Synthesis of triacetonamine N-alkyl derivatives reinvestigated

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Dedicated to Professor Rainer Beckert on his 60th birthday

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Abstract

The N-alkylated 2,2,6,6-tetramethylpiperidin-4-ones 3c–f were prepared from the acetal 6a of triacetonamine (3a) by alkylation followed by hydrolysis of the acetal functionality or alternatively from the corresponding secondary alcohol 2,2,6,6-tetramethylpiperidin-4-ol (7a) by N-alkylation and subsequent oxidation to introduce the ketone unit. Direct alkylation of 3a was only possible by using highly reactive halides such as allyl or benzyl bromide with low yields. Treatment of phorone (5) with primary amines 2c–f with an alkyl group greater than methyl did not lead to the desired heterocycles 3c–f since open-chain addition products 8 and 9 were formed instead. Consequently, the reactions of acetone (1) with benzyl- or n-butylamine (2e,f) in the presence of calcium chloride did not generate the corresponding N-alkylated derivatives of 3a.

Keywords: N-Alkylation, 2-aminothiazoles, 2,2,6,6-tetramethylpiperidin-4-ones, ring closure, steric hindrance, tertiary amines

Introduction

Sterically hindered amines are important compounds because of a variety of applications. Such compounds and their metal salts are particularly useful as bases in synthesis.1 Furthermore, hindered amines play an important role as precursors to persistent nitroxy radicals, which were used for spin labeling methods.2 Such amines have recently come into industrial use in a variety of gas-treating processes.3

Numerous 2,2,6,6-tetramethylpiperidines of type 4 and free radicals derived from these heterocycles are polymerization inhibitors and thermo- and photostabilizers, known as hindered amine light stabilizers and abbreviated as HALS (Scheme 1).4 Triacetonamine (3a) is the unique starting compound for the synthesis of the desired products 4.5 The piperidine derivative 3a can
be prepared from acetone (1) and ammonia (2a) in the presence of an acidic catalyst like calcium chloride$^6$ or from phorone$^7$ (5) and 2a or by other methods.$^8$ It was claimed that treatment of 1 with 2b, 2e, or 2f led analogously to 3b,e,f in 30, 85, and 15% yield, respectively.$^9$ On the other hand, it was reported that the heterocycles 3b–e can be prepared from 5 and primary amines 2b–e.$^{7a,b}$ Whereas synthesis of 3b from 5 and 2b was repeated by other authors several times,$^{10}$ the isolation of 3e after the generation from 5 and 2e was described recently to be problematic.$^{11}$

The reports on the N-alkylation of 3a are also contradictory. Methylation of 3a with the help of methyl iodide was successfully performed repeatedly,$^{12}$ while attempted methylation of 3a with formaldehyde and formic acid failed.$^{12a}$ Introduction of more bulky substituents meets with increasing steric resistance. Thus, treatment of 3a with ethyl iodide was reported to give complicated mixtures of products instead of desired 3c.$^{13}$ However, other authors claimed that the reaction of 3a with ethyl iodide or allyl bromide led to the corresponding hydrohalides of 3c and 3d, respectively.$^{14}$ On the other hand, N-alkylation of 2,2,6,6-tetramethylpiperidines 4, which do not possess an oxo group in 4-position, for example, 4a, is more easily achieved.$^{15}$

![Scheme 1. Syntheses of 2,2,6,6-tetramethylpiperidines.](image)

The aim of our work was to prepare the heterocycles 3c–f by novel methods and to prove unequivocally their structures by spectroscopic data since these compounds were previously characterized only by elemental analyses and melting points of derivatives in most cases. Moreover, we wanted to clarify whether 3c–f can be synthesized from 1 and 2 in the presence of acidic catalysts or by treatment of 5 with the corresponding primary amines 2.

**Results and Discussion**

We prepared the N-alkylated product 6c by treating the acetal 6a, which was easily available from ketone 3a,$^{16}$ with ethyl iodide in toluene in the presence of calcium carbonate (Scheme 2). Subsequent hydrolysis of 6c led to the triacetonamine derivative 3c. We tried also another route to get the product 3c because alkylation of 6a was only possible at high temperature and with low yield. The alcohol 7a, which is conveniently accessible from 3a,$^{12a}$ was subjected to ethyl
iodide and sodium carbonate in boiling methanol to afford pure 7c as described previously.\textsuperscript{17} When this method was transferred to the reaction of 7a with allyl bromide, n-butyl iodide, or benzyl bromide, the respective alkylation products 7d, 7e, and 7f were obtained as pure solids. Attempts to use other procedures for the synthesis of 7d,\textsuperscript{18} 7e,\textsuperscript{19} and 7f\textsuperscript{20} led only to crude mixtures of starting compounds and products. Oxidation of 7c–f with the help of Jones reagent furnished the desired N-alkylated triacetonamines 3c–f in moderate yields and high purity. These compounds were unequivocally characterized not only by elemental analyses but also by $^1$H and $^{13}$C NMR spectroscopic data for the first time.

