DOI: 10.1002/ejoc.201000312

Self-Acylation of 1-Adamantylacetic Acid in Trifluoroacetic Anhydride Medium: A Route to 2,4-Bis(1-adamantyl)acetoacetic Acid and Its Derivatives

Vladimir Kovalev,*[a] Elvira Shokova,[a] Alexander Shmailov,[a] Ivan Vatsouro,[a] and Viktor Tafeenko[a]

Keywords: Acylation / Aldol reactions / Carboxylic acids / Perfluorinated solvents / Synthetic methods

The self-acylation of 1-adamantylacetic acid (**1**) in trifluoroacetic anhydride, catalyzed by triflic acid, proceeds through the formation of the mixed 2,4-bis(1-adamantyl)acetoacetic–trifluoroacetic anhydride **2**, and it was used as an efficient approach to previously unknown 2,4-bis(1-adamantyl)acetoacetic acid (**3**), its esters **4**–**6** and amides **7**–**11**, and the sterically hindered 1-adamantyl(1-adamantylacetyl)ketene (**12**). The latter is stable in solution and can be isolated as a neat solid. Addition of methanol or primary amines to **12** gave the corresponding derivatives of acid **3**. Acid **3** was decarboxylated to 1,3-bis(1-adamantyl)acetone (**22**), whereas the heterocyclization of phenyl ester **6** with thiourea gave two isomeric adamantylated thiouracils **23** and **24**. The structures of *N*-benzylamide **7** and thiouracil **23** were confirmed by single-crystal X-ray analysis. The utilization of the self-acylation method for the conversion of some other aliphatic acids is discussed and preliminarily tested.

Introduction

β-Keto esters and β-keto acids bearing several electrophilic and nucleophilic centers are widely used in organic synthesis as polyfunctional reagents. The most common synthetic approaches to such compounds are self- and cross-Claisen-type condensations.[1,2] Among the large number of modifications of the Claisen reaction, the acid-catalyzed self-acylation of acid chlorides or anhydrides containing α-CH_2 protons seems to be one of the most attractive approaches to β-keto acids of the general formula $RCH_2C(O)CH(R)CO_2H$. However, due to the low stability of the latter, and difficulties with the selectivity of these condensations, the published data on the successful application of such reactions are limited. Already Meerwein has found[3] that the self-acylation of acetic anhydride in the presence of BF_3 has led to acetylacetone, and the anhydrides of propionic or butyric acid have transformed into the corresponding symmetrical dialkyl ketones; the initially formed self-acylation products undergo decarboxylation during the reaction treatment and hydrolysis. Later this method was extended to other aliphatic ketones.[4] For the aliphatic acid chlorides RCH_2COCl ($R \neq H$) the selective cyclotrimerization in the presence of $AlCl_3$ including, according to the authors, the initial formation of the corresponding β-keto acid chlorides as aluminum chelates has been reported.[5] Quite unexpectedly we have found no reports on the activation of acids of the type RCH_2CO_2H under acidic conditions to be used for the selective one-pot self-acylation and preparative synthesis of β-keto acids or their derivatives.

In this paper, the possibility of the acid-catalyzed self-acylation of 1-adamantylacetic acid (**1**) is investigated. In the literature there are several examples of selective electrophilic reactions that involve the methylene group of this acid. Thus, it is known[6] that 1-adamantylacetic acid chloride can be easily and selectively halogenated at the α-methylene group by bromine or iodine. When treated with sodium nitrite in trifluoroacetic anhydride (TFAA)/trifluoroacetic acid (CF_3CO_2H) medium, **1** was converted into 1-adamantylnitrile, probably through nitrosation of the α-CH_2 group, followed by decarboxylation and dehydration.[7] This led us to explore the reactions of activated derivatives of 1-adamantylacetic acid (**1**) in which the α-CH_2 group undergoes electrophilic acyl attack.

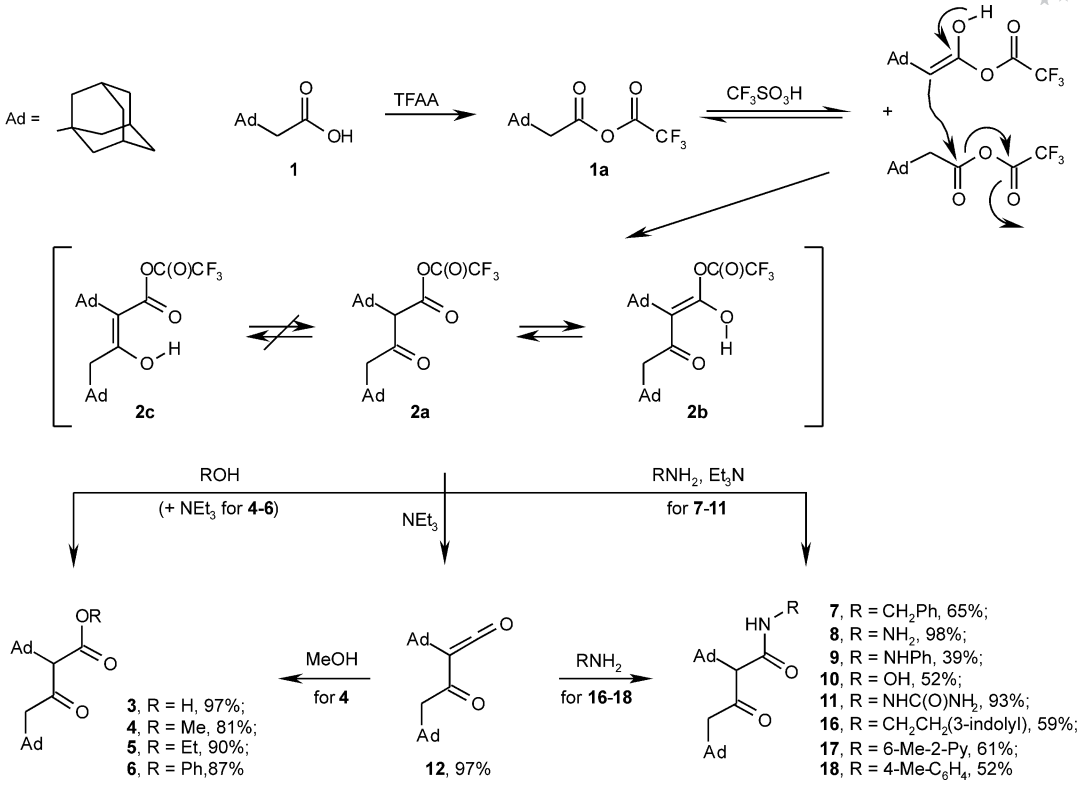
Results and Discussion

As a medium and a reagent for the activation of acid **1**, we chose TFAA because it is well known[8] that the mixed anhydrides of aliphatic carboxylic acids and trifluoroacetic acid are excellent acylating reagents. It was found that after heating at reflux in TFAA, followed by distillation of the solvent and quenching the reaction mixture with water, acid **1** returned unchanged. However, if the reaction was carried out in the presence of a small amount of triflic acid, in

[a] Chemistry Department of Moscow State University, Lenin's Hills, Moscow 119991, Russia
E-mail: kovalev@petrol.chem.msu.ru

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000312.

WILEY InterScience DISCOVER SOMETHING GREAT
© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Preparation of **2** and its applications.

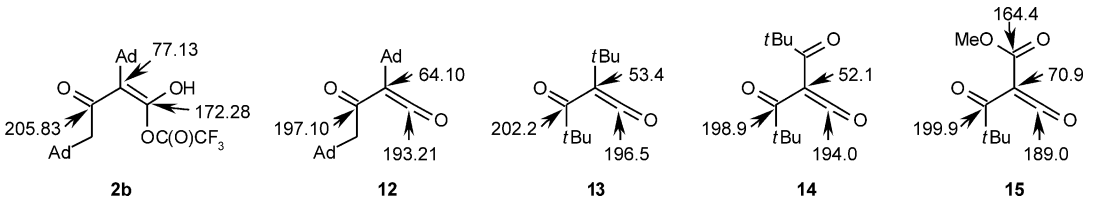
a few minutes the initially homogeneous reaction mixture started to become heterogeneous, and after 1–1.5 h a white solid formed. After 2–2.5 h TFAA was removed and the residue was thoroughly dried and then carefully treated with cold water or, after dissolution in dichloromethane, with different OH or NH nucleophiles (alcohols, benzylamine, hydrazine hydrate, phenylhydrazine, hydroxylamine, and semicarbazide). As a result, 2,4-bis(1-adamantyl)acetoacetic acid (**3**) and its derivatives − esters **4**–**6**, amide **7**, hydrazides **8** and **9**, hydroxamic acid **10**, and semicarbazide **11** − were obtained in high yields (Scheme 1).

