Synthesis of triacetonamine *N*-alkyl derivatives reinvestigated

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Dedicated to Professor Rainer Beckert on his 60th birthday

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**.

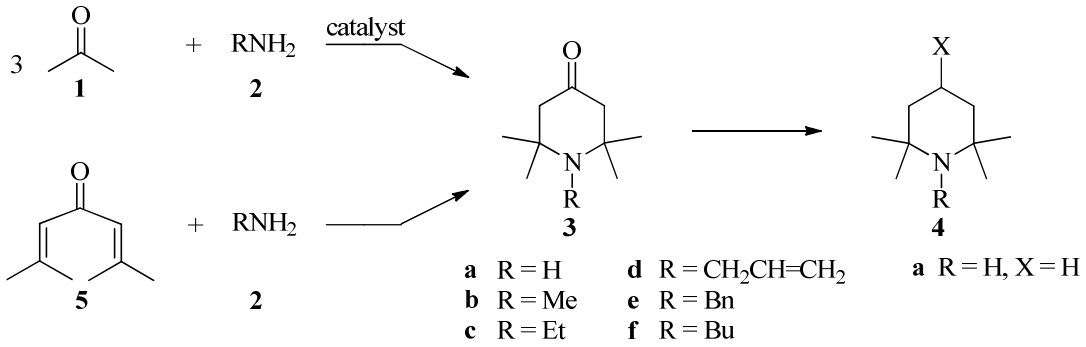
Keywords: *N*-Alkylation, 2-aminothiazoles, 2,2,6,6-tetramethylpiperidin-4-ones, ring closure, steric hindrance, tertiary amines

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 nitroxyl 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 **h**indered **a**mine **l**ight **s**tabilizers 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]



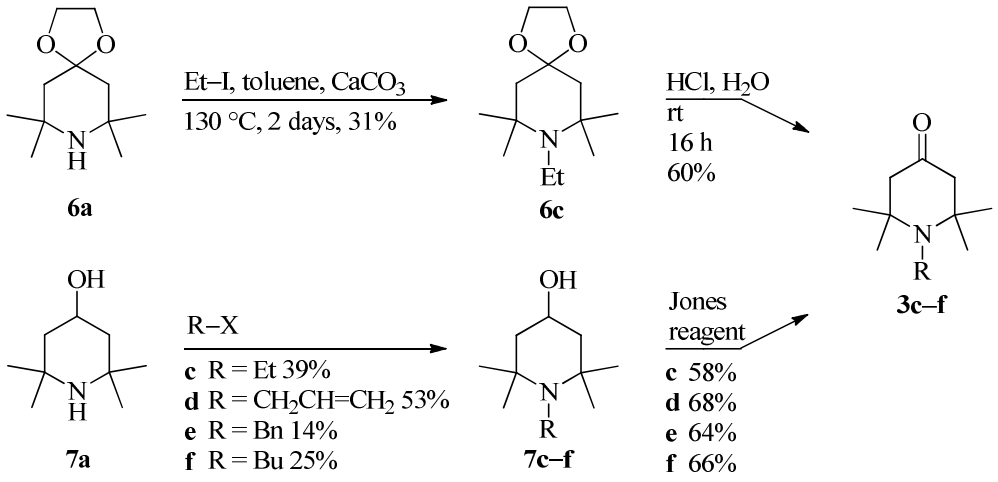
Scheme 1. Syntheses of 2,2,6,6-tetramethylpiperidines.

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.[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**,[18] **7e**,[19] and **7f**[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.

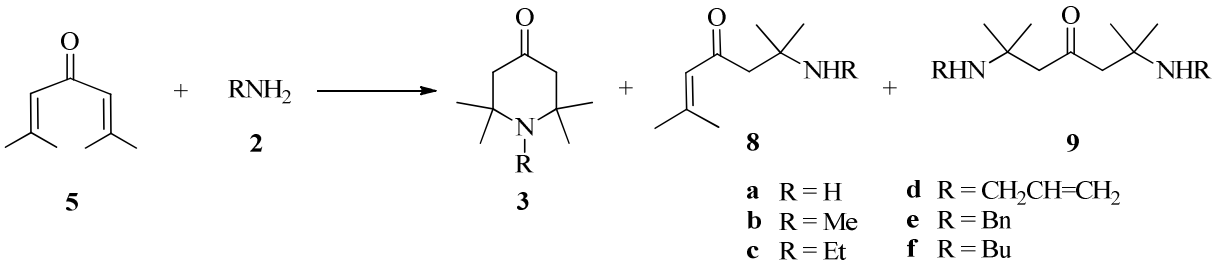


Scheme 2. Synthesis of *N*-alkylated triacetonamines **3c-f**.