![Scheme 2. Synthesis of N-alkylated triacetonamines 3c-f.](image-url)

In subsequent investigations, we treated phorone (5) with ammonia (2a) and the primary amines 2b–f as described several times in the literature (Scheme 3).\textsuperscript{7a,b,10,11} Surprisingly, we observed a product with piperidine structure only in the reactions with ammonia (2a) and with methylamine (2b). Even in these cases, the $^1$H and $^{13}$C NMR spectra of the crude reaction mixtures indicated that not only the desired heterocycles 3a and 3b but also the unstable simple addition products 8a and 8b were formed. Whereas treatment of 5 with 2a led to the main product 3a and only small amounts of 8a, the products 3b and 8b resulted from 5 and 2b in an approximate 3:2 ratio. Previously, in the unsuccessful attempt to methylate 3a with the help of formaldehyde and formic acid,\textsuperscript{12a} 8b was postulated to be an elusive intermediate to the final product phorone (5). When 5 was subjected to ethylamine (2c), we detected 8c as the only product in 80% yield. This result is contrary to an early report on the synthesis of isomeric 3c from 5 and 2c. In that report,\textsuperscript{7a,b} however, the product could be characterized only by the melting point (157–158 °C) and the elemental analysis of the corresponding chloroplatinate. When we prepared the hexachloroplatinates of 3c and 8c, we obtained substances with melting points of 150–157 and 147–152 °C, respectively. Although these melting points are relatively similar to each other and to the reported\textsuperscript{7a,b} value, a mixture of both substances showed a significant
melting point depression. Furthermore, NMR spectra indicated quite different compounds, which included a piperidin-4-one and an open-chain 6-aminohept-2-en-4-one structure.

On treatment of 5 with the amines 2d, 2e, or 2f, we got always mixtures of open-chain addition products 8 and 9 but no heterocycle of type 3. Thus, the reaction of allylamine (2d) afforded 8d (36% yield) and 9d (36%), whereas benzylamine (2e) led to 8e (29%) and 9e (58%), and n-butylamine (2f) gave 8f (31%) and 9f (41%). The separation of the amines 8 and diamines 9 proved to be difficult. For example, vacuum distillation was not possible because both compounds tended to cleave off the corresponding primary amine, which resulted in the formation of 5. Nevertheless, we were able to characterize these open-chain addition products for the first time. In previous reports, the generation of open-chain adducts of 2e and 5 was postulated to explain byproducts and decay products in the supposed synthesis of 3e from benzylamine and phorone.7a,b,11 Our results indicate that it will be difficult to prepare N-alkylated triacetonamines from 5 and primary amines RNH₂ if the substituents R are more bulky than methyl.

\[
\begin{align*}
\text{O} & \quad + \quad \text{RNH}_2 \\
5 & \quad \rightarrow \quad 3 & \quad + \quad 8 & \quad + \quad 9 \\
\text{a} \quad R = H & \quad \text{d} \quad R = \text{CH}_2\text{CH=CH}_2 \\
\text{b} \quad R = \text{Me} & \quad \text{e} \quad R = \text{Bn} \\
\text{c} \quad R = \text{Et} & \quad \text{f} \quad R = \text{Bu}
\end{align*}
\]

Scheme 3. Reactions of phorone (5) with ammonia (2a) or primary amines 2b-f.

When we treated the neat parent compound 3a with ethyl iodide or allyl bromide at room temperature, we did not get the hydroiodide of 3c or the hydrobromide of 3d as it was described in literature.14 The only products, which could be identified, were the hydroiodide and the hydrobromide of 3a. After modification of the reaction conditions, we were able to synthesize 3d and 3e by alkylation of 3a. Thus, subjection of 3a to allyl bromide in hexane in the presence of potassium carbonate (rt, 7 days) afforded 3d in 6% yield, and 3e was formed analogically with 1% yield. The yields of the isolated pure products were very low because of incomplete conversion of 3a and loss of material during purification by chromatography. When similar conditions were used to treat 3a with ethyl iodide, we did not obtain any desired product 3c.

The synthesis of triacetonamine (3a) from acetone (1) and ammonia (2a) can be transferred to the reaction of 1 with amine 2b to produce the heterocycle 3b. If modern (heterogeneous) acidic catalysts6b,c are used, the conversion to generate 3b is similar to that leading to 3a. However, the stability of 3b is significantly lower than that of 3a. For example, 3b is degraded much more rapidly in boiling water than 3a. These facts make it more difficult to isolate pure 3b.
from complex reaction mixtures. When we treated acetone (1) with benzyamine (2e) or n-butylamine (2f) in the presence of calcium chloride, we could not detect any heterocycles 3e or 3f, respectively, in the complicated mixtures of products with the help of 1H and 13C NMR spectroscopy. This outcome is in contrast to the literature9 but is plausible if compared with our results in connection with the reaction of phorone (5) with primary amines 2.