We suppose that in mixed anhydride **1a**, formed by the reaction of acid **1** with TFAA in the presence of triflic acid, enolization is easy and the acylating properties of the reactant are amplified. An aldol-type condensation of anhydride **1a** and its enol results in the formation of the mixed anhydride of 2,4-bis(1-adamantyl)acetoacetic and trifluoroacetic acids **2**, which, as we initially anticipated, exists in keto form **2a**, because 2,4-bis(1-adamantyl)acetoacetic acid (**3**) and its derivatives obtained from anhydride **2** do not tend to enolize in solutions, as shown by NMR spectroscopy.

Although hygroscopic, mixed anhydride **2** can be safely exposed to air for a short time and its manipulation does not require any special precautions when carrying out further reactions. Thus, we were able to characterize it by ^1H and ^{13}C NMR spectroscopy in dry $CDCl_3$. The ^1H NMR spectrum of this key intermediate does not contain the signal of the AdCH proton, suggesting that the compound exists exclusively in the enol form. On the other hand, the ^{13}C NMR spectrum contains the signal of the $AdCH_2C{=}O$ group at δ = 205.83 ppm, suggesting the structure of monotrifluoroacetoxylated 1-adamantyl-1-(1-adamantylacetyl)-ketene **2b**, but not enol **2c**. Treatment of the dichloromethane solution of **2** with a slight excess of triethylamine led almost immediately and quantitatively to α-oxoketene **12**, as clearly evidenced by the changes in the ^1H and ^{13}C NMR spectra after addition of triethylamine into the solution of **2** in $CDCl_3$. In the ^1H NMR spectrum of **12**, in addition to the signals of adamantane nuclei, there is only the singlet of the $AdCH_2$ methylene groups at δ = 2.10 ppm, whereas the ^{13}C NMR spectrum contains the signals of the carbonyl group at δ = 197.10 ppm ($AdCH_2\mathit{C}{=}O$), one from the central ketene carbon at δ = 193.21 ppm ($C{=}\mathit{C}{=}O$), and one from the sp^2 carbon atom of the ketene at δ = 64.10 ppm ($\mathit{C}{=}C{=}O$). For comparison, the essential ^{13}C NMR spectroscopic data for **2b**, α-oxoketene **12**, and known sterically hindered α-oxoketenes **13**–**15**[9–11] are given in Scheme 2.

Direct structural approval for **12** comes also from the highly characteristic and strong ketene absorption band in the IR spectrum at 2091 cm^{-1} (compare to dipivaloylketene, 2131 cm^{-1}[10]), and one carbonyl absorption band at 1654 cm^{-1}. Obtained α-oxoketene **12** is stable on the laboratory timescale, and it could be stored in isolated solutions of dry dichloromethane or hexane for several days; it is stable against TLC on SiO_2 with dry non-nucleophilic solvents. When kept in an unsealed vessel, solid **12** underwent slow decomposition to 1,3-bis(1-adamantyl)acetone.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Some ^{13}C NMR spectroscopic data for **2b**, **12**, and known stable α-oxoketenes.

α-Oxoketenes are known to undergo reactions of two main types: (i) addition of nucleophiles and (ii) cycloaddition reactions.[12] Addition of nucleophiles to α-oxoketenes is a familiar process and in general leads to β-keto acids derivatives. In our case, the interaction of α-oxoketene **12** with methanol, tryptamine, 2-amino-6-methylpyridine, and *p*-toluidine resulted in corresponding ester **4** and amides **16**–**18**. At the same time, **12** did not undergo dimerization in hexane, even when heated at reflux for 7 h, and it also did not participate in various [2+4] hetero-Diels–Alder cycloadditions with polarized multiple bond systems (acetone, benzaldehyde, dicyclohexylcarbodiimide, benzylideneaniline),[13] which are common for α-oxoketenes (e.g., **14**[14] and **15**[11]). It should be noted that known α-adamantylated ketenes demonstrate quite different reactivities depending on their structural features. For instance, the parent 1-adamantylketene could not be isolated as a neat compound, whereas it is stable in dilute ether solutions. It also readily reacts with HO and NH nucleophiles to give 1-adamantylacetic acid derivatives.[15] (1-Adamantyl)ethoxycarbonyl ketene available from ethyl 3-(1-adamantyl)-2-diazo-3-oxopropanoate both by thermal- or photodecomposition can be stored in hexane under an inert atmosphere at room temperature for several days and is a good precursor of adamantane-substituted malonic acid derivatives.[16] At the same time, both of the ketenes mentioned above are poorly active in 1,2-cycloaddition with benzylideneaniline. On the other hand, bis(1-adamantyl)ketene is extremely stable as a monomer and reacts slowly, even with water, leading to bis(1-adamantyl)acetic acid.[17]

The structures of β-keto acid **3** and its derivatives **4**–**11** and **16**–**18** were confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry (ESI). The ^1H NMR spectra contain singlets at δ = 3.16–3.58 ppm assigned to α-methine protons (AdCH). The signals at δ = 69.47–70.31 ppm in the ^{13}C NMR spectra of **4**–**11** and **16**–**18** correspond to tertiary carbon atoms of the keto forms. No enol forms were detected in $CDCl_3$ or $[D_6]DMSO$ in all the cases. Obviously, the presence of the bulky adamantane groups prevents enolization of these molecules. Similar observations have been made with some other sterically hindered β-keto acid derivatives.[11,18]

The structure of **7** was confirmed by X-ray analysis. A displacement ellipsoids plot of **7** is shown in Figure 1.

It should be noted that 2,4-bis(1-adamantyl)acetoacetic acid (**3**) could not be synthesized by the classic Claisen condensation. It is only known that the self-condensation of ethyl 1-adamantylacetate in the presence of lithium dicyclohexylamide led to 1,3-bis(1-adamantyl)acetone,[19] probably due to the hydrolysis and decarboxylation of the initially formed β-keto ester during the quenching of the reaction mixture. As for adamantane-containing β-keto acids, these compounds were synthesized in the form of the corresponding esters **19**–**21** by the acylation of malonic ester with 1-adamantanecarboxylic acid chloride[20] or 1-adamantylacetic acid chloride[21] or by the adamantylation of β-keto esters with 1-bromo-[22,23] or 1-hydroxyadamantanes.[24] These adamantylated keto esters were used in the synthesis of depsipeptides[25] and various heterocycles[21,22,24,26,27] including biologically active ones.

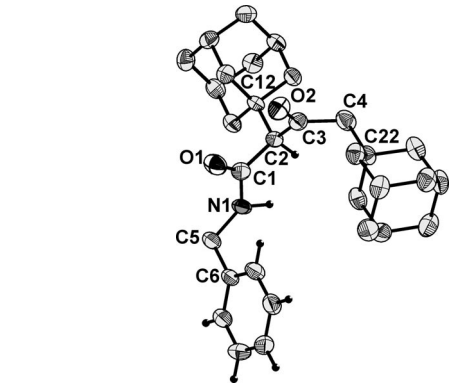
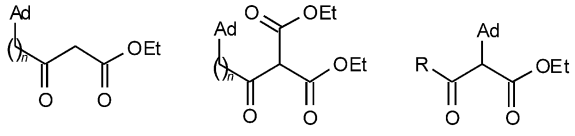


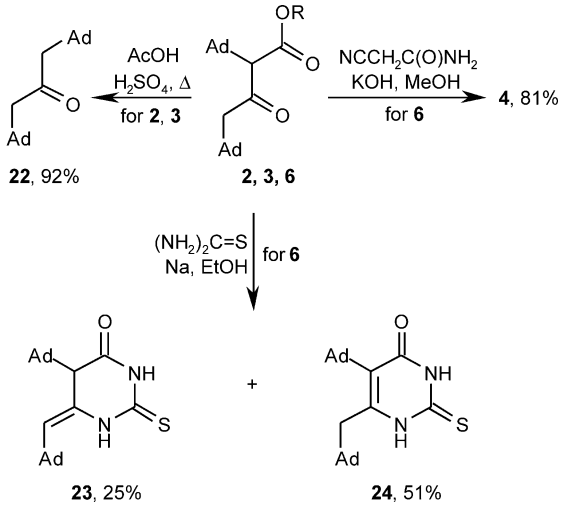
Figure 1. Displacements ellipsoids plot of **7** are shown at the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radii. Hydrogen atoms of the adamantyl moieties and some atoms labeling are omitted for clarity.