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).[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,[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,[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[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 RNH_2 if the substituents R are more bulky than methyl.



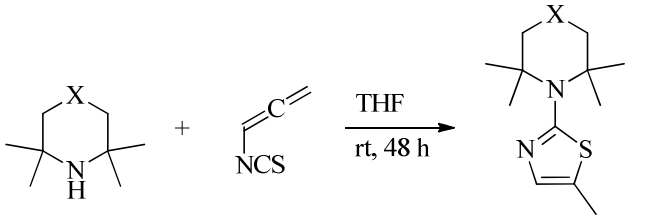
Scheme 3. Reactions of phorone (**5**) with ammonia (**2a**) or primary amines **2b-f**.

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 catalysts[6b,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 benzylamine (**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 ^{1}H and ^{13}C NMR spectroscopy. This outcome is in contrast to the literature[9] 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**.



3a X = CO **10** **11** X = CO 74%
4a X = CH_2 **12** X = CH_2 81%

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 triacetone *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 benzylamine (**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-dioxa-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 (ν_{max}, cm^{-1}): 2915 (CH). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.02 (t, ^{3}J = 7 Hz, 3H, $NCH_2\mathbf{CH_3}$), 1.12 (s, 12H, Me), 1.64 (s, 4H, $\mathbf{CH_2}C(Me)_2$), 2.53 (q, ^{3}J = 7 Hz, 2H, $N\mathbf{CH_2}$), 3.92 (s, 4H, $O\mathbf{CH_2}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.88 (q, $NCH_2\mathbf{CH_3}$), 27.83 (q, br, Me), 37.23 (t, $N\mathbf{CH_2}CH_3$), 47.54 (t, $\mathbf{CH_2}C(Me)_2$), 55.71 (s, $\mathbf{C}(Me)_2$), 63.54 (t, $O\mathbf{CH_2}$), 107.72 (s, O**C**O); 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_2O (10 mL) was added **6c** (0.35 g, 1.50 mmol). After stirring for 16 h at room temperature, the mixture was alkalized and extracted three times with Et_2O. 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 (ν_{max}, cm^{-1}): 2965 (CH), 1707 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.10 (t, ^{3}J = 7 Hz, 3H, $NCH_2\mathbf{CH_3}$), 1.12 (s, 12H, Me), 2.33 (s, 4H, $\mathbf{CH_2}C(Me)_2$), 2.58 (q, ^{3}J = 7 Hz, 2H, $N\mathbf{CH_2}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.63 (q, $NCH_2\mathbf{CH_3}$), 28.28 (q, br, Me), 37.91 (t, $N\mathbf{CH_2}CH_3$), 55.90 (t, $\mathbf{CH_2}C(Me)_2$), 59.90 (s, $\mathbf{C}(Me)_2$), 210.29 (s, **C**O); picrate of **3c** Anal. Calcd for $C_{11}H_{21}NO{\cdot}C_6H_9N_3O_7$ (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, $CDCl_3$): δ_H 0.99 (s, 6H, 2 x Me), 1.13 (s, 6H, 2 x Me), 1.52 („t“, *J* = 12 Hz, 2H, $\mathbf{CH_2}CHOH$), 1.75 (s, 1H, OH), 1.90 (dd, ^{2}J = 12 Hz, ^{3}J = 4.4 Hz, 2H, $\mathbf{CH_2}CHOH$), 3.82 (s, 2H, $N\mathbf{CH_2}$), 4.05 (m, 1H, **CH**OH), 7.44–7.15

