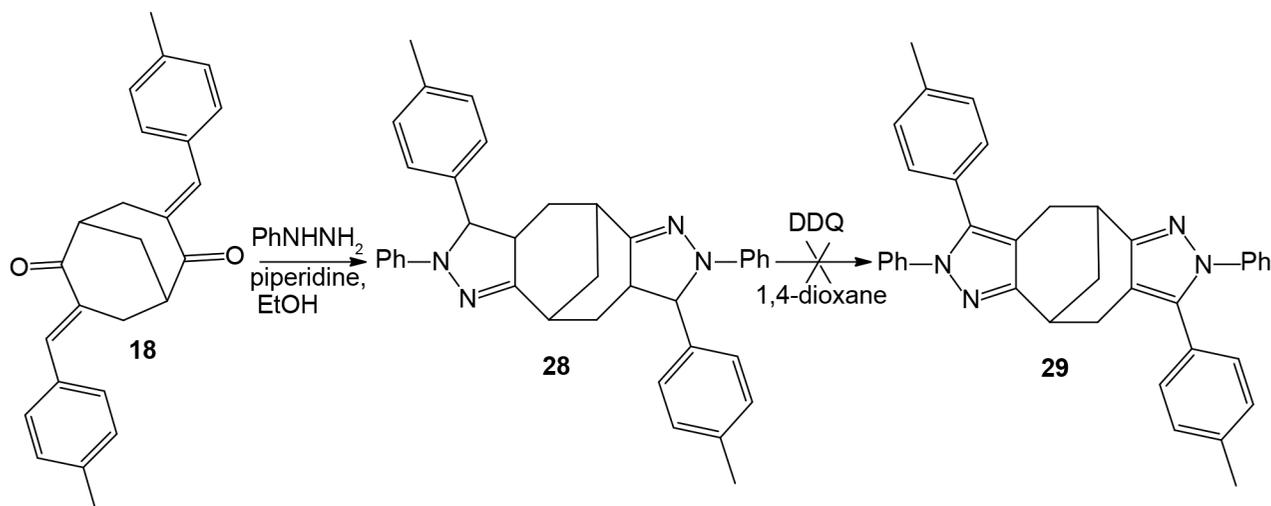
3,7-diarylidenebicyclo[3.3.1]nonane-2,6-dione 18 reacted with phenylhydrazine in the same manner as the above mentioned and delivered corresponding products 28. The fused products 28 precipitated during the reaction in low yield (14%). In contrast to the above mentioned case, the product (28) has not been oxidized and was separated as dihydropyrazoles (Scheme 6). Moreover, attempts to perform the dehydrogenation of compounds 28 with 2 equiv. of



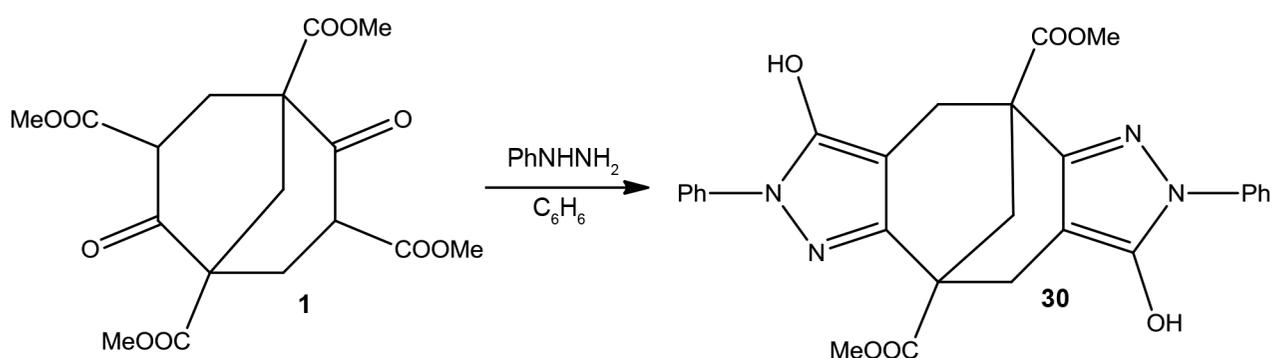
Scheme 4



Scheme 5



Scheme 6



Scheme 7

2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane [21–25] failed and pyrazole **29** has not been formed.