The low yields, observed in the alkylation reactions of 3a (see above), can lead to the assumption that the introduction of more bulky substituents at the N atom of 3a is always problematic. However, good yields can be achieved when quite different electrophiles are subjected to 3a. Highly reactive allenyl isothiocyanates like 10 are well known to produce a variety of thiazole derivatives when treated with nucleophiles (Scheme 4).21 Thus, triacetonamine (3a) was reacted with the cumulene 10 to furnish the N-arylpiperidin-4-one 11, and the secondary amine 4a was converted similarly to give the product 12. But even more sterically hindered amines, such as tert-amyl-tert-butylamine or bis(1,1-dimethylpropyl)amine, failed to give thiazole derivatives in the presence of isothiocyanate 10.

\[
\begin{align*}
\text{3a} & \quad X = \text{CO} \\
\text{4a} & \quad X = \text{CH}_2
\end{align*}
\]

\[
\begin{align*}
\text{10} & \quad \text{NCS} \\
\text{11} & \quad X = \text{CO} \quad 74\% \\
\text{12} & \quad X = \text{CH}_2 \quad 81\%
\end{align*}
\]

**Scheme 4.** Reactions of 2,2,6,6-tetramethylpiperidines with allenyl isothiocyanate (10).

**Conclusions**

With the help of the multi-step sequences via 6a and 6c or via 7a and 7c–f, it was possible for the first time to prepare the triaceton N-alkyl derivatives 3c–f (Scheme 2). The NMR data of 3c–f were utilized to analyze whether these products were formed by treatment of phorone (5) with the corresponding primary amines 2c–f (Scheme 3). However, the addition products 8 and 9 were obtained instead of nitrogen heterocycles. Moreover, the reactions of acetone (1) with benzyamine (2e) or n-butylamine (2f) in the presence of calcium chloride did not lead to any 2,2,6,6-tetramethylpiperidin-4-one 3e or 3f, respectively (Scheme 1). Simple N-alkylation of the parent compound 3a proved also to be problematic if the substituent at the N atom is more bulky than methyl. Our results clarify some contradictory reports from literature.7a,b,9,11,14 Finally, we showed that N-arylation of triacetonamine (3a) is possible with good yield when the starting compound is treated with highly electrophilic allenyl isothiocyanate (10) to give the 2-aminothiazole derivative 11 (Scheme 4).
**Experimental Section**

**General.** Melting points were determined with a Pentakon Dresden Boetius apparatus and were uncorrected. IR measurements were made on solutions in KBr cuvettes. $^1$H NMR and $^{13}$C NMR spectra were recorded with Varian Unity Inova 400 spectrometer at 400 and 100.6 MHz, respectively. Elemental analyses were performed with a Vario EL elemental analyzer from Elementar Analysensysteme GmbH Hanau. Some of the amino compounds were transformed into their picrate salts by using standard procedures$^{22}$ to get crystalline substances, which were appropriate for elemental analyses. Basic aluminum oxide and silica gel 60 (Macherey Nagel GmbH & Co. KG) were used for flash column chromatography. Mass spectra were determined with a Bruker micrOTOF-Q II 10228 spectrometer.

8-Ethyl-7,7,9,9-tetramethyl-1,4-dioxia-8-aza-spiro[4,5]decane (6c). A mixture of 6a$^{16}$ (1.00 g, 5.0 mmol), toluene (10 mL), ethyl iodide (0.81 mL, 1.57 g, 10 mmol), and calcium carbonate (0.65 g, 6.5 mmol) was heated in a glass ampoule at 130 °C for 2 days. After cooling and filtration, the solvent was removed at reduced pressure. The residue was washed with a small amount of cold (0 °C) methanol to give 6c.

6c. Colorless crystals, mp 49–52 °C, 0.35 g, yield 31%; IR ($\nu_{max}$, cm$^{-1}$): 2915 (CH). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 1.02 (t, $^3$J = 7 Hz, 3H, NCH$_2$CH$_3$), 1.12 (s, 12H, Me), 1.64 (s, 4H, CH$_2$C(Me)$_2$), 2.53 (q, $^3$J = 7 Hz, 2H, NCH$_2$), 3.92 (s, 4H, OCH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$C 20.88 (q, NCH$_2$CH$_3$), 27.83 (q, br, CH$_2$), 37.23 (t, NCH$_2$CH$_3$), 47.54 (t, CH$_2$C(Me)$_2$), 55.71 (s, C(Me)$_2$), 63.54 (t, OCH$_2$), 107.72 (s, OCO); Anal. Calcd for C$_{13}$H$_{25}$NO$_2$ (227.34): C, 68.68; H, 11.08; N, 6.16%. Found C, 68.51; H, 11.12; N, 6.25%.

1-Ethyl-2,2,6,6-tetramethylpiperidin-4-one (3c) from 6c. To a mixture of aqueous hydrogen chloride (5%, 10 mL) and Et$_2$O (10 mL) was added 6c (0.35 g, 1.50 mmol). After stirring for 16 h at room temperature, the mixture was alkalinized and extracted three times with Et$_2$O. The combined organic layers were washed twice with saturated aqueous sodium chloride and with water. After drying with MgSO$_4$, the solvent was removed at reduced pressure to give 3c.

3c. Yellow oil, 0.16 g; yield 60%; IR ($\nu_{max}$, cm$^{-1}$): 2965 (CH), 1707 (C=O). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 1.10 (t, $^3$J = 7 Hz, 3H, NCH$_2$CH$_3$), 1.12 (s, 12H, Me), 2.33 (s, 4H, CH$_2$C(Me)$_2$), 2.58 (q, $^3$J = 7 Hz, 2H, NCH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$C 20.63 (q, NCH$_2$CH$_3$), 28.28 (q, br, Me), 37.91 (t, NCH$_2$CH$_3$), 55.90 (t, CH$_2$C(Me)$_2$), 59.90 (s, C(Me)$_2$), 210.29 (s, CO); picrate of 3c Anal. Calcd for C$_{11}$H$_{21}$NO·C$_6$H$_5$NO$_3$O$_7$ (418.20): C, 49.51; H, 5.87; N, 13.59%. Found C, 48.97; H, 5.72; N, 13.74%.