(m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.50 (q, Me), 28.90 (q, Me), 50.12 (t, **C**$\mathbf{H_2}$CO), 55.83 (s, **C**$(Me)_2$), 64.32 (d, **CH**OH), 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 (ν_{max}, cm^{-1}): 3419 (OH), 2911 (CH). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.90 (t, 3H, $N(CH_2)_3\mathbf{CH_3}$, ^3J = 7.4 Hz), 1.11 (s, 6H, Me), 1.20 („sext“, 2H, $N(CH_2)_2\mathbf{CH_2}CH_3$, ^3J = 7.4 Hz), 1.31 („t“, J = 12 Hz, 2H, C**H**$_2$CH(OH), H_{ax}), 1.40–1.34 (m, 2H, $NCH_2\mathbf{CH_2}$), 1.79 (dd, ^2J = 12 Hz, ^3J = 4 Hz, 2H, **C**$\mathbf{H_2}$CH(OH), H_{eq}), 2.35 (t, 2H, N**C**$\mathbf{H_2}$), 3.94 (tt, $^3J_{ax}$ = 12 Hz, $^3J_{eq}$ = 4 Hz, 1H, **CH**(OH)). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.09 (q, $N(CH_2)_3\mathbf{CH_3}$), 20.55 (t, $N(CH_2)_2\mathbf{CH_2}CH_3$), 21.97 (q, Me), 34.20 (q, Me), 37.99 (t, $NCH_2\mathbf{CH_2}$), 43.97 (t, N**C**$\mathbf{H_2}$), 50.08 (t, **C**$\mathbf{H_2}$CHOH), 55.85 (s, **C**$(Me)_2$), 64.02 (d, **CH**OH).

1-Ethyl-2,2,6,6-tetramethylpiperidin-4-one (3c) from 7c. A solution of **7c**[17] (0.50 g, 2.7 mmol) in distilled acetone (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 CrO_3 and 130 mL of concd. H_2SO_4 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 $NaHCO_3$ (50 mL) and NaCl (50 mL), and dried with $MgSO_4$. 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 **7d**[18] (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 (ν_{max}, cm^{-1}): 2969 (CH), 1703 (C=O), 1637 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.12 (s, 12H, Me), 2.37 (s, 4H, **C**$\mathbf{H_2}C(Me)_2$), 3.23 (dt, ^3J = 5 Hz, ^4J = 1.7 Hz, 2H, C**H**$_2$CH=CH_2), 4.99–5.03 (dq, ^3J =10 Hz, ^4J = 1.7 Hz, 1H, C**H**=CH_2), 5.19–5.25 (dq, $^3J_{trans}$ = 17 Hz, ^4J = 1.7 Hz, 1H, CH=**CH**$_2$), 5.87–5.91 (ddt, $^3J_{trans}$ = 17 Hz, $^3J_{cis}$ = 10 Hz, ^3J = 5 Hz, 1H, CH_2C**H**=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.31 (q, br, Me), 46.28 (t, **CH**$_2$CH=CH_2), 55.83 (t, CO**CH**$_2$), 59.98 (s, **C**$(Me)_2$), 113.49 (t, CH=**CH**$_2$), 141.93 (d, CH_2**CH**=CH_2), 210.16 (s, **C**O); picrate of **3d** Anal. Calcd for $C_{12}H_{21}NO{\cdot}C_6H_9N_3O_7$ (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 **7e**[19] (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 (ν_{max}, cm^{-1}): 3081 (C=C), 2973 (CH), 1707 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.13 (s, 12H, Me), 2.47 (s, 4H, **C**$\mathbf{H_2}C(Me)_2$), 3.91 (s, 2H, **CH**$_2$Ph), 7.17–7.49 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.33 (q, br, Me), 47.52 (t, **CH**$_2$Ph), 55.89 (t, **CH**$_2$CO), 60.05 (s, **C**$(Me)_2$), 125.88 (d), 126.52 (d), 128.00 (d), 144.58 (s, ArC), 210.01 (s, **C**O); Anal. Calcd for $C_{16}H_{23}NO$ (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**[20] (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, $CDCl_3$): δ_H 0.91 (t, 3H, $N(CH_2)_3\mathbf{CH_3}$, ^3J = 7.4 Hz), 1.11 (s, 12H, Me), 1.25 („sext“, 2H, $N(CH_2)_2\mathbf{CH_2}CH_3$, ^3J = 7.4 Hz), 1.43–1.51 (m, 2H, $NCH_2\mathbf{CH_2}$), 2.32 (s, 4H, $\mathbf{CH_2}C(Me)_2$), 2.44 (m, 2H, $N\mathbf{CH_2}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.05 (q, $N(CH_2)_3\mathbf{CH_3}$), 20.55 (t, $N(CH_2)_2\mathbf{CH_2}CH_3$), 28.27 (q, br, Me), 37.75 (t, $NCH_2\mathbf{CH_2}$), 44.35 (t, $N\mathbf{CH_2}$), 55.87 (t, $CO\mathbf{CH_2}$), 59.82 (s, $\mathbf{C}(Me)_2$), 210.26 (s, **C**O); picrate of **3f** Anal. Calcd for $C_{13}H_{25}NO\cdot C_6H_3N_3O_7$ (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_2O (3×). The aqueous solution was alkalized with the help of aqueous potassium hydroxide (6 molar) and extracted with Et_2O (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 13:1 ratio.