19, *n* = 0, 1 **20**, *n* = 0, 1 **21**, R = H, Me, Et, *n*Pr, *n*Bu

We have studied some transformations of keto acid **3** and its ester **6** (Scheme 3). As expected, heating of β-keto acid **3** in a mixture of diluted acetic and sulfuric acids was easily decarboxylated, giving 1,3-bis(1-adamantyl)acetone **22** quantitatively. The same was obtained by heating mixed anhydride **2** under these conditions. It should be noted that our method of synthesis of 1,3-bis(1-adamantyl)acetone is much more convenient and easier than those described earlier.[19,28]

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Transformations of keto acid **3** and its ester **6**.

The condensation of phenyl ester **6** with thiourea in ethanol in the presence of NaOEt gave expected thiouracil **24** along with isomeric pyrimidine derivative **23**, having the exocyclic double bond. These compounds were isolated in 51 and 25% yield, respectively, after column chromatography on silica. The structure of **23** was confirmed by X-ray analysis. Figure 2 shows the molecular structure and the atom labeling scheme of **23**.

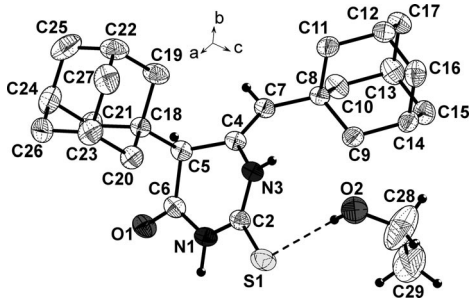
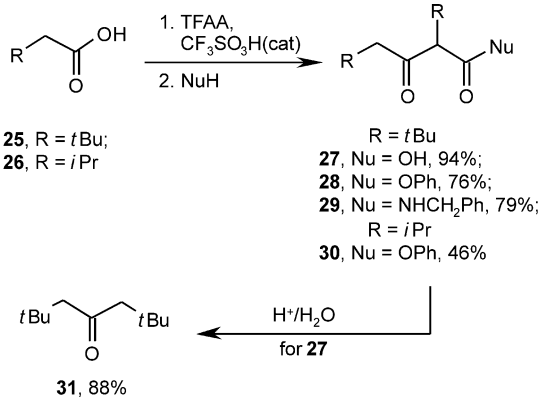


Figure 2. The asymmetric unit of **23**, showing the atom labeling scheme; ellipsoids are shown at the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radii. Hydrogen atoms of the adamantyl moiety are omitted for clarity.

Unexpectedly, β-keto esters **5** and **6** were not transformed into heterocyclic compounds when reacted with hydrazine hydrate, phenylhydrazine, or cyanoacetamide. In the case of hydrazine, the starting esters returned unchanged, although it is known[20–22,26] that adamantylated β-keto esters **19** and **21** could be transformed into the corresponding pyrazoles quite easily under these conditions. An attempt to obtain a pyridine structure according to the method previously developed for ethyl acetoacetate[29] by boiling phenyl ester **6** with cyanoacetamide in methanol in the presence of KOH resulted only in the formation of methyl ester **4** by interesterification. We could also not get the oxime of **22** by its reaction with hydroxylamine in the presence of various bases (NEt_3, pyridine). The latter result is consistent with the known data[30] on the low reactivity of the carbonyl group in 1,3-bis(*tert*-butyl)acetone, which does not form the semicarbazide, oxime, hydrazone, and 2,4-dinitrophenylhydrazone under ordinary conditions.

In order to evaluate the applicability of the TFAA-mediated self-acylation method as a common route to β-keto acids, we checked it on a series of α-CH_2 carboxylic acids: acetic, propionic, isovaleric, *tert*-butylacetic, phenylacetic, 1-naphthylacetic, and phenoxyacetic acids. Among the acids tested, only *tert*-butylacetic and isovaleric acids **25** and **26** yielded the dimeric self-acylation products more or less selectively, whereas the others gave polymeric adducts. Moreover, in contrast to 1-adamantylacetic acid (**1**), which gave TFAA-insoluble anhydride **2**, mixed anhydrides **25**·CF_3CO_2H and **26**·CF_3CO_2H remained dissolved in the reaction mixture, so they were not separated as pure compounds, but reacted directly with HO and NH nucleophiles (Scheme 4). As a result, 2,4-bis(*tert*-butyl)acetoacetic acid (**27**),[31] its phenyl ester **28**, and *N*-benzylamide **29**, as well as phenyl ester **30** were obtained in moderate to good yield. In the case of β-keto acid **27**, the sample obtained contained up to 10% of 1,3-bis(*tert*-butyl)acetone (**31**), which formed easily from **27** upon heating under acidic conditions.



Scheme 4. Self-acylation of acids **25** and **26**.

Conclusions

In summary, we have found the previously unknown self-acylation of 1-adamantylacetic acid (**1**) in TFAA in the presence of CF_3SO_3H, yielding the versatile mixed 2,4-bis(1-adamantyl)acetoacetic–trifluoroacetic anhydride **2**. Upon treatment with water or various OH and NH nucleophiles, this anhydride could be easily converted into 2,4-bis(1-adamantyl)acetoacetic acid (**3**) and its esters, amides, hydrazides, etc. Moreover, the reaction of anhydride **2** with triethylamine led to stable α-oxoketene **12**, which reacts with methanol, tryptamine, 2-amino-6-methylpyridine, and *p*-toluidine to give the corresponding esters and amides of 2,4-bis(1-adamantyl)acetoacetic acid. Acid **3** is easily decarboxylated to 1,3-bis(1-adamantyl)acetone (**22**), whereas the reaction of its phenyl ester with thiourea gave isomeric diadamantylated thiouracil derivatives **23** and **24**. As a preliminary result, the TFAA-mediated self-acylation method

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

could also be applied for the synthesis of some selected β-keto acids and their derivatives, whereas the detailed study of the scope and limitations of the method is in progress.

Experimental Section

General Methods: ^1H and ^{13}C (APT) NMR spectra were measured with a Bruker Avance 400 spectrometer with solvent signals as internal reference. ESI mass spectra were recorded with an Agilent 1100 LC/MS instrument. IR spectrum was recorded with a Thermo Scientific Nicolet IR 200 FTIR spectrometer. X-ray measurements were performed with an Enraf–Nonius CAD-4 diffractometer. Chemicals were of commercial grade and used without further purification. Column chromatography was performed on silica (Merck Kieselgel 60). Solvents were purified and dried according to standard procedures. TFAA was freshly distilled from P_2O_5. 1-Adamantylacetic acid (**1**) was prepared according to a published procedure.[32]

Trifluoroacetic 2,4-Bis(1-adamantyl)acetoacetic Anhydride (2): A solution of 1-adamantylacetic acid (**1**; 194 mg, 1 mmol) in a mixture of TFAA/CF_3SO_3H (97.5:2.5, 2 mL) was kept at 60–65 °C for 2–2.5 h and cooled. The excess amount of the solvent mixture was carefully decanted from the solid formed, and the residue was dried under reduced pressure. Yield: 95–99% (221–231 mg), yellowish solid, m.p. 88–90 °C. Freshly prepared anhydride **2** was used without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ = = 2.69 (s, 2 H, $AdCH_2$), 2.13 (br. s, 3 H, CH^{Ad}), 2.08 (br. s, 3 H, CH^{Ad}), 2.03 (br. s, 6 H, CH_2^{Ad}), 1.78–1.65 (m, 18 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = = 205.84 (C=O), 172.75 (CO_2COCF_3), 157.99 (q, J = 41.9 Hz, $COCF_3$), 119.34 (q, J = 317.0 Hz, $COCF_3$), 76.82 [AdCO(Ad)*C*=C], 53.75 ($AdCH_2$), 42.33, 40.56 (CH_2^{Ad}), 37.78, 37.07 (C^{Ad}), 35.93, 35.72 (CH_2^{Ad}), 28.65, 28.46 (CH^{Ad}) ppm.[33]