The synthesis of pyrazoles from other *bis*-benzylidene derivatives (**15–16**, **19–21**, **24–25**) was unsuccessful. Variation of such reaction conditions as solvents (2-propanol, 1,4-dioxane), reaction duration and the ratio of phenylhydrazine and *bis*-benzylidenes did not give the desired product. In all cases the starting *bis*-benzylidene derivatives (**15–16**, **19–21**, **24–25**) were recovered.

The  $\beta$ -ketoesters can be used for synthesis of pyrazole derivatives [26] too. The condensation reaction of the so-called “Meerwein ester” (**1**) with phenylhydrazine was performed in the benzene without any catalyst (Scheme 7).

The result of this reaction was the dimethyl-di(3-hydroxy-*N*-phenyl)pyrazol[2,3-*c*:6,7-*c'*]bicyclo[3.3.1]nonane-1,5-carboxylate (**30**). The di-fused product **30** was poorly soluble in usual solvents. The presence of a hydroxy group in **30** was proved by IR (absorption band at  $3044\text{ cm}^{-1}$ ).  $^{13}\text{C}$  NMR and elemental analysis data are also consistent with the structure of **30**.

## EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer FT-IR spectrometer Spectrum BX II in KBr.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Unity Inova spectrometer at 300 and

75 MHz, respectively, using residual signals of solvents as an internal standard. Melting points were determined in open capillaries with a Gallenkamp apparatus and are uncorrected. Elemental analysis was performed with a Flash 2000 CHNS-O analyzer (Thermo Fisher Scientific). Column chromatography was performed using Silica gel 60 (0.040–0.063 mm) (Merck). All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F254 aluminum plates (Merck). Visualization was accomplished by UV light or with *p*-anisaldehyde and basic potassium permanganate solutions. Meerwein ester [15], bicyclo[3.3.1]nonane-2,6-dione [15], 6,6-ethylene-dioxybicyclo[3.3.1]nonan-2-one [27], 6,6-ethylene-dithiobicyclo[3.3.1]nonan-2-one [28], 8-nitro-7-quinolincarbaldehyde [29], 3-phenyl-2-propynal [30] were synthesized according to the reported procedures. Benzaldehydes and phenylhydrazine are commercially available.

### General procedure for the preparation of substituted-benzylidenebicyclo[3.3.1]nonanones

A mixture of bicyclo[3.3.1]nonanone derivative (1 mmol), aldehyde (2.5 mmol) and solid NaOH (2 mmol) was ground with a mortar and pestle at room temperature under the hood (Table). The reaction mixture was poured into 5% HCl solution, extracted with benzene ( $3 \times 20\text{ ml}$ ). The organic layer was dried over anhydrous  $\text{CaCl}_2$ . The solvent was

evaporated under reduced pressure. The solid residue was purified by flash chromatography on silica gel.