8a. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.22 (s, 6H, $CH_2C(\mathbf{Me})_2$), 1.86 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.12 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.52 (s, 2H, $\mathbf{CH_2}C(Me)_2$), 6.02 (br. s, 1H, $\mathbf{CH}=C(Me)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.58 (q, $CH=C(\mathbf{Me})_2$), 27.61 (q, $CH_2C(\mathbf{Me})_2$), 30.47 (q, $CH=C(\mathbf{Me})_2$), 49.06 (s, $CH_2\mathbf{C}(Me)_2$), 56.06 (t, $\mathbf{CH_2}C(Me)_2$), 124.87 (d, $\mathbf{CH}=C(Me)_2$), 155.44 (s, $CH=\mathbf{C}(Me)_2$), 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_2SO_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, $CDCl_3$): δ_H 0.99 (s, 6H, $CH_2C(\mathbf{Me})_2$), 1.73 (s, 3H, $CH=C(\mathbf{Me})_2$), 1.98 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.13 (s, 3H, NMe), 2.36 (s, 2H, $\mathbf{CH_2}C(Me)_2$), 5.90 (s, 1H, $\mathbf{CH}=C(Me)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.35 (q, $CH=C(\mathbf{Me})_2$), 26.54 (q, $CH_2C(\mathbf{Me})_2$), 27.41 (q, $CH=C(\mathbf{Me})_2$), 28.46 (q, NMe), 51.42 (t, $\mathbf{CH_2}C(Me)_2$), 52.71 (s, $CH_2\mathbf{C}(Me)_2$), 124.89 (d, $\mathbf{CH}=C(Me)_2$), 154.91 (s, $CH=\mathbf{C}(Me)_2$), 200.45 (s, **C**O).

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_2SO_4 (15%) and washed with Et_2O (3×). The aqueous solution was made alkaline with aqueous potassium hydroxide (6

molar) and extracted with Et_2O (3×). The combined organic layers were dried with $MgSO_4$ to give the product **8c** after removal of the solvent at reduced pressure.

8c. Yellow oil, 7.32 g, yield 80%; IR (ν_{max}, cm^{-1}): 3330 (NH), 2967 (CH), 1675 (CO). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.08 (t, ^3J = 7 Hz, 3H, $NCH_2\mathbf{CH_3}$), 1.13 (s, 6H, $CH_2C(\mathbf{Me})_2$), 1.86 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.11 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.51 (s, 2H, $\mathbf{CH_2}C(Me)_2$), 2.55 (q, ^3J = 7 Hz, 2H, $N\mathbf{CH_2}$) 6.03 (s, 1H, $\mathbf{CH}=C(Me)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 15.73 (q, $NCH_2\mathbf{CH_3}$), 20.64 (q, $CH=C(\mathbf{Me})_2$), 27.48 (q, $CH_2C(\mathbf{Me})_2$), 27.69 (q, $CH=C(\mathbf{Me})_2$), 36.42 (t, $N\mathbf{CH_2}$), 52.15 (t, $\mathbf{CH_2}C(Me)_2$), 53.08 (s, $CH_2\mathbf{C}(Me)_2$), 125.22 (d, $\mathbf{CH}=C(Me)_2$), 155.13 (s, $CH=\mathbf{C}(Me)_2$), 200.87 (s, **C**O). HRMS: $C_{11}H_{21}NO$ requires *m/z* 184.1696. Found 184.1688.

6-Allylamino-2,6-dimethylhept-2-en-4-one (8d) and 2,6-Bis-allylamino-2,6-dimethyl heptan-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. ^{1}H NMR spectra indicated that **8d** and **9d** were formed in an approximate 2:1 ratio.