1-Benzyl-2,2,6,6-tetramethylpiperidin-4-ol (7e). We prepared 7e from 7a$^{12a}$ by using benzyl bromide and a known procedure, which was successful in the synthesis of 7c.$^{17}$ The product 7e was mentioned in literature,$^{19}$ but spectroscopic data or the melting point were not published.

7e. White solid, mp 100 °C, 0.20 g, yield 14%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 0.99 (s, 6H, 2 x Me), 1.13 (s, 6H, 2 x Me), 1.52 („t“, $^3$J = 12 Hz, 2H, CH$_2$CHOH), 1.75 (s, 1H, OH), 1.90 (dd, $^2$J = 12 Hz, $^3$J = 4.4 Hz, 2H, CH$_2$CHOH), 3.82 (s, 2H, NCH$_2$), 4.05 (m, 1H, CHOH), 7.44–7.15
(m, 5H, ArH). 13C NMR (100 MHz, CDCl3): δC 24.50 (q, Me), 28.90 (q, Me), 50.12 (t, CH2CO), 55.83 (s, C(Me2)), 64.32 (d, CHOH), 125.87 (d), 126.50 (d), 127.98 (d), 142.50 (s, Ar-C).

1-Butyl-2,2,6,6-tetramethylpiperidin-4-ol (7f). We synthesized 7f from 7a and n-butyl iodide by utilizing a known procedure, which was successful to prepare 7c.17 The product 7f was mentioned in literature,20 however, spectroscopic data were not given.

7f. White solid, mp 73 °C, 0.32 g, yield 25%; IR (vmax, cm−1): 3419 (OH), 2911 (CH). 1H NMR (400 MHz, CDCl3): δH 0.90 (t, 3H, N(CH2)2CH3, 3J = 7.4 Hz), 1.11 (s, 6H, Me), 1.20 („s sext„, 2H, N(CH2)2CH2CH3, 3J = 7.4 Hz), 1.31 („t„, J = 12 Hz, 2H, CH2CH(OH), Hα), 1.40–1.34 (m, 2H, NCH2CH2), 1.79 (dd, 3J = 12 Hz, 3J = 4 Hz, 2H, CH2CH(OH), Hβ), 2.25 (t, 2H, NCH2), 2.35 (t, 2H, NCH2), 3.94 (tt, 3Jax = 12 Hz, 3Jeq = 4 Hz, 1H, CH(OH)). 13C NMR (100 MHz, CDCl3): δC 14.09 (q, N(CH2)2CH3), 20.55 (t, N(CH2)2CH2CH3), 21.97 (q, Me), 34.20 (q, Me), 37.99 (t, NCH2CH2), 43.97 (t, NCH2), 50.08 (t, CH2CHOH), 55.85 (s, C(Me2)), 64.02 (d, CHOH).

1-Ethyl-2,2,6,6-tetramethylpiperidin-4-one (3c) from 7c. A solution of 7c17 (0.50 g, 2.7 mmol) in distilled aceton (50 mL) was flushed with nitrogen for 1 h and then cooled to 0 °C. Jones reagent (5.93 mL, prepared from 33.5 g of CrO3 and 130 mL of concd. H2SO4 filled up by water to a total volume of 250 mL) was slowly added. After an additional reaction time of 1 h, water (50 mL) was added, and the mixture was made alkaline and extracted with pentane (5×). The combined organic layers were washed with saturated aqueous NaHCO3 (50 mL) and NaCl (50 mL), and dried with MgSO4. After removal of the solvent under reduced pressure, 3c was isolated as a yellow oil (0.28 g, 58% yield), which was identical with 3c prepared from 6c.

1-Allyl-2,2,6,6-tetramethylpiperidin-4-one (3d) from 7d. This product was prepared from 7d18 (0.50 g, 2.6 mmol) by oxidation with the help of Jones reagent as described for 3c. However, the reaction time was prolonged to 4 h. The product 3d was stored under inert gas and with cooling.

3d. Yellow oil, 0.34 g, yield 68%; IR (vmax, cm−1): 2969 (CH), 1703 (C=O), 1637 (C=C). 1H NMR (400 MHz, CDCl3): δH 1.12 (s, 12H, Me), 2.37 (s, 4H, CH2C(Me2)), 3.23 (dt, 3J = 5 Hz, 4J = 1.7 Hz, 2H, CH2CH=CH2), 4.99–5.03 (dq, 3J = 10 Hz, 4J = 1.7 Hz, 1H, CH=CH2), 5.19–5.25 (dq, 3Jtrans = 17 Hz, 4J = 1.7 Hz, 1H, CH=CH2), 5.87–5.91 (ddt, 3Jtrans = 17 Hz, 3Jgax = 10 Hz, 3J = 5 Hz, 1H, CH2CH=CH2). 13C NMR (100 MHz, CDCl3): δC 28.31 (q, br, Me), 46.28 (t, CH2CH=CH2), 55.83 (t, COCH2), 59.98 (s, C(Me2)), 113.49 (t, CH=CH2), 141.93 (d, CH2CH=CH2), 210.16 (s, CO); pircate of 3d Anal. Calcd for C12H21NO·C6H5N3O7 (430.20): C, 50.94; H, 5.70; N, 13.20%. Found C, 50.47; H, 5.48; N, 13.13%.