**3-benzylidene-6,6-ethylenedithiobicyclo[3.3.1]nonane-2-one (15).** Eluent toluene ( $R_f = 0.22$ ), yield 0.240 g (78%), white powder, melting point 156–158 °C. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2910 (C-H), 2864 (S-CH<sub>2</sub>), 1674 (C=C-C=O), 1585 (C=C), 1429 (S-CH<sub>2</sub>), 708 (phenyl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 1.96–2.23 (m, 6H, CH<sub>2</sub>), 2.37 (dd,  $J = 14.0$  Hz,  $J = 2.9$  Hz, 1H, CH<sub>2</sub>), 2.51–2.55 (m, 1H, CH<sub>2</sub>), 2.70–2.71 (m, 1H, CH), 3.09 (ddd,  $J = 18.4$  Hz,  $J = 7.5$  Hz,  $J = 3.1$  Hz, 1H, CH-C=O), 3.30–3.39 (m, 4H, SCH<sub>2</sub>CH<sub>2</sub>S), 7.36–7.55 (m, 5H, phenyl), 7.59–7.61 (m, 1H, benzylidene); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 30.6, 30.9, 34.1, 36.6, 38.7, 39.7, 42.0 (SCH<sub>2</sub>CH<sub>2</sub>S), 42.4 (SCH<sub>2</sub>CH<sub>2</sub>S), 74.2, 128.7, 129.2, 131.1, 134.6, 135.7, 136.6, 204.5 (C=O); Anal. calcd. for C<sub>18</sub>H<sub>20</sub>OS<sub>2</sub> (316.48): C, 68.31%; H, 6.37%; S, 20.26; Found: C, 68.15%; H, 6.42%; S, 20.32.

**3-benzylidene-6,6-ethylenedioxybicyclo[3.3.1]nonane-2-one (16).** Eluent dry CH<sub>2</sub>Cl<sub>2</sub> ( $R_f = 0.17$ ), yield 0.110 g (54%), white powder, melting point 149–150 °C. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2947 (C-H), 1675 (C=C-C=O), 1587 (C=C), 1102 (C-O-C as), 1025 (C-O-C sym), 694 (phenyl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 1.65–1.77 (m, 2H, CH<sub>2</sub>), 1.93–1.98 (m, 2H, CH<sub>2</sub>), 2.09–2.32 (m, 4H, CH<sub>2</sub>), 2.63–3.27 (m, 2H, CH-C=O, CH), 3.97–4.04 (m, 4H, ethylenedioxy), 7.57–7.31 (m, 5H, phenyl), 7.63–7.68 (m, 1H, benzylidene); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 28.5, 28.6, 29.7, 36.3, 42.7, 64.5 (OCH<sub>2</sub>CH<sub>2</sub>O), 64.6 (OCH<sub>2</sub>CH<sub>2</sub>O), 110.0 (O-CRR'-O), 128.5, 128.9, 130.9, 134.4, 135.6, 136.7, 204.6 (C=O); Anal. calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>3</sub> (284.35): C, 76.03%; H, 7.09%; Found: C, 76.00%; H, 7.45%.

**3,7-dibenzylidenebicyclo[3.3.1]nonane-2,6-dione (17).** Eluent dry CH<sub>2</sub>Cl<sub>2</sub> ( $R_f = 0.28$ ), yield 0.301 g (92%), white powder, melting point 194–196 °C. The physicochemical and spectral characteristics of compound 17 correspond to those given in [15, 16].

**3,7-di-*p*-methylbenzylidenebicyclo[3.3.1]nonane-2,6-dione (18).** Eluent toluene ( $R_f = 0.30$ ), yield 0.244 g (68%), white powder, melting point 172–175 °C. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2920 (C-H), 1676 (C=C-C=O), 1584 (C=C), 789 (aryl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 2.39 (s, 6H, CH<sub>3</sub>), 2.45–4.47 (m, 2H, CH<sub>2</sub>), 3.05–3.15 (m, 4H, CH<sub>2</sub>), 3.25–3.36 (m, 2H, bridgehead CH), 7.19–7.24 (m, 4H), 7.30–7.35 (m, 4H), 7.54–7.57 (m, 2H, benzylidene); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 29.1, 34.7, 42.8, 64.8, 128.5, 129.1, 132.1, 132.5, 135.6, 137.8, 202.7 (C=O); Anal. calcd. for C<sub>25</sub>H<sub>24</sub>O<sub>2</sub> (356.46): C, 84.24%; H, 6.79%; Found: C, 84.11%; H, 6.51%.