2,4-Bis(1-adamantyl)acetoacetic Acid (3): A sample of **2** obtained from **1** (1 mmol) was carefully treated with cold water, and the precipitate formed was filtered, washed with water, and dried. Yield: 97% (180 mg), white solid, m.p. 190–195 °C (decomp.). $C_{24}H_{34}O_3$ (370.53): calcd. C 77.80, H 9.25; found C 77.95, H 9.37. ^1H NMR (400 MHz, $CDCl_3$, CF_3CO_2D): δ = 3.58 (s, 1 H, AdCH), 2.52 (d, J = 13.5 Hz, 1 H, $AdCH_2$), 2.25 (d, J = 13.5 Hz, 1 H, $AdCH_2$), 2.05 (br. s, 3 H, CH^{Ad}), 1.98 (br. s, 3 H, CH^{Ad}), 1.80–1.55 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, CF_3CO_2D): δ = 213.93 (C=O), 172.76 (CO_2H), 69.47 (AdCH), 60.04 ($AdCH_2$), 42.48, 40.43 (CH_2^{Ad}), 40.05 (C^{Ad}), 36.41, 36.06 (CH_2^{Ad}), 35.14 (C^{Ad}), 28.63, 28.49 (CH^{Ad}) ppm. MS (ESI): *m*/*z* (%) = 409.1 (70) $[M + K]^+$, 393.2 (100) $[M + Na]^+$, 371.1 (71) $[M + H]^+$.

Methyl 2,4-Bis(1-adamantyl)acetoacetate (4): Dry methanol (3 mL) and triethylamine (0.28 mL, 2 mmol) were added to a stirred and cooled (0–5 °C) solution of **2** (obtained from 1 mmol of **1**) in dry CH_2Cl_2 (4 mL). Stirring was continued for 6 h at room temperature, and the solvent was then evaporated to dryness. The residue was redissolved in CH_2Cl_2, washed with 1 N HCl and water, and dried with $MgSO_4$. The residue, after removal of the solvent, was crystallized from methanol. Yield: 81% (155 mg), white solid, m.p. 101–102 °C. $C_{25}H_{36}O_3$ (384.55): calcd. C 78.08, H 9.44; found C 78.31, H 9.31. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3 H, OCH_3), 3.19 (s, 1 H, AdCH), 2.19 (s, 2 H, $AdCH_2$), 1.94 (br. s, 3 H, CH^{Ad}), 1.90 (br. s, 3 H, CH^{Ad}), 1.75–1.55 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.94 (C=O), 168.56 (CO_2CH_3), 70.30 (AdCH), 57.88 ($AdCH_2$), 51.62 (OCH_3), 42.09, 40.03 (CH_2^{Ad}), 37.18 (C^{Ad}), 36.74, 36.62 (CH_2^{Ad}), 33.65 (C^{Ad}), 28.52 (CH^{Ad}) ppm. MS (ESI): *m*/*z* (%) = 407.0 (100) $[M + Na]^+$, 384.9 (34) $[M + H]^+$.

Ethyl 2,4-Bis(1-adamantyl)acetoacetate (5): Obtained from **1** (1 mmol), ethanol (3 mL), and triethylamine (0.28 mL, 2 mmol) as described for **4**. Yield: 90% (180 mg), colorless oil. $C_{26}H_{38}O_3$ (398.58): calcd. C 78.35, H 9.61; found C 78.18, H 9.49. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.11 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.16 (s, 1 H, AdCH), 2.18 (s, 2 H, $AdCH_2$), 1.92 (br. s, 3 H, CH^{Ad}), 1.89 (br. s, 3 H, CH^{Ad}), 1.74–1.58 (m, 24 H, CH_2^{Ad}), 1.21 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.00 (C=O), 167.97 (CO_2CH_2), 70.32 (AdCH), 60.48 (OCH_2), 57.89 ($AdCH_2$), 42.08, 39.97 (CH_2^{Ad}), 37.07 (C^{Ad}), 36.71, 36.62 (CH_2^{Ad}), 33.63 (C^{Ad}), 28.49 (CH^{Ad}), 14.17 (CH_3) ppm.

Phenyl 2,4-Bis(1-adamantyl)acetoacetate (6): Obtained from **1** (2 mmol), a solution of phenol (470 mg, 5 mmol), and triethylamine (0.82 mL, 6 mmol) in dry CH_2Cl_2 (6 mL) as described for **4**. Instead of crystallization, the product was purified by column chromatography (CH_2Cl_2/hexane, 1:1). Yield: 87% (390 mg), white solid, m.p. 121–122 °C. $C_{30}H_{38}O_3$ (446.62): calcd. C 80.68, H 8.58; found C 80.83, H 8.35. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 2 H, Ph), 7.24 (m, 1 H, Ph), 7.07 (m, 2 H, Ph), 3.47 (s, 1 H, AdCH), 2.39 (d, J = 16.6 Hz, 1 H, $AdCH_2$), 2.35 (d, J = 16.6 Hz, 1 H, $AdCH_2$), 2.02 (br. s, 3 H, CH^{Ad}), 1.97 (br. s, 3 H, CH^{Ad}), 1.80–1.60 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.50 (C=O), 166.59 (CO_2Ph), 150.37 (C^{Ph}), 129.40, 125.92, 121.43 (CH^{Ph}), 70.16 (AdCH), 58.20 ($AdCH_2$), 42.21, 40.93 (CH_2^{Ad}), 37.71 (C^{Ad}), 36.75, 36.63 (CH_2^{Ad}), 33.87 (C^{Ad}), 28.56, 28.54 (CH^{Ad}) ppm. MS (ESI): *m*/*z* (%) = 469.2 (68) $[M + Na]^+$, 447.1 (100) $[M + H]^+$.

2,4-Bis(1-adamantyl)-*N*-benzylacetoacetamide (7): Obtained from **1** (1 mmol), benzylamine (0.21 mL, 2 mmol), and triethylamine (0.41 mL, 3 mmol) as described for **6**. Yield: 65% (150 mg), white solid, m.p. 213-215 °C. $C_{31}H_{41}NO_2$ (459.67): calcd. C 81.00, H 8.99, N 3.05; found C 80.63, H 9.12, N 3.16. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (t, J = 6.6 Hz, 1 H, NH), 7.24–7.30 (m, 5 H, Ph), 4.57 (dd, J = 14.8, 6.6 Hz, 1 H, $PhCH_2$), 4.36 (dd, J = 14.8, 6.6 Hz, 1 H, $PhCH_2$), 3.44 (s, 1 H, AdCH), 2.45 (d, J = 13.3 Hz, 1 H, $AdCH_2$), 2.07 (d, J = 13.3 Hz, 1 H, $AdCH_2$), 1.98 (br. s, 3 H, CH^{Ad}), 1.93 (br. s, 3 H, CH^{Ad}), 1.80–1.50 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.80 (C=O), 165.92 (CONH), 138.51 (C^{Ph}), 128.51, 127.69, 127.25 (CH^{Ph}), 72.13 (AdCH), 61.08 ($AdCH_2$), 43.31 ($PhCH_2$), 42.46, 40.54 (CH_2^{Ad}), 38.46 (C^{Ad}), 36.59, 36.46 (CH_2^{Ad}), 34.44 (C^{Ad}), 28.65, 28.48 (CH^{Ad}) ppm. MS (ESI): *m*/*z* (%) = 498.3 (18) $[M + K]^+$, 482.3 (45) $[M + Na]^+$, 460.3 (100) $[M + H]^+$.