1-Benzyl-2,2,6,6-tetramethylpiperidin-4-one (3e) from 7e. This product was synthesized from 7e19 (0.20 g, 0.80 mmol) by oxidation with Jones reagent as described for 3d.

3e. Colorless crystals, mp 102 °C, 0.13 g, yield 64%; IR (vmax, cm−1): 3081 (C=C), 2973 (CH), 1707 (C=O). 1H NMR (400 MHz, CDCl3): δH 1.13 (s, 12H, Me), 2.47 (s, 4H, CH2C(Me2)), 3.91 (s, 2H, CH2Ph), 7.17–7.49 (m, 5H, ArH). 13C NMR (100 MHz, CDCl3): δC 28.33 (q, br, Me), 47.52 (t, CH2Ph), 55.89 (t, CH2CO), 60.05 (s, C(Me2)), 125.88 (d), 126.52 (d), 128.00 (d), 144.58 (s, ArC), 210.01 (s, CO); Anal. Calcd for C16H23NO (245.18): C, 78.32; H, 9.45; N, 5.71%. Found C, 77.77; H, 9.38; N, 5.81%.
1-Butyl-2,2,6,6-tetramethylpiperidin-4-one (3f). This product was prepared from 7f\(^2\) (0.50 g, 2.3 mmol) by oxidation with Jones reagent as described for 3c. However, the reaction time was prolonged to 6 h. The product 3f was stored under inert gas and with cooling.

3f. Yellow oil, 0.32 g, yield 66%; IR (ν\(_{max}\), cm\(^{-1}\)) 2968 (CH), 1708 (C=O). \(^1\)H NMR (400 MHz, CDCl3): δH 0.91 (t, 3H, N(CH\(_2\)\(_2\)NMe), 3J = 7.4 Hz), 1.11 (s, 12H, Me), 1.25 („sext“, 2H, N(CH\(_2\)\(_2\)CH\(_2\)CH\(_3\)), 3J = 7.4 Hz), 1.43–1.51 (m, 2H, NCH\(_2\)CH\(_2\)), 2.32 (s, 4H, CH\(_2\)C(Me\(_2\))), 2.44 (m, 2H, NCH\(_2\)). \(^13\)C NMR (100 MHz, CDCl3): δc 14.05 (q, N(CH\(_2\)\(_2\)NMe)), 20.55 (t, N(CH\(_2\)\(_2\)CH\(_2\)CH\(_3\))), 28.27 (q, br, Me), 37.75 (t, NCH\(_2\)CH\(_2\)), 55.87 (t, COCH\(_2\)), 59.82 (s, C(Me\(_2\))), 210.26 (s, CO); picrate of 3f Anal. Calcd for C\(_{13}\)H\(_{25}\)NO\(_3\)C\(_6\)H\(_3\)N\(_3\)O\(_7\) (440.19): C, 51.81; H, 6.41; N, 12.72%. Found C, 51.89; H, 6.42; N, 12.72%.

6-Amino-2,6-dimethylhept-2-en-4-one (8a). To an aqueous solution of ammonia (2a) (19%, 22 mL) was added phorone (5) (7.8 mL, 6.90 g, 50 mmol). The mixture was stirred at room temperature for 48 h until a clear yellow solution had been formed, which was acidified with aqueous hydrogen chloride (0.5 molar) and washed with Et\(_2\)O (3×). The aqueous solution was alkalized with the help of aqueous potassium hydroxide (6 molar) and extracted with Et\(_2\)O (3×). The combined organic layers were dried with MgSO\(_4\). After removal of the solvent at reduced pressure, a solid (1.51 g, 19%) remained. \(^1\)H NMR spectra indicated that 3a and 8a were formed in an approximate 1:3 ratio.

8a. \(^1\)H NMR (400 MHz, CDCl3): δH 1.22 (s, 6H, CH\(_2\)C(Me\(_2\))), 1.86 (s, 3H, CH=C(Me\(_2\))), 2.12 (s, 3H, CH=C(Me\(_2\))), 2.52 (s, 2H, CH\(_2\)C(Me\(_2\))), 6.02 (br. s, 1H, CH=C(Me\(_2\))). \(^13\)C NMR (100 MHz, CDCl3): δc 20.58 (q, CH=C(Me\(_2\))), 27.61 (q, CH\(_2\)C(Me\(_2\))), 30.47 (q, CH=C(Me\(_2\))), 49.06 (s, CH\(_2\)C(Me\(_2\))), 56.06 (t, CH\(_2\)C(Me\(_2\))), 124.87 (d, CH=C(Me\(_2\))), 155.44 (s, CH=C(Me\(_2\))), 200.43 (s, C=O).