**3,7-di-*p*-chlorbenzylidenebicyclo[3.3.1]nonane-2,6-dione (19).** Eluent toluene ( $R_f = 0.26$ ), yield 0.123 g (31%), white powder, melting point 172–175 °C. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2927 (C-H), 1682 (C=C-C=O), 1592 (C=C), 1093 (*p*-phenyl-Cl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 2.47–2.48 (m, 2H, CH<sub>2</sub>), 3.03–3.11

(m, 4H, CH<sub>2</sub>), 3.23–3.28 (m, 2H, bridgehead CH), 7.30–7.41 (m, 8H), 7.56 (d,  $J = 6.1$ , 2H, benzylidene); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 21.3, 34.6, 35.1, 127.9, 129.1, 134.6, 136.2, 137.3, 142.1, 202.3 (C=O); Anal. calcd. for C<sub>23</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>2</sub> (397.29): C, 69.53%; H, 4.57%; Cl, 17.85%; Found: C, 69.39%; H, 4.69%; Cl, 17.80%.

**3,7-di-*m*-brombenzylidenebicyclo[3.3.1]nonane-2,6-dione (20).** Eluent toluene ( $R_f = 0.15$ ), yield 0.240 g (49%), yellow powder, melting point 133–136 °C. The physicochemical and spectral characteristics of the obtained compound 20 correspond to those given in [16].

**3,7-dicinamylidenebicyclo[3.3.1]nonane-2,6-dione (21).** The product was recrystallized from ethanol, the yield 0.262 g (90%); light yellow powder, melting point 244–245 °C. The physicochemical characteristics of compound 21 correspond to those given in [15]. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2925 (C-H), 1667 (C=O), 1563 (C=C), 1575 (C=C), 974 (trans CH=CH), 752 (aryl); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 2.31–2.36 (m, 2H, CH<sub>2</sub>), 2.88–2.90 (m, 4H, CH<sub>2</sub>), 3.10–3.15 (m, 2H, bridgehead CH), 7.10–7.16 (m, 6H), 7.31–7.41 (m, 8H), 7.64 (d,  $J = 6.6$  Hz, 2H).

**3,7-di-*m*-(pyridin-4-yl)benzylidenebicyclo[3.3.1]nonane-2,6-dione (24).** Eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH (4 : 1) ( $R_f = 0.15$ ), yield 0.067 g (14%), yellowish powder, melting point 200–201 °C. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2919 (C-H), 1661 (C=O), 1594 (C=C), 1589 (C=N), 766 (aryl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 2.53 (s, 2H), 3.13–3.19 (m, 4H), 3.31–3.39 (m, 2H), 7.46–7.58 (m, 10H), 7.63 (m, 2H), 8.72 (d,  $J = 4.5$  Hz, 2H, benzylidene); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 29.1, 34.7, 42.9, 121.9, 128.1, 129.4, 129.7, 131.1, 132.9, 136.0, 138.4, 138.9, 147.9, 150.6, 202.7 (C=O); Anal. calcd. for C<sub>33</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> (482.57): C, 82.13%; H, 5.43%; N, 5.81%; Found: C, 82.05%; H, 5.60%; N, 5.90%.

**3,7-di-*o*-nitrobenzylidenebicyclo[3.3.1]nonane-2,6-dione (25).** Eluent dry CH<sub>2</sub>Cl<sub>2</sub> ( $R_f = 0.17$ ), yield 0.056 g (19%), yellow powder, melting point 92–93 °C. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2922 (C-H), 1673 (C=C-C=O), 1583 (C=C), 1515 (C-NO<sub>2</sub>), 1345 (C-NO<sub>2</sub>), 741 (aryl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 2.07–2.26 (m, 2H, CH<sub>2</sub>), 2.40–2.80 (m, 4H, CH<sub>2</sub>), 2.95–3.07 (m, 2H, bridgehead CH), 7.33–7.36 (m, 2H), 7.52–7.58 (m, 2H), 7.68–7.74 (m, 4H), 7.78 (d,  $J = 2.8$  Hz, 2H, benzylidene); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 26.9, 30.1, 31.8, 125.3, 129.7, 130.9, 131.1, 131.4, 132.6, 133.9, 135.9, 201.9 (C=O); Anal. calcd. for C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub> (418.39): C, 66.02%; H, 4.34%; N, 6.70%; Found: C, 66.12%; H, 4.61%; N, 6.54%.