8d. Yellow oil, 3.50 g, yield 36%; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.12 (s, 6H, $CH_2C(\mathbf{Me})_2$), 1.84 (br. s, 3H, $CH=C(\mathbf{Me})_2$), 2.12 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.50 (s, 2H, $\mathbf{CH_2}C(Me)_2$), 3.13 (dt, ^3J = 5 Hz, ^4J = 1.7 Hz, 2H, $\mathbf{CH_2}CH=CH_2$), 5.02 (dq, ^3J =10 Hz, ^4J = 1.7 Hz, 1H, $\mathbf{CH}=CH_2$), 5.14 (dq, $^3J_{trans}$ = 17 Hz, ^4J = 1.7 Hz, 2H, $CH=\mathbf{CH_2}$), 5.87 (ddt, $^3J_{trans}$ = 17 Hz, $^3J_{cis}$ = 10 Hz, ^3J = 5 Hz, 1H, $CH_2\mathbf{CH}=CH_2$), 6.00 (br. s, 1H, -$\mathbf{CH}=C(Me)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.43 (q, $CH=C(\mathbf{Me})_2$), 27.12 (q, $CH_2C(\mathbf{Me})_2$), 45.23 (t, $\mathbf{CH_2}CH=CH_2$), 52.94 (s, $CH_2\mathbf{C}(Me)_2$), 53.10 (t, $\mathbf{CH_2}C(Me)_2$), 115.40 (t, $CH=\mathbf{CH_2}$); 126.07 (d, $\mathbf{CH}=C(Me)_2$), 137.23 (d, $CH_2\mathbf{CH}=CH_2$), 155.07 (s, $CH=\mathbf{C}(Me)_2$), 200.57 (s, **C**=O). HRMS: $C_{12}H_{21}NO$ requires *m/z* 196.1690. Found 196.1696.

9d. Yellow oil, 2.27 g, yield 36%; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.11 (s, 12H, $CH_2C(\mathbf{Me})_2$), 2.50 (s, 4H, $\mathbf{CH_2}C(Me)_2$), 3.10 (dt, ^3J = 5 Hz, ^4J = 1.7 Hz, 4H, $\mathbf{CH_2}CH=CH_2$), 5.02 (dq, ^3J =10 Hz, ^4J = 1.7 Hz, 2H, $\mathbf{CH}=CH_2$), 5.14 (dq, $^3J_{trans}$ = 17 Hz, ^4J = 1.7 Hz, 4H, $CH=\mathbf{CH_2}$), 5.87 (ddt, $^3J_{trans}$ = 17 Hz, $^3J_{cis}$ = 10 Hz, ^3J = 5 Hz, 2H, $CH_2\mathbf{CH}=CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 27.65 (q, $CH_2C(\mathbf{Me})_2$), 52.51 (s, $CH_2\mathbf{C}(Me)_2$), 52.53 (t, $\mathbf{CH_2}C(Me)_2$), 115.40 (t, $CH=\mathbf{CH_2}$); 137.13 (d, $CH_2\mathbf{CH}=CH_2$), 210.86 (s, **C**=O). picrate of **9d** Anal. Calcd for $C_{15}H_{28}N_2O\cdot C_6H_3N_3O_7$ (487.26): 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-dimethyl heptan-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. ^{1}H NMR spectra indicated that **8e** and **9e** were formed in an approximate 1:1 ratio.

8e. Yellow oil, 3.53 g, yield 29%; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.18 (s, 6H, $CH_2C(\mathbf{Me})_2$), 1.84 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.03 (br. s, 1H, NH), 2.09 (s, 3H, $CH=C(\mathbf{Me})_2$), 2.58 (s, 2H, $\mathbf{CH_2}C(Me)_2$), 3.63 (s, 2H, $\mathbf{CH_2}$Ph), 6.01 (br. s, 1H, $\mathbf{CH}=C(Me)_2$), 7.17–7.49 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.57 (q, $CH=C(\mathbf{Me})_2$), 27.57 (q, CH_2-$C(\mathbf{Me})_2$), 27.62 (q, $CH=C(\mathbf{Me})_2$), 46.32 (t, $\mathbf{CH_2}$Ph), 52.30 (t, $\mathbf{CH_2}C(Me)_2$), 52.97 (s, $CH_2\mathbf{C}(Me)_2$), 125.17 (d,