2,6-Dimethyl-6-methylaminohept-2-en-4-one (8b). To an aqueous solution of 2b (4.3 mL, 40%) was added 5 (7.8 mL, 6.90 g, 50 mmol). The mixture was stirred at room temperature for 48 h. Thereafter, workup was performed as described for the reaction of 2a with 5. In this case, a mixture (2.21 g, 25%) of the products 3b and 8b with an approximate 3:2 ratio was formed. When the workup was conducted with aqueous H\(_2\)SO\(_4\) (15%) instead of aqueous HCl (0.5 molar), the proportion of 8b was significantly lower whereas the yield of 3b (15%) was nearly unchanged.

8b. Yellow oil, 0.88 g, yield 10%; \(^1\)H NMR (400 MHz, CDCl3): δH 0.99 (s, 6H, CH\(_2\)C(Me\(_2\))), 1.73 (s, 3H, CH=C(Me\(_2\))), 1.98 (s, 3H, CH=C(Me\(_2\))), 2.13 (s, 3H, NMe), 2.36 (s, 2H, CH\(_2\)C(Me\(_2\))), 5.90 (s, 1H, CH=C(Me\(_2\))). \(^13\)C NMR (100 MHz, CDCl3): δc 20.35 (q, CH=C(Me\(_2\))), 26.54 (q, CH\(_2\)C(Me\(_2\))), 27.41 (q, CH=C(Me\(_2\))), 28.46 (q, NMe), 51.42 (t, CH\(_2\)C(Me\(_2\))), 52.71 (s, CH\(_2\)C(Me\(_2\))), 124.89 (d, CH=C(Me\(_2\))), 154.91 (s, CH=C(Me\(_2\))), 200.45 (s, CO).

6-Ethylamino-2,6-dimethylhept-2-en-4-one (8c). To a mixture of 2c (3.31 mL, 2.25 g, 50 mmol) and water (5 mL) was added 5 (7.8 mL, 6.90 g, 50 mmol). After stirring at room temperature for 48 h, the reaction mixture was acidified with aqueous H\(_2\)SO\(_4\) (15%) and washed with Et\(_2\)O (3×). The aqueous solution was made alkaline with aqueous potassium hydroxide (6
molar) and extracted with Et₂O (3×). The combined organic layers were dried with MgSO₄ to give the product 8c after removal of the solvent at reduced pressure.

8c. Yellow oil, 7.32 g, yield 80%; IR (νmax, cm⁻¹): 3330 (NH), 2967 (CH), 1675 (CO). ¹H NMR (400 MHz, CDCl₃): δH 1.08 (t, 3J = 7 Hz, 3H, NCH₂CH₃), 1.13 (s, 6H, CH₂C(Me₂)), 1.86 (s, 3H, CH=C(Me₂)), 2.11 (s, 3H, CH=C(Me₂)), 2.51 (s, 2H, CH₂C(Me₂)), 2.55 (q, 3J = 7 Hz, 2H, NCH₂) 6.03 (s, 1H, CH=C(Me₂)). ¹³C NMR (100 MHz, CDCl₃): δC 15.73 (q, NCH₂CH₃), 20.64 (q, CH=C(Me₂)), 27.48 (q, CH₂C(Me₂)), 27.69 (q, CH=C(Me₂)), 36.42 (t, NCH₂), 52.15 (t, CH₂C(Me₂)), 53.08 (s, CH₂C(Me₂)), 125.22 (d, CH=C(Me₂)), 155.13 (s, CH=C(Me₂)), 200.87 (s, CO). HRMS: C₁₁H₁₄NO requires m/z 184.1696. Found 184.1688.

6-Allylamo-2,6-dimethylhept-2-en-4-one (8d) and 2,6-Bis-allylamino-2,6-dimethylheptan-4-one (9d). A mixture of 2d (3.74 mL, 2.85 g, 50 mmol) and water (5 mL) was treated with 5 (7.8 mL, 6.90 g, 50 mmol) as described for the reaction of 2c with 5. In this case, a mixture (5.77 g) of the products 8d and 9d was obtained. ¹H NMR spectra indicated that 8d and 9d were formed in an approximate 2:1 ratio.

8d. Yellow oil, 3.50 g, yield 36%; ¹H NMR (400 MHz, CDCl₃): δH 1.12 (s, 6H, CH₂C(Me₂)), 1.84 (br. s, 3H, CH=C(Me₂)), 2.12 (s, 3H, CH=C(Me₂)), 2.50 (s, 2H, CH₂C(Me₂)), 3.13 (dt, 3J = 5 Hz, 4J = 1.7 Hz, 2H, CH₂CH=CH₂), 5.02 (dq, 3Jtrans = 17 Hz, 4J = 1.7 Hz, 2H, CH=CH₂), 5.14 (dq, 3Jtrans = 17 Hz, 4J = 1.7 Hz, 4H, CH=CH₂), 5.87 (ddt, 3Jcis = 10 Hz, 3J = 5 Hz, 1H, CH₂CH=CH₂), 6.00 (br. s, 1H, -CH=CH=CH₂). ¹³C NMR (100 MHz, CDCl₃): δC 20.43 (q, CH=C(Me₂)), 27.12 (q, CH₂C(Me₂)), 45.23 (t, CH₂CH=CH₂), 52.94 (s, CH₂C(Me₂)), 53.10 (t, CH₂C(Me₂)), 115.40 (t, CH=CH₂); 126.07 (d, CH=C(Me₂)), 137.23 (d, CH₂CH=CH₂), 155.07 (s, CH=C(Me₂)), 200.57 (s, C=O). HRMS: C₁₂H₁₄NO requires m/z 196.1690. Found 196.1696.