2,4-Bis(1-adamantyl)acetoacetylhydrazide (8): To a stirred mixture of hydrazine hydrate (0.4 mL, 6 mmol) and CH_2Cl_2 (2 mL) was added a solution of **2** (obtained from 1 mmol of **1**) in dry CH_2Cl_2 (6 mL). The stirring was continued for 6 h at room temperature, and the solvent was evaporated to dryness. The solid formed upon addition of water was filtered, washed with water, and dried. Yield: 98% (190 mg), white solid, m.p. 320–325 °C (decomp.). $C_{24}H_{36}N_2O_2$ (384.56): calcd. C 74.96, H 9.44, N 7.28; found C 75.11, H 9.27, N 7.04. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (br. s, 1 H, NH), 4.05 (br. s, 2 H, NH_2), 3.44 (s, 1 H, AdCH), 2.37 (d, J = 13.8 Hz, 1 H, $AdCH_2$), 2.07 (d, J = 13.8 Hz, 1 H, $AdCH_2$), 1.94 (br. s, 3 H, CH^{Ad}), 1.90 (br. s, 3 H, CH^{Ad}), 1.75–1.45 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.27 (C=O), 166.74 (CONH), 71.03 (AdCH), 60.61 ($AdCH_2$), 42.32, 40.43 (CH_2^{Ad}), 38.26 (C^{Ad}), 36.73, 36.34 (CH_2^{Ad}), 34.20 (C^{Ad}), 28.55, 28.41 (CH^{Ad}) ppm. MS (ESI): *m*/*z* (%) = 407.9 (43) $[M + Na]^+$, 385.0 (100) $[M]^+$.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

2,4-Bis(1-adamantyl)-*N'*-phenylacetoacetylhydrazide (9): Obtained from **1** (1 mmol), phenylhydrazine (0.10 mL, 1 mmol), and triethylamine (0.2 mL, 1.5 mmol) as described for **8**. The product was purified by column chromatography (CH_2Cl_2). Yield: 39% (90 mg), pale-brown solid, m.p. 221–225 °C. $C_{30}H_{40}N_2O_2$ (460.65): calcd. C 78.22, H 8.75, N 6.08; found C 78.35, H 8.60, N 6.35. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (s, 1 H, NH), 7.21 (m, 2 H, Ph), 6.89 (m, 1 H, Ph), 6.83 (m, 2 H, Ph), 3.51 (s, 1 H, AdCH), 2.49 (d, J = 13.2 Hz, 1 H, $AdCH_2$), 2.14 (d, J = 13.2 Hz, 1 H, $AdCH_2$), 2.03 (br. s, 3 H, CH^{Ad}), 1.97 (br. s, 3 H, CH^{Ad}), 1.80–1.58 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.65 (C=O), 166.05 (CONH), 148.16 (C^{Ph}), 129.02, 121.14, 113.90 (CH^{Ph}), 71.66 (AdCH), 60.85 ($AdCH_2$), 42.52, 40.56 (CH_2^{Ad}), 38.56 (C^{Ad}), 36.57, 36.38 (CH_2^{Ad}), 34.59 (C^{Ad}), 28.63, 28.48 (CH^{Ad}) ppm. MS (ESI): m/z (%) = 460.3 (100) $[M]^+$.

2,4-Bis(1-adamantyl)-*N*-hydroxyacetoacetamide (10): Obtained from **1** (1 mmol), hydroxylamine hydrochloride (104 mg, 1.5 mmol), and triethylamine (0.48 mL, 3.5 mmol) as described for **8**. The product was purified by column chromatography (CH_2Cl_2/MeOH, 99:1). Yield: 52% (100 mg), white solid, m.p. 150–152 °C. $C_{24}H_{35}NO_3$ (385.54): calcd. C 74.77, H 9.15, N 3.63; found C 74.98, H 9.01, N 3.38. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.55 (s, 1 H, OH), 8.94 (s, 1 H, NH), 2.80 (s, 1 H, AdCH), 2.28 (d, J = 15.1 Hz, 1 H, $AdCH_2$), 2.00 (d, J = 15.1 Hz, 1 H, $AdCH_2$), 1.89 (br. s, 6 H, CH^{Ad}), 1.74–1.51 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 204.53 (C=O), 163.76 (CONH), 67.82 (AdCH), 55.06 ($AdCH_2$), 41.62, 39.65, 36.50, 36.39 (CH_2^{Ad}), 35.82, 33.03 (C^{Ad}), 27.98, 27.95 (CH^{Ad}) ppm. MS (ESI): m/z (%) = 385.4 (100) $[M]^+$.

2-[2,4-Bis(1-adamantyl)acetoacetyl]hydrazinecarboxamide (11): Obtained from **1** (1 mmol), semicarbazide hydrochloride (168 mg, 1.5 mmol), and triethylamine (0.48 mL, 3.5 mmol) as described for **8**. Yield: 93% (200 mg), white solid, m.p. 139–141 °C. $C_{25}H_{37}N_3O_3$ (427.58): calcd. C 70.23, H 8.72, N 9.83; found C 70.30, H 8.85, N 9.61. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (br. s, 1 H, NH), 8.52 (br. s, 1 H, NH), 5.76 (br. s, 2 H, NH_2), 3.43 (s, 1 H, AdCH), 2.41 (d, J = 13.0 Hz, 1 H, $AdCH_2$), 2.06 (d, J = 13.0 Hz, 1 H, $AdCH_2$), 1.96 (br. s, 3 H, CH^{Ad}), 1.91 (br. s, 3 H, CH^{Ad}), 1.70–1.51 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.62 (C=O), 167.78 (CONH), 160.04 ($CONH_2$), 71.21 (AdCH), 60.59 ($AdCH_2$), 42.23, 40.28 (CH_2^{Ad}), 38.58 (C^{Ad}), 36.75, 36.33 (CH_2^{Ad}), 34.60 (C^{Ad}), 28.60, 28.50 (CH^{Ad}) ppm. MS (ESI): m/z (%) = 352.3 (100) $[M - NH_2NHCONH_2]^+$.

1-Adamantyl-1-(1-adamantylacetyl)ketene (12): Triethylamine (0.28 mL, 2 mmol) was added to a cooled (0–5 °C) solution of **2** (obtained from 1 mmol of **1**) in dry CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. From the solid residue the target product was extracted with dry hexane (3 × 3 mL). Yield: 97% (170 mg), light-yellow solid, m.p. 93–95 °C. IR (neat): $\tilde{\nu}$ = 2091 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 2.06 (s, 2 H, $AdCH_2$), 2.02–1.90 (m, 12 H, CH^{Ad}, CH_2^{Ad}), 1.71–1.63 (m, 18 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 198.70 (C=O), 191.22 (C=*C*=O), 63.21 (*C*=C=O), 56.32 ($AdCH_2$), 41.87, 40.21, 36.05, 36.90 (CH_2^{Ad}), 33.47 (C^{Ad}), 33.21 (CH_2^{Ad}), 28.26, 28.14 (CH^{Ad}) ppm.[34] MS (ESI): m/z (%) = 352.0 (100) $[M]^+$.

2,4-Bis(1-adamantyl)-*N*-[2-(3*H*-indol-3-yl)ethyl]acetoacetamide (16): A solution of tryptamine (160 mg, 1 mmol) in dry CH_2Cl_2 (3 mL) was added to a stirred solution of **12** (obtained from 1 mmol of **1**) in dry CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 4 h and then purified by chromatography (dry CH_2Cl_2). Yield: 59% (2 steps, 150 mg), white solid, m.p. 105–107 °C. $C_{34}H_{44}N_2O_2$ (512.73): calcd. C 79.65, H 8.65, N 5.46; found C 79.38, H 8.72, N 5.71. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (br. s, 1 H, NH), 7.63 (d, J = 7.9 Hz, 1 H, Ind), 7.35 (d, J = 8.1 Hz, 1 H, Ind), 7.20–7.09 (m, 2 H, Ind, NH), 7.06 (d, J = 2.2 Hz, 1 H, Ind), 3.63 (m, 2 H, $NHCH_2CH_2$), 3.36 (s, 1 H, AdCH), 2.98 (m, 2 H, $NHCH_2CH_2$), 2.39 (d, J = 13.6 Hz, 1 H, $AdCH_2$), 2.06 (d, J = 13.6 Hz, 1 H, $AdCH_2$), 1.92 (br. s, 6 H, CH^{Ad}), 1.72–1.50 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.63 (C=O), 165.93 (CONH), 136.39, 127.20 (C^{Ind}), 121.98, 121.94, 119.22 (CH^{Ind}), 112.74 (C^{Ind}), 111.10 (CH^{Ind}), 72.08 (AdCH), 60.93 ($AdCH_2$), 42.36, 40.41 (CH_2^{Ad}), 39.49 ($NHCH_2CH_2$), 38.18 (C^{Ad}), 36.58, 36.39 (CH_2^{Ad}), 34.18 (C^{Ad}), 28.44, 28.43 (CH^{Ad}), 25.43 ($NHCH_2CH_2$) ppm. MS (ESI): m/z (%) = 512.6 (100) $[M]^+$.