**Bis-(2-nitrobenzyl)ether (25a).** Eluent toluene ( $R_f = 0.11$ ), yield 0.075 g (16%), melting point 160–161 °C. The physicochemical and spectral characteristics of compound 25a correspond to those given in [31].

**Di-(N,3-diphenylpyrazole[2,3-*c*:6,7-*c'*])bicyclo[3.3.1]nonane (27).** A mixture of di-benzylidenebicyclo[3.3.1]nonane derivative (1 mmol), phenylhydrazine (2.2 mmol) and 1 drop

of piperidine in ethanol was refluxed. The reaction mixture was refluxed for 20 h. The precipitate was collected by filtration and washed with ethanol (2 × 10 ml). The product was recrystallized from ethanol, the yield 0.076 g (15%); white powder, melting point 304–305 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 2 910 (C-H), 1 503 (heterocyclic ring), 772 (heterocyclic ring), 694 (phenyl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 2.25 (t, *J* = 2.7, 2H, CH<sub>2</sub>), 2.76 (d, *J* = 15.6 Hz, 2H, CH<sub>2</sub>), 3.07 (dd, *J* = 15.6 Hz, *J* = 5.4 Hz, 2H, CH<sub>2</sub>), 3.76 (d, *J* = 2.7, 2H, bridgehead CH), 7.23–7.75 (m, 20H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 26.7, 28.8, 29.7, 112.6, 125.3, 127.0, 127.7, 128.1, 128.7, 129.6, 133.9, 140.1, 142.8, 149.3 (C=N); Anal. calcd. for C<sub>35</sub>H<sub>28</sub>N<sub>4</sub> (504.62): C, 83.30%; H, 5.59%; N, 11.10%; Found: C, 83.40%; H, 5.71%; N, 11.23%.

**Di-(3-di-*p*-methylphenyl-N-phenyl-3,4-dihydropyrazol[2,3-*c*:6,7-*c'*])bicyclo[3.3.1]nonane (28).** A mixture of dibenzylidenebicyclo[3.3.1]nonane derivative (1 mmol), phenylhydrazine (2.2 mmol) and 1 drop of piperidine in ethanol was refluxed. The reaction mixture was refluxed for 8 h. The precipitate was collected by filtration and washed with ethanol (2 × 10 ml). The product was recrystallized from ethanol 0.050 g (14%); white powder, melting point 308–309 °C. IR (Kr)  $\nu$  (cm<sup>-1</sup>): 2 926 (C-H), 1 598 (C=N), 1 498 (heterocyclic ring), 750 (phenyl); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 1.93 (dd, *J* = 16.9 Hz, *J* = 7.9 Hz, 2H, CH<sub>2</sub>), 2.07 (m, 2H, CH<sub>2</sub>), 2.38 (s, 6H, CH<sub>3</sub>), 2.42–2.54 (m, 2H, bridgehead CH), 3.02 (td, *J* = 11.6 Hz, *J* = 8.0 Hz, 2H), 3.29–3.21 (m, 2H, PhCHCHC=N), 4.40 (d, *J* = 12.5 Hz, 2H, PhCH-N), 6.85 (t, *J* = 7.7 Hz, 4H, aryl), 6.97 (d, *J* = 8.8 Hz, 4H, aryl), 7.12–7.22 (m, 10H, phenyl), 7.27 (d, *J* = 8.2 Hz, 4H, aryl); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 21.4, 32.7, 35.7, 36.1, 54.7, 75.5, 115.4, 120.5, 126.2, 128.9, 130.1, 137.7, 138.3, 147.3, 156.1 (PhCH-N); Anal. calcd. for C<sub>37</sub>H<sub>36</sub>N<sub>4</sub> (501.50): C, 82.80%; H, 6.76%; N, 10.44%; Found: C, 82.65%; H, 6.70%; N, 10.32%.

**Dimethyl-di(3-hydroxy-N-phenyl)pyrazol[2,3-*c*:6,7-*c'*] bicyclo[3.3.1]nonane-1,5-carboxylate (30).** Meerwein ester (1, 1 mmol 0.384 g) was dissolved in 30 ml of toluene. Phenylhydrazine (2 mmol, 0.216 g) was added to the reaction mixture and refluxed for 16 h using a Dean-Stark water separation apparatus. The precipitate was collected by filtration and washed with toluene (2 × 10 ml). The crude product was purified by flash chromatography with silica gel eluting with EtOAc (R<sub>f</sub> = 0.35). The yield of the separated product 0.115 g (23%); white powder, melting point 312–315 °C. IR (nujol)  $\nu$  (cm<sup>-1</sup>): 2 924 (C-H), 1 736 (C=O), 1 597 (heterocyclic ring), 1 262 (C-O), 1 231 (C-O); 767 (heterocyclic ring), 693 (phenyl); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 2.48 (s, 2H, CH<sub>2</sub>), 3.00 (s, 4H, CH<sub>2</sub>), 3.72 (s, 6H, CH<sub>3</sub>), 7.24–7.64 (m, 10H, phenyl), 11.2 (s, 2H, OH); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 31.1, 37.7, 44.7, 52.9, 96.2, 121.7, 126.2, 129.5, 139.5, 149.3, 149.9, 174.2 (C=O); Anal. calcd. for C<sub>35</sub>H<sub>28</sub>N<sub>4</sub> (501.50): C, 64.79%; H, 4.83%; N, 11.19%; Found: C, 64.60%; H, 4.99%; N, 11.27%.

## CONCLUSIONS

In summary, the condensation reaction between various arylaldehydes (5–14) and bicyclo[3.3.1]nonanones (2–4) in the presence of solid NaOH without any solvent resulted in the corresponding  $\alpha$ ,  $\beta$ -unsaturated ketones (15–21, 24 and 25). Using this simple, fast, and easy to handle procedure, target compounds can be synthesized in up to gram scale. Unfortunately, this approach has more limitations – the best results were obtained when liquid aldehydes were used for condensation. Also compounds bearing oxidative properties should be avoided.

The fused bicycloderivatives 27, 28 and 30 were synthesized in mediocre yields. The aromatization of products and elevation of the yield is still a topic of research.

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## References

1. J. D. G. Paulo, A. Correia, M. P. C. Campello, I. Santos, *Polyhedron*, **23**, 331 (2004).
2. C. Q. Ma, L. Q. Zhang, J. H. Zhou, et al., *J. Mater. Chem.*, **12**, 3481 (2002).
3. O. Rosati, M. Curini, M. C. Marcotullio, et al., *Bioorg. Med. Chem.*, **15**, 3463 (2007).
4. Z. Sui, J. Guan, M. P. Ferro, et al., *Bioorg. Med. Chem.*, **10**, 601 (2000).
5. K. Y. Lee, J. M. Kim, J. N. Kim, *Tetrahedron Lett.*, **44**, 6737 (2003).
6. C. J. Wallentin, E. Orentas, M. T. Johnson, et al., *Cryst. Eng. Comm.*, **11**, 1837 (2009).
7. D. G. I. Kingston, D. J. Newman, *Curr. Opin. Drug Discovery Dev.*, **10**, 130 (2007).
8. T. Ganesh, A. Norris, S. Sharma, et al., *Bioorg. Med. Chem.*, **14**, 3447 (2006).
9. T. Godau, F. Platzmann, F. W. Heinemann, N. Burzlaff, *Dalton Trans.*, 254 (2009).
10. G. A. Nishiguchi, A. L. Rodriguez, J. A. Katzenellenbogen, *Bioorg. Med. Chem. Lett.*, **12**, 947 (2002).
11. A. J. Léavai, *Heterocyclic Chem.*, **3**, 1 (2002).
12. I. K. Moiseev, V. P. Konovalova, *Chem. Heterocycl. Compd.*, **4**, 528 (1982).
13. T. K. Shkineva, I. L. Dalinger, S. A. Shevelev, *Chem. Heterocycl. Compd.*, **31**, 509 (1995).
14. E. A. Shokova, V. V. Kovalev, *Russ. Chem. Rev.*, **80**, 927 (2011).
15. H. Meerwein, W. Schürmann, *Ann. Chem.*, **398**, 196 (1913).
16. H. Stetter, A. Reischl, *Chem. Ber.*, **93**, 1253 (1960).