9d. Yellow oil, 2.27 g, yield 36%; ¹H NMR (400 MHz, CDCl₃): δH 1.11 (s, 12H, CH₂C(Me₂)), 2.50 (s, 4H, CH₂C(Me₂)), 3.10 (dt, 3J = 5 Hz, 4J = 1.7 Hz, 4H, CH₂CH=CH₂), 5.02 (dq, 3J = 10 Hz, 4J = 1.7 Hz, 2H, CH=CH₂), 5.14 (dq, 3Jtrans = 17 Hz, 4J = 1.7 Hz, 4H, CH=CH₂), 5.87 (ddt, 3Jcis = 10 Hz, 3J = 5 Hz, 2H, CH₂CH=CH₂). ¹³C NMR (100 MHz, CDCl₃): 27.65 (q, CH₂C(Me₂)), 52.51 (s, CH₂C(Me₂)), 52.53 (t, CH₂C(Me₂)), 115.40 (t, CH=CH₂); 137.13 (d, CH₂CH=CH₂), 179.69 (s, C=O), picrate of 9d Anal. Calcd for C₁₃H₁₃N₂O·C₆H₅N₃O₇: C, 45.64; H, 4.82; N, 15.77%. Found C, 45.33; H, 4.78; N, 12.72%.

6-Benzylamino-2,6-dimethylhept-2-en-4-one (8e) and 2,6-Bis-benzylamino-2,6-dimethylheptan-4-one (9e). A mixture of 2e (5.46 mL, 5.36 g, 50 mmol) and water (5 mL) was treated with 5 (7.8 mL, 6.90 g, 50 mmol) as described for the reaction of 2c with 5. In this case, a mixture (8.63 g) of the products 8e and 9e was obtained. ¹H NMR spectra indicated that 8e and 9e were formed in an approximate 1:1 ratio.

8e. Yellow oil, 3.53 g, yield 29%; ¹H NMR (400 MHz, CDCl₃): δH 1.18 (s, 6H, CH₂C(Me₂)), 1.84 (s, 3H, CH=C(Me₂)), 2.03 (br. s, 1H, NH), 2.09 (s, 3H, CH=C(Me₂)), 2.58 (s, 2H, CH₂C(Me₂)), 3.63 (s, 2H, CH₂Ph), 6.01 (br. s, 1H, CH=C(Me₂)), 7.17–7.49 (m, 5H, ArH). ¹³C NMR (100 MHz, CDCl₃): δC 20.57 (q, CH=C(Me₂)), 27.57 (q, CH₂C(Me₂)), 27.62 (q, CH=C(Me₂)), 46.32 (t, CH₂Ph), 52.30 (t, CH₂C(Me₂)), 52.97 (s, CH₂C(Me₂)), 125.17 (d,
CH=C(Me)$_2$, 140.68 (s, ArC), 155.00 (s, CH=C(Me)$_2$), 200.58 (s, CO). HRMS: C$_{16}$H$_{23}$NO requires m/z 246.1852. Found 246.1852.

9e. Yellow oil, 5.10 g, yield 58%; $^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 1.19 (s, 12H, CH$_2$C(Me)$_2$), 2.57 (s, 4H, CH$_2$C(Me)$_2$), 3.67 (s, 4H, CH$_2$Ph), 7.16–7.33 (m, 10H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$): δc 27.45 (q, CH$_2$C(Me)$_2$), 46.81 (t, CH$_2$Ph), 52.30 (t, CH$_2$C(Me)$_2$), 52.89 (s, CH$_2$C(Me)$_2$), 140.68 (s, ArC), 210.91 (s, CO). HRMS: C$_{23}$H$_{32}$N$_2$O requires m/z 353.2574. Found 353.2587.

6-Butylamino-2,6-dimethylhept-2-en-4-one (8f) and 2,6-Bis-butylamino-2,6-dimethylheptan-4-one (9f). A mixture of 2f (4.94 mL, 3.66 g, 50 mmol) and water (5 mL) was treated with 5 (7.8 mL, 6.90 g, 50 mmol) as described for the reaction of 2e with 5. In this case, a mixture (6.10 g) of the products 8f and 9f was obtained. $^1$H NMR spectra indicated that 8f and 9f were formed in an approximate 3:2 ratio.

8f. Yellow oil, 3.22 g, yield 31%; $^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 0.87 (t, 3H, N(CH$_2$)$_3$CH$_3$, $^3$J = 7 Hz), 1.10 (s, 6H, CH$_2$C(Me)$_2$), 1.32 (m, 2H, N(CH$_2$)$_2$CH$_2$CH$_3$), 1.40 (m, 2H, NCH$_2$CH$_2$), 1.68 (br. s, 1H, NH), 1.84 (s, 3H, CH=C(Me)$_2$), 2.09 (s, 3H, CH=C(Me)$_2$), 2.44 (m, 2H, NCH$_2$), 2.48 (s, 2H, CH$_2$C(Me)$_2$), 6.02 (br. s, 1H, CH=C(Me)$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): δc 13.99 (q, N(CH$_2$)$_3$CH$_3$), 20.59 (t, N(CH$_2$)$_2$CH$_2$CH$_3$), 27.27 (q, CH=C(Me)$_2$), 27.54 (q, CH$_2$C(Me)$_2$), 32.90 (t, NCH$_2$CH$_2$), 41.94 (t, NCH$_2$), 52.32 (s, CH$_2$C(Me)$_2$), 52.40 (t, CH$_2$C(Me)$_2$), 125.29 (d, CH=C(Me)$_2$), 154.75 (s, CH=C(Me)$_2$), 200.85 (s, CO). HRMS: C$_{13}$H$_{23}$NO requires m/z 212.007. Found 212.0209.