2,4-Bis(1-adamantyl)-*N*-(6-methylpyridin-2-yl)acetoacetamide (17): Obtained from **1** (1 mmol) and 2-amino-6-methylpyridine (108 mg, 1 mmol) as described for **16** with the reaction time increased to 24 h. Yield: 61% (2 steps, 140 mg), white solid, m.p. 90–92 °C. $C_{30}H_{40}N_2O_2$ (460.65): calcd. C 78.22, H 8.75, N 6.08; found C 78.37, H 8.63, N 5.92. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1 H, NH), 7.98 (d, J = 8.2 Hz, 1 H, Py), 7.54 (t, J = 8.2 Hz, 1 H, Py), 6.87 (d, J = 7.4 Hz, 1 H, Py), 3.43 (s, 1 H, AdCH), 2.47 (s, 3 H, CH_3), 2.45 (d, J = 14.2 Hz, 1 H, $AdCH_2$), 2.20 (d, J = 14.2 Hz, 1 H, $AdCH_2$), 2.00 (br. s, 3 H, CH^{Ad}), 1.93 (br. s, 3 H, CH^{Ad}), 1.69–1.50 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.09 (C=O), 164.88 (CONH), 157.09, 150.30 (C^{Py}), 138.22, 119.14, 110.55 (CH^{Py}), 72.87 (AdCH), 60.87 ($AdCH_2$), 42.39, 40.56 (CH_2^{Ad}), 38.99 (C^{Ad}), 36.63, 36.39 (CH_2^{Ad}), 34.22 (C^{Ad}), 28.65, 28.48 (CH^{Ad}), 24.12 (CH_3) ppm. MS (ESI): m/z (%) = 460.5 (100) $[M]^+$.

2,4-Bis(1-adamantyl)-*N*-(4-methylphenyl)acetoacetamide (18): Obtained from **1** (1 mmol) and 4-toluidine (107 mg, 1 mmol) as described for **17**. Yield: 52% (2 steps, 120 mg), white solid, m.p. 197–200 °C. $C_{31}H_{41}NO_2$ (459.67): calcd. C 81.00, H 8.99, N 3.05; found C 81.18, H 8.90, N 3.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1 H, NH), 7.46 (d, J = 8.1 Hz, 2 H, Tol), 7.13 (d, J = 8.1 Hz, 2 H, Tol), 3.45 (s, 1 H, AdCH), 2.49 (d, J = 13.8 Hz, 1 H, $AdCH_2$), 2.32 (s, 3 H, CH_3), 2.17 (d, J = 13.8 Hz, 1 H, $AdCH_2$), 2.01 (br. s, 3 H, CH^{Ad}), 1.95 (br. s, 3 H, CH^{Ad}), 1.67–1.60 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.22 (C=O), 163.96 (CONH), 135.06, 133.79 (C^{Tol}), 129.38, 119.99 (CH^{Tol}), 72.62 (AdCH), 61.19 ($AdCH_2$), 42.47, 40.60 (CH_2^{Ad}), 39.04 (C^{Ad}), 36.63, 36.42 (CH_2^{Ad}), 34.37 (C^{Ad}), 28.69, 28.49 (CH^{Ad}), 20.82 (CH_3) ppm. MS (ESI): m/z (%) = 460.4 (100) $[M + H]^+$, 459.7 (70) $[M]^+$.

1,3-Bis(1-adamantyl)acetone (22): A mixture of acid **3** (or anhydride **2**) obtained from **1** (1 mmol), water (2.7 mL), acetic acid (4.5 mL), and H_2SO_4 (0.5 mL) was stirred at reflux for 5 h and cooled. The solid formed was filtered, washed with water, and dried. Yield: 92% (150 mg), white solid, m.p. 235–240 °C (ref.[19] 235–249 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 4 H, $AdCH_2$), 1.95 (br. s, 6 H, CH^{Ad}), 1.90 (br. s, 3 H, CH^{Ad}), 1.70–1.60 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9 (C=O), 58.77 ($AdCH_2$), 42.50, 36.78 (CH_2^{Ad}), 33.65 (C^{Ad}), 28.59 (CH^{Ad}) ppm.

Reaction of 6 with Thiourea: To a stirred solution of thiourea (87 mg, 1.14 mmol) in anhydrous ethanol (2 mL) was added a solution of NaOEt (52 mg, 0.76 mmol) in anhydrous EtOH (1 mL), followed after 5 min with ester **6** (170 mg, 0.38 mmol). The mixture was heated at reflux for 3 h, cooled, and concentrated. The residue was acidified with 1 N HCl to pH 6, and the solid formed was filtered, washed with water, and dried. The product mixture was separated by column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH, 99:1) to give thiouracils **23** and **24**.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(6*E*)-5-(1-Adamantyl)-6-(1-adamantylmethylene)-2-thioxotetrahydropyrimidin-4(1*H*)-one (23). Yield: 25% (39 mg), white solid, m.p. 230–245 °C (decomp.). $C_{25}H_{34}N_2OS$ (410.62): calcd. C 73.13, H 8.35, N 6.82, S 7.81; found C 73.18, H 8.20, N 6.65, S 7.72. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1 H, NH), 8.46 (s, 1 H, NH), 4.30 (s, 1 H, AdCH=C), 2.52 (s, 1 H, AdCH), 2.03 (br. s, 3 H, CH^{Ad}), 2.02 (br. s, 3 H, CH^{Ad}), 1.85–1.65 (m, 24 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.87 (C=O), 166.32 (C=S), 127.97 (Ad*C*H=C), 124.56 (C^{6U}), 58.60 (AdCH), 42.95, 39.93 (CH_2^{Ad}), 37.79 (C^{Ad}), 36.40, 36.36 (CH_2^{Ad}), 35.92 (C^{Ad}), 28.72, 28.25 (CH^{Ad}) ppm.

5-(1-Adamantyl)-6-(1-adamantylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (24): Yield: 51% (80 mg), white solid, m.p. 340–345 °C (decomp.). $C_{25}H_{34}N_2OS$ (410.62): calcd. C 73.13, H 8.35, N 6.82, S 7.81; found C 73.25, H 8.43, N 6.68, S 7.69. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.20 (s, 1 H, NH), 11.01 (s, 1 H, NH), 2.65 (s, 2 H, $AdCH_2$), 2.12 (s, 3 H, CH_2^{Ad}), 1.97 (br. s, 3 H, CH^{Ad}), 1.94 (br. s, 3 H, CH^{Ad}), 1.65–1.50 (m, 18 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, CF_3CO_2D): δ = 170.79 (C=O), 164.21 (C=S), 150.84 (C^{5U}), 125.92 (C^{6U}), 45.04 ($AdCH_2$), 42.85, 40.95 (CH_2^{Ad}), 39.91 (C^{Ad}), 36.46, 36.35 (CH_2^{Ad}), 35.43 (C^{Ad}), 28.78, 28.72 (CH^{Ad}) ppm.

Reaction of 6 with Cyanoacetamide: To a stirred warm solution of **6** (200 mg, 0.45 mmol) and cyanoacetamide (42 mg, 0.5 mmol) in methanol (8 mL) was added a solution of KOH (38 mg, 0.68 mmol) in methanol (0.7 mL). The mixture was stirred at reflux for 12 h, cooled, and then concentrated. The paste-like residue was acidified with 1 N HCl to pH 6 and allowed to stand overnight. The water solution was carefully decanted from the solid formed, the procedure was repeated with warm water until all the phenol was removed. The solid was filtered and dried to give pure methyl ester **4** in 81% yield (140 mg).

2,4-Bis(*tert*-butyl)acetoacetic Acid (27): Obtained from **25** (1 mmol) as described for **3**. The oil formed after the evaporation of TFAA was washed with cold water, and the wet residue slowly transformed into a crystalline solid. Yield: 94% (105 mg), white solid, m.p. 70–72 °C. (ref.[31] 78 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.46 (s, 1 H, *t*BuCH), 2.51 (d, *J* = 15.6 Hz, 1 H, *t*BuCH$_2$), 2.38 (d, *J* = 15.6 Hz, 1 H, *t*BuCH$_2$), 1.08 [s, 9 H, C(CH$_3$)$_3$], 1.00 [s, 9 H, C(CH$_3$)$_3$] ppm.