17. A. F. M. Rahman, R. Ali, Y. Jahng, A. A. Kadi, *Molecule*, **17**, 571, (2012).
18. N. V. Averina, A. A. Semioschkin, G. S. Borisova, N. S. Zefirov, *Zh. Org. Khim.*, **33**, 550 (1997).
19. N. V. Averina, G. S. Borisova, A. A. Borisenko, N. S. Zefirov, *Zh. Org. Khim.*, **37**, 1010 (2001).
20. A. Hassner, T. C. Mead, *Tetrahedron*, **20**, 2201 (1964).
21. V. A. Chebanov, S. M. Desenko, T. W. Gurley, in: *Azaheterocycles Based on  $\alpha$ ,  $\beta$ -Unsaturated Carbonyls*, p. 37, Springer (2008).
22. A. Nakhai, J. Bergman, *Tetrahedron*, **65**, 2298 (2009).
23. K. Y. Lee, S. Gowrisankar, J. N. Kim, *Tetrahedron Lett.*, **46**, 5387 (2005).
24. R. K. Behera, A. K. Behera, R. Pradhan, A. Pati, M. Patra, *Synth. Commun.*, **36**, 3729 (2006).
25. C. Ainsworth, *Org. Synth.*, **39**, 27 (1959).
26. G. W. Craig, M. Eberle, C. Lamberth, T. Vettiger, *J. Prakt. Chem.*, **342**, 505 (2000).
27. S. Stončius, G. Bagdžiūnas, J. Malinauskienė, E. Butkus, *Chirality*, **20**, 337 (2008).
28. T. Doerner, R. Gleiter, T. A. Robbins, P. Chayangkoon, D. A. Lightner, *J. Am. Chem. Soc.*, **114**, 3235 (1992).
29. E. C. Riesgo, X. Jin, R. P. Thummel, *J. Org. Chem.*, **61**, 3017 (1996).
30. M. Journet, D. Cai, L. M. DiMichele, R. D. Larsen, *Tetrahedron Lett.*, **39**, 6427 (1998).
31. B. A. Gellert, N. Kahlcke, M. Feurer, S. Roth, *Chem. Eur. J.*, **17**, 12203 (2011).

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### **$\alpha$ , $\beta$ -NESOČIŪJŲ KARBONILINIŲ BICIKLINIŲ JUNGINIŲ SINTEZĖ IR JŲ SAŲVEIKA SU FENILHIDRAZINU**

#### *S a n t r a u k a*

$\alpha$ ,  $\beta$ -nesotieji karboniliniai bicikliniai junginiai buvo susintetinti atliekant reakcijas grūstuvėlyje be tirpiklio. Gautieji produktai toliau buvo kondensuojami su fenilhidrazinu rūgštiniėje ir neutralioje aplinkoje, bet tik šarminėje (esant piperidinui) terpėje buvo gauti norimi produktai. Gautų junginių išeigos mažos (maks. 20 %).