9f. Yellow oil, 2.88 g, yield 41%; $^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ 0.87 (t, 6H, N(CH$_2$)$_3$CH$_3$, $^3$J = 7 Hz), 1.09 (s, 12H, CH$_2$C(Me)$_2$), 1.32 (m, 4H, N(CH$_2$)$_2$CH$_2$CH$_3$), 1.40 (m, 4H, NCH$_2$CH$_2$), 2.44 (m, 4H, NCH$_2$), 2.48 (s, 4H, CH$_2$C(Me)$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): δc 13.99 (q, N(CH$_2$)$_3$CH$_3$), 20.62 (t, N(CH$_2$)$_2$CH$_2$CH$_3$), 27.62 (q, CH$_2$C(Me)$_2$), 32.92 (t, NCH$_2$CH$_2$), 42.02 (t, NCH$_2$), 52.84 (s, CH$_2$C(Me)$_2$), 52.85 (t, CH$_2$C(Me)$_2$), 211.19 (s, CO). HRMS: C$_{17}$H$_{36}$N$_2$O requires m/z 285.2908. Found 285.2900.

1-Allyl-2,2,6,6-tetramethylpiperidin-4-one (3d) from 3a. To a solution of 3a (3.88 g, 25 mmol) in hexane (50 mL) was added potassium carbonate (7.0 g, 51 mmol) and allyl bromide (4.29 mL, 6.0 g, 50 mmol). The mixture was stirred at room temperature for 7 days. Thereafter, the precipitated potassium salts were filtered off, and the solvent was removed by distillation. The residue was purified by flash chromatography (silica gel, Et$_2$O and hexane 1:1) to give 3d (0.32 g, 6%) as a yellow oil, which was identical with 3d prepared from 7d.

1-Benzyl-2,2,6,6-tetramethylpiperidin-4-one (3e) from 3a. When 3a was treated with benzyl bromide, as described for the reaction of 3a with allyl bromide, the product 3e (1% yield) was formed as colorless needles, which were identical with 3e prepared from 7e.

2,2,6,6-Tetramethyl-1-(5-methylthiazol-2-yl)piperidin-4-one (11). To a solution of 3a (153 mg, 1.0 mmol) in anhydrous THF (2 mL) was added 10 (1.10 mL, 1.0 mmol, 9.6% in THF). After stirring for 48 h at room temperature, the solvent was removed at reduced pressure. The crude product was purified by flash chromatography on silica gel (ether/hexane 1:3 to 1:1, v/v) to give 11.
11. Yellow crystalline solid, mp 84–86 °C, 0.19 g, yield 74%; IR (νmax, cm⁻¹): 2999 (CH), 1708 (CO), 1528 (C=C). ¹H NMR (400 MHz, CDCl₃): δH 1.27 (s, 12H, CH₂C(Me)₂), 2.40 (d, 4J = 1 Hz, 3H, CH=CMe), 2.54 (s, 4H, CH₂C(Me)₂), 7.19 (q, 4J = 1 Hz, 1H, CH=CMe). ¹³C NMR (100 MHz, CDCl₃): δC 12.58 (q, CH=CMe), 29.90 (q, CH₂C(Me)₂), 54.90 (t, CH₂C(Me)₂), 58.70 (s, CH₂C(Me)₂), 132.70 (s, CH=CMe), 136.17 (d, CH=CMe), 166.36 (s, N=CS) 208.98 (s, CO).

12. Yellow crystalline solid, mp 47–49 °C, 0.19 g, yield 81%; IR (νmax, cm⁻¹): 3005, 2974, 2928 (CH), 1532 (C=C). ¹H NMR (400 MHz, CDCl₃): δH 1.13 (s, 12H, CH₂C(Me)₂), 1.54–1.57 (m, 4H, CH₂CH₂CH₂), 1.67–1.75 (m, 2H, CH₂CH₂CH₂), 2.39 (d, 4J = 1 Hz, 3H, CH=CMe), 7.18 (q, 4J = 1 Hz, 1H, CH=CMe). ¹³C NMR (100 MHz, CDCl₃): δC 12.67 (q, CH=CMe), 17.72 (t, CH₂CH₂CH₂), 28.73 (q, CH₂C(Me)₂), 40.56 (t, CH₂C(Me)₂), 55.10 (s, CH₂C(Me)₂), 132.74 (s, CH=CMe), 135.89 (d, CH=CMe), 168.21 (s, N=CS). Anal. Calcd for C₁₃H₂₂N₂S (238.15) C, 65.50; H, 9.30; N, 13.45%. Found C, 65.09; H, 9.07; N, 13.37%.

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References