Phenyl 2,4-Bis(*tert*-butyl)acetoacetate (28): Obtained from **25** (1 mmol) and a solution of phenol (190 mg, 2 mmol) and triethylamine (0.41 mL, 3 mmol) in dry CH_2Cl_2 (6 mL) as described for **6**. The product was purified by column chromatography (CH_2Cl_2/hexane, 1:1). Yield: 76% (110 mg), colorless oil. $C_{18}H_{26}O_3$ (290.40): calcd. C 74.45, H 9.02; found C 73.97, H 8.95. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 2 H, Ph), 7.23 (m, 1 H, Ph), 7.04 (m, 2 H, Ph), 3.59 (s, 1 H, *t*BuCH), 2.58 (d, *J* = 16.4 Hz, 1 H, *t*BuCH$_2$), 2.50 (d, *J* = 16.4 Hz, 1 H, *t*BuCH$_2$), 1.18 [s, 9 H, C(CH$_3$)$_3$], 1.06 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.86 (C=O), 167.25 (CO_2Ph), 150.35 (C^{Ph}), 129.42, 125.98, 121.33 (CH^{Ph}), 68.21 (*t*BuCH), 56.90 (*t*BuCH$_2$), 34.78 [*C*(CH$_3$)$_3$], 31.15 [*C*(CH$_3$)$_3$], 29.47 [C(*C*H$_3$)$_3$], 28.18 [C(*C*H$_3$)$_3$] ppm.

2,4-Bis(*tert*-butyl)-*N*-benzylacetoacetamide (29): Obtained from **25** (1 mmol), benzylamine (0.21 mL, 2 mmol), and triethylamine (0.41 mL, 3 mmol) as described for **6**. Yield: 79% (120 mg), white solid, m.p. 121–122 °C. $C_{19}H_{29}NO_2$ (303.44): calcd. C 75.21, H 9.63, N 4.62; found C 75.63, H 9.42, N 4.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.73 (m, 6 H, NH, Ph), 4.44 (dd, *J* = 14.8, 5.8 Hz, 1 H, PhCH$_2$), 4.39 (dd, *J* = 14.8, 5.8 Hz, 1 H, PhCH$_2$), 3.49 (s, 1 H, *t*BuCH), 2.53 (d, *J* = 15.0 Hz, 1 H, *t*BuCH$_2$), 2.30 (d, *J* = 15.0 Hz, 1 H, *t*BuCH$_2$), 1.03 [s, 9 H, C(CH$_3$)$_3$], 0.97 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.65 (C=O), 166.80 (CONH), 138.21 (C^{Ph}), 128.5, 127.64, 127.30 (CH^{Ph}), 69.88 (*t*BuCH), 59.22 (*t*BuCH$_2$), 43.47 (PhCH$_2$), 35.96 [*C*(CH$_3$)$_3$], 31.41 [*C*(CH$_3$)$_3$], 29.48 [C(*C*H$_3$)$_3$], 28.42 [C(*C*H$_3$)$_3$] ppm.

Phenyl 2,4-Bis(isopropyl)acetoacetate (30): Obtained from **26** (2 mmol) and a solution of phenol (560 mg, 6 mmol) and triethylamine (0.83 mL, 6 mmol) in dry CH_2Cl_2 (6 mL) as described for **6**. The product was purified by column chromatography (CH_2Cl_2/hexane, 1:1). Yield: 46% (130 mg), colorless oil. $C_{16}H_{22}O_3$ (262.35): calcd. C 73.25, H 8.45; found C 72.96, H 8.87. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 2 H, Ph), 7.22 (m, 1 H, Ph), 7.04 (m, 2 H, Ph), 3.43 (d, *J* = 9.4 Hz, 1 H, *i*PrCHCO), 2.55 [m, 1 H, (CH$_3$)$_2$C*H*], 2.53 (dd, *J* = 17.2, 7.0 Hz, 1 H, *i*PrCH$_2$), 2.47 (dd, *J* = 17.2, 6.6 Hz, 1 H, *i*PrCH$_2$), 2.23 [m, 1 H, (CH$_3$)$_2$C*H*], 1.09 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CH), 0.99 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CH), 0.94 [d, *J* = 6.7 Hz, 6 H, (C*H*$_3$)$_2$CH] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.98 (C=O), 167.54 (CO_2Ph), 150.31 (C^{Ph}), 129.37, 125.98, 121.18 (CH^{Ph}), 66.71 (*i*Pr*C*HCO), 51.71 (*i*PrCH$_2$), 28.64, 23.88 [(CH$_3$)$_2$*C*H], 22.35, 22.33, 20.45, 20.34 [(*C*H$_3$)$_2$CH] ppm.

1,3-Bis(*tert*-butyl)acetone (31): Obtained from **27** (100 mg, 0.47 mmol) as described for **22**. The oil formed was taken up in CH_2Cl_2, washed with water, dried, and then concentrated. Yield: 88% (70 mg), colorless oil (Lit.[30a] oil, b.p. 112.4 °C/76.5 Torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 4 H, *t*BuCH$_2$), 0.99 [s, 18 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.14 (C=O), 56.97 (*t*BuCH$_2$), 31.01 [*C*(CH$_3$)$_3$], 29.67 [C(*C*H$_3$)$_3$] ppm.

X-ray Crystallographic Analysis of 7 and 23: Crystals of compounds **7** and **23** suitable for X-ray analysis were grown at room temperature from ethanol/CH_2Cl_2 (2:1) and ethanol/H_2O (2:1) solutions, respectively. The data were collected at room temperature [295(2) K] by using graphite monochromated Cu-K_α (1.54179 Å) radiation, ω-scan mode. The WinGX standard procedure was applied for data reduction.[35] Two standard reflections were measured every 120 min as intensity control. No absorption correction was applied. The structure was solved and refined with the SHELX program.[36] The non-hydrogen atoms were refined by using the anisotropic full-matrix least-squares procedure. The hydrogen atoms attached to carbon atoms were placed in the calculated positions and allowed to ride on their parent atoms [C–H 0.93–0.97 for **7** and 0.97–0.98 for **23**; U_{iso} = 1.2U_{eq} (parent atom)]. Hydrogen atoms attached to nitrogen and oxygen were determined from a difference Fourier synthesis and refined freely. The isotropic displacement parameters for freely refined hydrogen atoms are in the range of 0.049(1)–0.07 Å for **7** and 0.04–0.07(1) Å for **23**. Refinement was made against all reflections. The threshold expression of $F^2 > 2\sigma(F^2)$ was used for calculation of *R* factors, the final values of which are 0.086 for **7** and 0.071 for **23**. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using DIAMOND software.[37] CCDC-765964 (for **7**) and -765965 (for **23**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for 7: $C_{31}H_{41}NO_2$, *M* = 459.7, monoclinic, *a* = 13.056(4) Å, *b* = 25.726(2) Å, *c* = 14.877(1) Å, β = 94.48(1)°, *V* = 4981.8(4) Å^3, space group $P2_1/n$, *Z* = 8, $D_{calcd.}$ = 1.226 g cm^{-3}, μ(Mo-K_α) = 0.917. Crystal size = 0.28 × 0.14 × 0.14 mm; 8392 reflections of which 3701 > 2σ(*I*).

Crystal Data for 23: $C_{25}H_{34}N_2O{\cdot}C_2H_6O$, *M* = 456.67, monoclinic, *a* = 6.803(2) Å, *b* = 15.954(2) Å, *c* = 23.138(3) Å, β = 90.85(1)°, *V* = 2510.8(8) Å^3, space group $P2_1/c$, *Z* = 8, $D_{calcd.}$ = 1.208 g cm^{-3},

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

μ(Mo-K_α) = 1.335. Crystal size = 0.1 × 0.1 × 0.4 mm; 4824 reflections of which 3380 > 2σ(I).

Supporting Information (see footnote on the first page of this article): Detailed X-ray crystal analysis data for **7** and **23**.

Acknowledgments

Financial support from the Russian Foundation for Basic Research (project No. 09-03-00971) is gratefully acknowledged.