CH=C(Me)$_2$), 140.68 (s, ArC), 155.00 (s, CH=**C**(Me)$_2$), 200.58 (s, **C**O). 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_2C(**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, $CDCl_3$): δ_C 27.45 (q, CH_2C(**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, **C**O). HRMS: $C_{23}H_{32}N_2O$ 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-dimethyl heptan-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 **2c** 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$_3$**, ^3J = 7 Hz), 1.10 (s, 6H, CH_2C(**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, N**CH$_2$**), 2.48 (s, 2H, **CH$_2$**C(Me)$_2$), 6.02 (br. s, 1H, **CH**=C(Me)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 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_2C(**Me**)$_2$), 32.90 (t, NCH$_2$**CH$_2$**), 41.94 (t, N**CH$_2$**), 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: $C_{13}H_{25}NO$ requires *m/z* 212.2007. Found 212.2009.

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$_3$**, ^3J = 7 Hz), 1.09 (s, 12H, CH_2C(**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, N**CH$_2$**), 2.48 (s, 4H, **CH$_2$**C(Me)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.99 (q, N(CH$_2$)$_3$**CH$_3$**), 20.62 (t, N(CH$_2$)$_2$**CH$_2$**CH$_3$), 27.62 (q, CH_2C(**Me**)$_2$), 32.92 (t, NCH$_2$**CH$_2$**), 42.02 (t, N**CH$_2$**), 52.84 (s, CH_2**C**(Me)$_2$), 52.85 (t, **CH$_2$**C(Me)$_2$), 211.19 (s, **C**O). HRMS: $C_{17}H_{36}N_2O$ 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_2O 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 (ν_{max}, cm^{-1}): 2999 (CH), 1708 (CO), 1528 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.27 (s, 12H, $CH_2C(\mathbf{Me})_2$), 2.40 (d, ^4J = 1 Hz, 3H, CH=C**Me**), 2.54 (s, 4H, $\mathbf{CH_2}C(Me)_2$), 7.19 (q, ^4J = 1 Hz, 1H, **CH**=CMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 12.58 (q, CH=C**Me**), 29.90 (q, $CH_2C(\mathbf{Me})_2$), 54.90 (t, $\mathbf{C}H_2C(Me)_2$), 58.70 (s, $CH_2\mathbf{C}(Me)_2$), 132.70 (s, CH=**C**Me), 136.17 (d, **C**H=CMe), 166.36 (s, N=CS) 208.98 (s, CO). Anal. Calcd for $C_{13}H_{20}N_2OS$ (252.13) C, 61.87; H, 7.99; N 11.10; S, 12.71%. Found C, 61.49; H, 7.82; N, 10.87; S, 12.70%.

2,2,6,6-Tetramethyl-1-(5-methylthiazol-2-yl)piperidin (12). Compound **12** was synthesized according to the procedure described for **11**. Purification by flash chromatography (silica gel, ether/hexane 1:6 to 1:4, v/v) gave **12**.

12. Yellow crystalline solid, mp 47–49 °C, 0.19 g, yield 81%; IR (ν_{max}, cm^{-1}): 3005, 2974, 2928 (CH), 1532 (C=C). ^{1}H NMR (400 MHz, CDCl3): δ_H 1.13 (s, 12H, $CH_2C(\mathbf{Me})_2$), 1.54–1.57 (m, 4H, $\mathbf{CH_2}C(Me)_2$), 1.67–1.75 (m, 2H, $CH_2CH_2CH_2$), 2.39 (d, ^4J = 1 Hz, 3H, CH=C**Me**), 7.18 (q, ^4J = 1 Hz, 1H, **CH**=CMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 12.67 (q, CH=C**Me**), 17.72 (t, $CH_2CH_2CH_2$), 28.73 (q, $CH_2C(\mathbf{Me})_2$), 40.56 (t, $\mathbf{CH_2}C(Me)_2$), 55.10 (s, $CH_2\mathbf{C}(Me)_2$), 132.74 (s, CH=**C**Me), 135.89 (d, **CH**=CMe), 168.21 (s, N=CS). Anal. Calcd for $C_{13}H_{22}N_2S$ (238.15) C, 65.50; H, 9.30; N, 11.75; S, 13.45%. Found C, 65.09; H, 9.07; N, 11.54; S, 13.37%.

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