[1] S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto, V. Zanirato, *Chem. Rev.* **1995**, *95*, 1065–1114.
[2] a) G. Zhou, D. Lim, D. M. Coltart, *Org. Lett.* **2008**, *10*, 3809–3812; b) A. R. Katritzky, Z. Wang, M. Wang, C. R. Wilkerson, C. D. Hall, N. G. Akhmedov, *J. Org. Chem.* **2004**, *69*, 6617–6622 and references cited therein.
[3] H. Meerwein, D. Vossen, *J. Prakt. Chem.* **1934**, *141*, 149–166.
[4] E. H. Man, C. R. Hauser, *J. Am. Chem. Soc.* **1950**, *72*, 3294–3295.
[5] G. Sartori, G. Casnati, F. Bigi, D. Baraldi, *Tetrahedron Lett.* **1991**, *32*, 2153–2156 and references cited therein.
[6] a) E. R. Talaty, A. E. Dupuy Jr., A. E. Cancienne Jr., *J. Heterocycl. Chem.* **1967**, *4*, 657–658; b) P. A. Krasutskii, I. G. Semenova, M. I. Novikova, A. G. Yurchenko, V. P. Tikhonov, V. M. Belikov, Yu. N. Belokon', *J. Org. Chem. (USSR)* **1985**, *21*, 1327–1332; c) P. A. Krasutskii, N. S. Chesskaya, V. N. Rodionov, O. P. Baula, A. G. Yurchenko, *J. Org. Chem. (USSR)* **1985**, *21*, 1533–1539.
[7] Y. I. Smushkevich, V. Y. Smushkevich, M. I. Usorov, *J. Chem. Res. (S)* **1999**, 407.
[8] E. J. Bourne, M. Stacey, J. C. Tatlow, R. Worrall, *J. Chem. Soc.* **1954**, 2006–2012.
[9] R. Leung-Toung, C. Wentrup, *Tetrahedron* **1992**, *48*, 7641–7645.
[10] C. O. Kappe, R. A. Evans, C. H. L. Kennard, C. Wentrup, *J. Am. Chem. Soc.* **1991**, *113*, 4234–4237.
[11] A. Stadler, K. Zangger, F. Belaj, G. Kollenz, *Tetrahedron* **2001**, *57*, 6757–6763.
[12] G. Kollenz, W. Heilmayer, C. O. Kappe, B. Wallfisch, C. Wentrup, *Croat. Chem. Acta* **2001**,*74*, 815–823.
[13] All attempts to carry out the cycloaddition reactions were performed as follows: under dry argon, a solution of α-oxo ketene **12** (0.5 mmol) in hexane (3 mL) was treated with the dienophile (1 equiv.), and the mixture was stirred for 9 h at room temp. Analysis of the reaction mixture showed no products, but the starting α-oxo ketene unmodified.
[14] C. O. Kappe, C. Wentrup, G. Kollenz, *Monatsh. Chem.* **1993**, *124*, 1133–1141.
[15] J. Strating, J. Scharp, H. Wynberg, *Rec. Trav. Chim.* **1970**, *89*, 23–31.
[16] M. Ohno, M. Itoh, T. Ohashi, S. Eguchi, *Synthesis* **1993**, 793–796.
[17] G. A. Olah, A.-h. Wu, O. Farooq, *Synthesis* **1989**, 566–567.
[18] G. Kollenz, S. Holzer, C. O. Kappe, T. S. Dalvi, W. M. F. Fabian, H. Sterk, M. W. Wong, C. Wentrup, *Eur. J. Org. Chem.* **2001**, 1315–1322.
[19] H. Stetter, G. Becker, *Justus Liebigs Ann. Chem.* **1976**, 1992–1996.
[20] H. Stetter, E. Rauscher, *Chem. Ber.* **1960**, *93*, 2054–2057.
[21] F. N. Stepanov, L. I. Sidorova, N. A. Dovgan', *Zh. Org. Khim. (USSR)* **1972**, *8*, 1834–1837.
[22] A. Gonzalez, J. Marquet, M. Moreno-Mañas, *Tetrahedron* **1986**, *42*, 4253–4257.
[23] J. Clariana, S. García-Granda, V. Gotor, A. Gutiérrez-Fernández, A. Luna, M. Moreno-Mañas, A. Vallribera, *Tetrahedron: Asymmetry* **2000**, *11*, 4549–4557.
[24] a) J. P. Jonak, S. F. Zakrzewski, L. H. Mead, M. T. Hakala, *J. Med. Chem.* **1970**, *13*, 1170–1172; b) J. P. Jonak, S. F. Zakrzewski, L. H. Mead, *J. Med. Chem.* **1972**, *15*, 662–664; c) J. P. Jonak, L. H. Mead, Y. K. Ho, S. F. Zakrzewski, *J. Med. Chem.* **1973**, *16*, 724–725.
[25] M. Matković, J. Veljković, K. Mlinarić-Majerski, K. Molčanov, B. Kojić-Prodić, *J. Mol. Struct.* **2007**, *832*, 191–198.
[26] B. Orzeszko, Z. Kazimierczuk, J. K. Maurin, A. E. Laudy, B. J. Starościak, J. Vilpo, L. Vilpo, J. Balzarini, A. Orzeszko, *Il. Farmaco* **2004**, *59*, 929–937.
[27] a) K. M. Bormasheva, O. N. Nechaeva, I. K. Moiseev, *Russ. J. Org. Chem.* **2008**, *44*, 1760–1764; b) I. K. Moiseev, N. V. Makarova, M. N. Zemtsova, *Russ. J. Org. Chem.* **2001**, *37*, 453–474.
[28] a) J. W. Schulenberg, US Patent 3839460, **1974** [*Chem. Abstr.* **1975**, *82*, 16399]; b) D. H. R. Barton, H. Togo, S. Z. Zard, *Tetrahedron* **1985**, *41*, 5507–5516.
[29] J. M. Bobbitt, D. A. Scola, *J. Org. Chem.* **1960**, *25*, 560–564.
[30] a) A. L. Liberman, T. V. Vasina, *J. Gen. Chem. (USSR)* **1962**, *32*, 3179–3182; b) F. C. Whitmore, C. D. Wilson, J. V. Capinjola, C. O. Tongberg, G. H. Fleming, R. V. McGrew, J. N. Cosby, *J. Am. Chem. Soc.* **1941**, *63*, 2035–2041.
[31] The only published synthesis of this compound involved the pyrolysis of *tert*-butyl ketene bis(trimethylsilyl)acetal followed by the solvolysis of the formed disilylated 2-*tert*-butyl-3-oxo-5,5-dimethylhexanoic acid: C. Ainsworth, Y.-N. Kuo, *J. Organomet. Chem.* **1972**, *46*, 73–87.
[32] a) K. Bott, *Chem. Ber.* **1968**, *101*, 564–573; b) V. V. Kovalev, L. M. Alimbarova, E. A. Shokova, G. S. Katrukha, *Pharm. Chem. J.* **2009**, *43*, 485–490.
[33] For the preparation of the NMR sample, anhydride **2** was additionally washed with fresh TFAA, dried, and then dissolved in freshly dried $CDCl_3$.
[34] Initially, **12** was obtained and characterized directly in the NMR tube: dry triethylamine (0.07 mL, 0.5 mmol) was added to the NMR tube, containing a solution of **2** (obtained from 0.5 mmol of **1**) in freshly prepared dry $CDCl_3$. The sample was stored at room temperature for 0.5 h and then the spectra were acquired. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 2 H, $AdCH_2$), 1.78–1.71 (m, 12 H, CH^{Ad}, CH_2^{Ad}), 1.51–1.38 (m, 18 H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.10 (C=O), 193.21 (C=*C*=O), 64.10 (*C*=C=O), 56.73 ($AdCH_2$), 42.09, 40.48, 36.20, 36.11 (CH_2^{Ad}), 33.64 (C^{Ad}), 33.53 (CH_2^{Ad}), 28.32, 28.16 (CH^{Ad}) ppm.
[35] K. Harms, S. Wocadlo, *XCAD-4: Program for Processing CAD-4 Diffractometer Data*, University of Marburg, Germany, **1995**.
[36] G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.
[37] K. Brandenburg, *DIAMOND*, Release 2.1d. Crystal Impact GbR, Bonn, Germany, **2000**.

Received: March 5, 2010
Published Online: May 19, 2010

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim