149 (32), 135 (52), 121 (45), 107 (53), 93 (50), 79 (54), 69 (36), 57 (40), 41 (43).

Fraction 2: 2e-*tert*-butyl-9e-iodo-4,4-dimethyladamantane[10] (**40**, 20.5 mg, 0.06 mmol); yield 12%, colorless viscous oil; IR 1385 (m, CH_3), 1365 (s, $C(CH_3)_3$), 710; MS 331 (0.4, $M^+ - CH_3$), 219 (100, $M^+ - I$), 163 (26, $M^+ - I - C_4H_8$), 149 (22), 135 (12), 121 (13), 107 (17), 91 (24), 79 (36), 69 (24), 57 (84), 41 (43).

Reaction of 13 with HI. **13** (60 mg, 0.23 mmol) in 10 mL of CCl_4/HI(g); CC: PE/AC (50:1).

4-Hydroxy-2-methyl-11-methylene-2,4-ethanoadamantane[10] (**34**, 35.2 mg, 0.17 mmol): yield 75%; colorless viscous oil; IR 3595 (m, OH), 3440 (m, br, OH), 3075 (2, C=CH_2), 1375 (m, CH_3); MS 204 (100, M^+), 189, (62, $M^+ - CH_3$), 176 (15, $M^+ - C_2H_4$), 161 (30, $M^+ - C_2H_4 - CH_3$), 150 (16), 133 (15), 123 (52), 109 (46), 105 (24), 95 (28), 91 (36), 79 (41), 67 (18), 55 (20), 41 (33).

Reaction of 14 with HI. **14** (19.8 mg, 0.08 mmol) in 5 mL of CCl_4/HI(g); CC: PE/AC (50:1).

27 (9.8 mg, 0.05 mmol): yield 60%.

Acknowledgment. The authors are deeply grateful to Prof. M. A. McKervey (Belfast, Northern Ireland) for valuable discussions and helpful suggestions. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Supplementary Material Available: Tables of ^{13}C and ^1H NMR chemical shifts and positional assignments as well as the ^1H and ^{13}C NMR spectra for compounds **20–26**, **29–36**, and **38–42** (43 pages). Ordering information is given on any current masthead page.

Transacetoacetylation with *tert*-Butyl Acetoacetate: Synthetic Applications

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Reaction of various nucleophiles with *tert*-butyl acetoacetate (*t*-BAA, **1a**) is shown to be a convenient method for the preparation of a wide variety of acetoacetic acid derivatives. This material can be used to prepare acetoacetates and acetoacetamides from a wide variety of alcohols and amines. Reaction of **1a** with an unhindered primary amine such as *n*-heptylamine under standard conditions gives unwanted byproducts due to the formation of the enamines **24** and **25**. Formation of these byproducts can be minimized by dilution and/or altering the mode of addition.

Introduction

Acetoacetylated materials (**1**) are of interest as chemical intermediates in the pharmaceutical, agrichemical, chemical, and polymer industries.[1,2] The lachrymatory properties of diketene along with concerns regarding its toxicity and shipping have predicated a need for alternative acetoacetylation technologies. One such "diketene-free" approach which has been described by Clemens, Hyatt,[3a,b] and Kato[3c,d] involves the thermal reaction of 2,2,6-trimethyl-4*H*-dioxin-4-one (**2**) with nucleophiles to produce acetoacetic acid derivatives in good yield (eq 1). Mechanistic studies have suggested that this reaction proceeds via the intermediacy of acetylketene (**3**).[3e] While the laboratory utility of dioxinone **2** has been well documented, it has yet to gain widespread use. Another "diketene-free" approach to the preparation of acetoacetates involves the transesterification of the corresponding nucleophile with an appropriate acetoacetate (transacetoacetylation). This approach appeared particularly worthy of attention since it should, in principle, be readily amenable to industrial application. While the use of this reaction has been demonstrated by the work of Bader,[4a,b] Taber,[4c] Gilbert,[4d] and

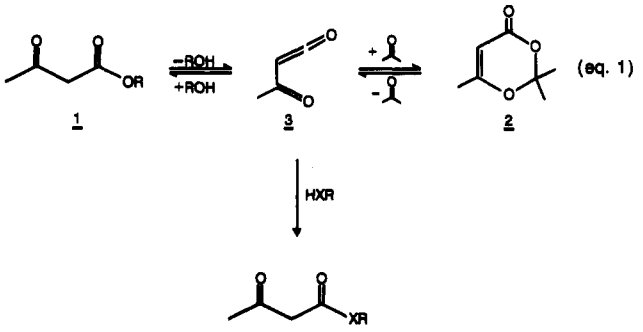


Table I. Rate Constants for Reaction of Various Acetoacetates (1a–g) and 2,2,6-Trimethyl-4*H*-dioxin-4-one (2) with *n*-Butyl Alcohol at Various Temperatures

entry	compound	R	T (°C)	$k \times 10^4$ [a]
1	**1a**	tBu	91.9	1.65
2	**1a**	tBu	98.7	2.50
3	**1a**	tBu	106.0	5.16
4	**1b**	Et	91.9	0.102
5	**1b**	Et	98.7	0.190
6	**1b**	Et	106.0	0.370
7	**1c**	Me	91.9	0.097
8	**1d**	iBu	91.9	0.138
9	**1e**	iPr	91.9	0.140
10	**1f**	$HC(iPr)_2$	91.9	0.083
11	**1g**	tAm	91.9	1.46
12	TKD (**2**)[b]		91.9	1.07
13	TKD (**2**)[b]		98.5	3.08
14	TKD (**2**)[b]		106.7	6.32

[a] First-order rate constant in s^{-1}. Data from ref 5a unless otherwise indicated. [b] See ref 3e for a complete listing of kinetic parameters for this compound.

(1) (a) Clemens, R. J. Proceedings of the Fifteenth Water-Borne and Higher-Solids Coatings Symposium; 1988, 55. (b) Rector, F. D.; Blount; W. W.; Leonard, D. R. *Ibid.* 1988, 68. (c) Witzeman, J. S.; Nottingham, W. D.; Rector, F. D. *Ibid.* 1989, 400.

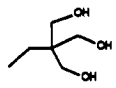
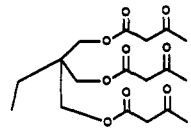
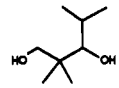
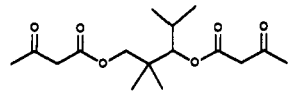
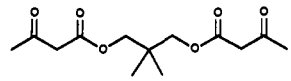
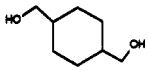
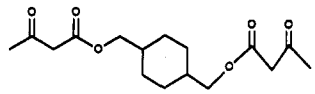
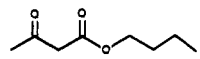
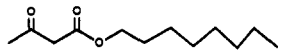
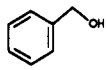
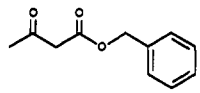
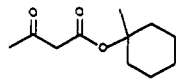
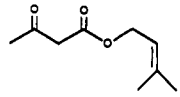
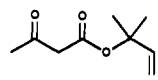
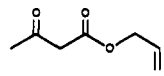
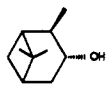
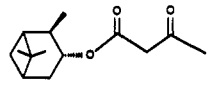
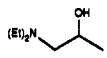
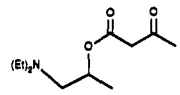
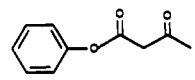
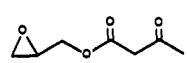
(2) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241.

(3) (a) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431. (b) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *Ibid.* **1984**, *49*, 5105. (c) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315. (d) Sato, M.; Ogasawara, H.; Yohizumi, E.; Kato, T. *Ibid.* **1983**, *31*, 1902. (e) Clemens, R. J.; Witzeman, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186.

(4) (a) Bader, A. R.; Cummings, L. O.; Vogel, H. A. *J. Am. Chem. Soc.* **1951**, *73*, 4195. (b) Bader, A. R.; Vogel, H. A. *Ibid.* **1952**, *74*, 3992. (c) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618. (d) Gilbert, J. C.; Kelly, T. A. *Ibid.* **1988**, *53*, 449. (e) Carroll, M. F.; *Proc. XIth Intern. Congr. Pure Appl. Chem.* **1947**, *2*, 39; *Chem. Abstr.* **1951**, *45*, 7015e. (f) Cossy, J.; Thelland, A. *Synthesis* **1989**, 753.

0022-3263/91/1956-1713$02.50/0

Table II. Yields from Reaction of Various Alcohols with *tert*-Butyl Acetoacetate

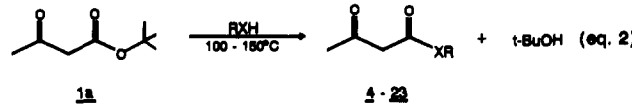
alcohol	product	structure no.	method[a]	% yield
		4	B	90
		5	A	87
		6	A B	87 81
		7	A	69[b]
		8	A	87
		9	B	83
		10	B	89
		11	B	83
		12	B	97
		13	B	72[c]
		14	C	74
		15	B	90
		16	B	84
		17	B	74
		18	B	73

[a] See the Experimental Section for a description of the methods. [b] Yield of crystalline material, some cis isomer lost in recrystallization. [c] Reaction also produced 5–10% of 6-methyl-5-hepten-2-one, presumably from Carroll rearrangement of the acetoacetate product.

Cossy,[4f] the utility of this process in large scale and/or industrial processes has been limited by the long reaction times, excess reagents, dilute solutions, and/or large amounts of DMAP catalyst required. Spectroscopic[5a] and kinetic[5a,b] studies have indicated that the transacetoacetylation reaction proceeds via a mechanism in which acetylketene (3) is formed in the rate-limiting unimolecular step. Our recent kinetic studies[5a] on this reaction demonstrated that the more hindered *tert*-butyl acetoacetate (*t*-BAA, **1a**) is ca. 15–20-fold more reactive than the more commonly used methyl or ethyl analogues (Table I). The purpose of this work was thus to examine the general synthetic utility of *t*-BAA in the preparation of acetoacetates and acetoacetamides under conditions of industrial and preparative relevance.

Results and Discussion

A variety of acetoacetates (Table II) and acetoacetamides (Table III) have been prepared by reaction of the corresponding nucleophile with *t*-BAA (eq 2). The

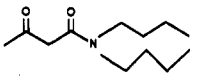
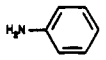
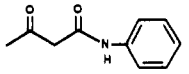
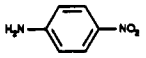
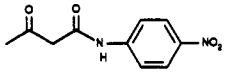
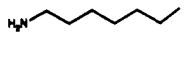
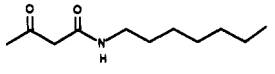
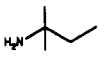
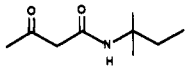


1a **4 - 23**

preparations are easily carried out by heating the acetoacetate and nucleophile at 100–150 °C in toluene or xylene in the absence of any catalyst.[6a,b] This is most easily

(5) (a) Witzeman, J. S. *Tetrahedron Lett.* **1990**, *31*, 1401. (b) Campbell, D. S.; Lawrie, C. W. *J. Chem. Soc., Chem Commun.* **1971**, 355.

Table III. Yields from Reaction of Various Amines with *tert*-Butyl Acetoacetate

amine	product	structure no.	method[a]	% yield
$HN(n\text{-}C_4H_9)_2$		19	A	96
		20	A	83
		21	B	86
		22	D	77[b]
		23	D C	80 71

[a] See the Experimental Section for a description of the methods. [b] Reaction also gave enamines **24** and **25** (see text).

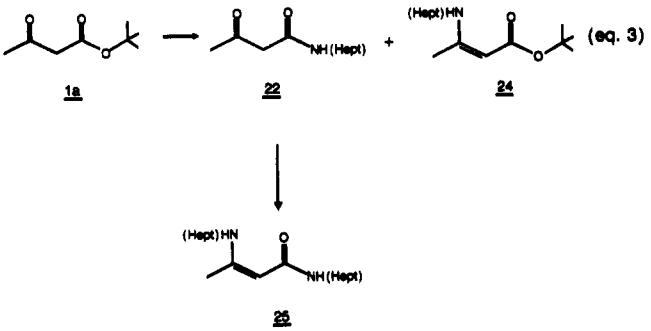
accomplished by heating the solution in an open Erlenmeyer flask (method A) or in a flask equipped with a distillation column and still head (method B). For low-boiling nucleophiles which are not easily separated from *tert*-butyl alcohol by distillation, the reaction can be affected by heating **1a** and a slight excess of the nucleophile under reflux for 1–3 h (method C). This latter method is quite effective for preparation of allyl acetoacetate (**14**). The more rapid rate of the transacetoacetylation reactions of **1a** relative to the ethyl or methyl analogues makes this reaction quite facile even at 100 °C.

The reaction thus appears to be quite general, can usually be carried out with equimolar amounts of alcohol and acetoacetate in concentrated solutions, does not require catalysts,[6b] and is much more rapid than other transacetoacetylation processes. The ability to carry out these reactions stoichiometrically and in good yield makes isolation of the resultant product quite simple, usually via simple distillation or, when possible, recrystallization.

While methods A–C are, in general, readily applicable to the preparation of a wide variety of acetoacetates and acetoacetamides, several interesting observations regarding these preparations are worthy of mention. The acetoacetylation of 1-methyl-1-cyclohexanol to give **11** illustrates that higher boiling tertiary alcohols can be acetoacetylated with *t*-BAA. Similarly, the tertiary allylic alcohol 2-methyl-3-buten-2-ol can also be acetoacetylated with *t*-BAA to give **13** in good yield. This reaction also produces 5–10% of 6-methyl-5-hepten-2-one, presumably via Carroll rearrangement[6c,d] (formally an Oxy-Claisen rearrangement of the enolized acetoacetate followed by decarboxylation) of **13**. By slow addition of **1a** to a preheated solution of toluene and the alcohol it was possible to obtain the desired acetoacetate in good yield. Gilbert[4d] has noted that this material cannot be prepared using ethyl acetoacetate. The use of *t*-BAA thus offers a decided advantage over other acetoacetates in the acetoacetylation of hindered alcohols, particularly ones such as **13**, which are unstable toward heating.[6e] The highly hindered isopinocampheol acetoacetate can also be prepared from the corresponding alcohol and **1a** in good yield. The good yields obtained in the preparation of **16** and **18** indicate that this reaction tolerates other functionality as well.

The yield for preparation of phenyl acetoacetate (**17**) under standard reaction conditions was poor, but could be improved significantly when cyclohexane was used to help azeotropically remove *tert*-butyl alcohol from the reaction. The sluggishness of the reaction between **1a** and phenol presumably reflects the thermodynamic preference for alkyl acetoacetates over the phenyl analogue.[3e] The presence of dehydroacetic acid in some of these reaction mixtures indicates that phenyl acetoacetate may itself be thermally unstable.

The preparation of acetoacetamides from secondary or aromatic amines proceeds readily and in good yield (Table III). Reaction of **1a** with *n*-heptylamine under standard transacetoacetylation conditions produces in addition to the desired acetoacetamide **22**, the enamines **24** and **25** in a proportion of 3.8:7.8:1 (eq 3). Since the transacetoacetylation process has been shown to be a first-order reaction, while the formation of enamines is presumably second-order, it was anticipated that more dilute conditions would favor formation of **22** over **24**. Initial experiments in which the concentrations of the reagents were reduced from ca. 4 to 1 M did, in fact, show an increased yield of **22** along with a concomitant increase in the yield of **25**. This latter observation suggested that **25** arises from subsequent reaction of **22** rather than **24**, which was further indicated by control experiments (see the Experimental Section). It was possible to prepare **22** in acceptable yield by slow addition of *n*-heptylamine to a dilute, preheated solution of **1a** (method D). No such complication was noted with the more sterically hindered *tert*-amylamine, which produced the *tert*-amyl acetoacetamide (**23**) in 80% yield. This approach thus offers a convenient alternative to the methodology recently described by Cossy.[4f]



The preceding demonstrates the synthetic utility of *tert*-butyl acetoacetate in the transacetoacetylation reac-

(6) (a) Other nonnucleophilic solvents such as ketones and esters can also be used in this reaction. Compounds 4–6 have also been prepared in the absence of solvent in >90% yield on 400–800-g scales. (b) Studies of the effect of pTSA on the reaction of **1a** and/or ethyl acetoacetate (EAA, **1b**) with hexanediol indicated that this acid had no effect on the rate of the transacetoacetylation reaction while facilitating the subsequent and undesirable decomposition of the acetoacetate product. (c) Carroll, M. F. *J. Chem. Soc.* **1940**, 704, 1266; **1941**, 507. (d) Kimel, W. U.S. Patent 2,638,484 (1953); *Chem. Abstr.* **1954**, *48*, 2763. (e) The inability to prepare **13** from EAA (**1b**) and the corresponding alcohol is presumably due to both the much slower rate of this reaction as well as the thermal instability of the resulting product.

tion. This reagent is storage stable, inexpensive, and commercially available. These factors along with the ease and versatility of preparations employing **1a** demonstrate that this reagent has industrial as well as laboratory utility.

Experimental Section

All solvents and reagents used were high-purity reagent-grade materials and were used without further purification. Gas chromatographic analysis were conducted using an automatic injector on a 0.25 mm × 30 m DB-5 capillary column. Typical conditions used for the gas chromatographic analysis were: injector T = 180 °C (or less), initial T = 70 °C, hold time 2–5 min, 5 °C/min to 135 °C then 20 °C/min to 240. In order to get reproducible and reliable GC analyses, particularly of the thermally labile *tert*-butyl acetoacetate, it is necessary to keep the injector temperature below 180 °C. Using these conditions it is possible to monitor the reactions and accurately assay purity of all materials discussed here except phenyl acetoacetate. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, in $CDCl_3$ solvent. The multiplicity of carbons, when given, was assigned by use of the DEPT pulse sequence.[7a] The spectral data given are for the keto form of the acetoacetate. All materials showed a 5–20% contribution of the enol form, which is characterized by an upfield methyl at ca. 1.85–1.97 ppm, an olefinic H at 4.85–5.4 ppm, and an O*H* resonance at >10.5 ppm. High-resolution ammonia CI spectra (CI-HRMS) were obtained according to the method of Haddon.[7b] Elemental analyses were determined in the Physical and Analytical Chemistry Division of the Eastman Chemical Company Research Laboratories.

Method A. This method consisted of heating the solution of nucleophile, *tert*-butyl acetoacetate in xylene on a hot plate. (*Caution*: Potential for fire exists). At approximately 120 °C the evolution of *tert*-butyl alcohol was apparent. The reaction was stopped once the solution reached the boiling point of xylene (ca. 10–15 min after boiling first noted).

Method B. The nucleophile, *t*-BAA, and solvent were heated in a flask equipped with distillation column (Vigreux, Oldershaw, or Penn-State packed) still head and thermometers in the base and head of the system. The system was brought to reflux under an N_2 atmosphere and the *tert*-butyl alcohol byproduct was collected once the temperature in the still head reached 75–90 °C (bp *t*-BuOH = 82 °C). The distillate was typically 85–99% *tert*-butyl alcohol as determined by gas chromatography, with the remainder being reaction solvent. For thermally sensitive materials the heating time can be reduced by dropwise addition of the *t*-BAA to a preheated (ca. 90–120 °C) solution of nucleophile and solvent.

Method C. This procedure is the method of choice for low-boiling nucleophiles and consists of merely heated the nucleophile, *t*-BAA, and solvent at reflux with gas chromatographic monitoring. Reaction times are typically on the order of 30 min to 1 h after reflux has been established. For these volatile nucleophiles it was usually desirable to use 1.2–2.0 equiv of nucleophile.

The following acetoacetates were prepared by methods A, B, and/or C as indicated in the abbreviated format.

2,2-Bis(hydroxymethyl)butanol Trisacetoacetate (Trimethylolpropane Trisacetoacetate) (4).[8a] Method B from 47.5 g (0.354 mol) of trimethylolpropane and 171.0 g (1.081 mol) of **1a** in 100 mL of xylene. Yield: 123 g (90%). ^{1}H NMR: δ 0.90 (t, J = 7.50 Hz, 3 H), 1.49 (q, J = 7.50 Hz, 2 H), 2.27 (s, 9 H), 3.50 (s, 6 H), 4.10 (s, 6 H). ^{13}C NMR: δ 6.81 (CH_3), 22.45 (CH_2), 29.93 (CH_3), 40.50 (C), 49.53 (CH_2), 64.13 (CH_2), 166.95, 200.61. IR (neat): 2979, 2939, 2890, 1749, 1716, 1465, 1410, 1360, 1320, 1258, 1150, 1035 cm^{-1}. CI-HRMS (NH_3 CI gas): 404.1929 (calcd for $C_{18}H_{26}O_9$ + NH_4^+ 404.1921).

2,2,4-Trimethylpentane-1,3-diol Bisacetoacetate (5). Method A by heating 10.1 g (0.069 mol) of 2,2,4-trimethylpentane-1,3-diol and 22.4 g (0.142 mol) of **1a** in xylene (30 mL) in a stirred Erlenmeyer flask at reflux for 30 min. The resulting material was short-path distilled to give 18.8 g (87%) of **5**, bp 152 °C (0.05 mmHg). ^{1}H NMR: δ 0.90 (d, J = 6.8 Hz, 3 H), 0.97 (s, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 1.01 (s, 3 H), 1.99–2.13 (m, 1 H), 2.29 (s, 6 H), 3.50 (s, 2 H), 3.52 (s, 2 H), 3.83 (d, J = 11.0 Hz, 1 H), 4.01 (d, J = 11.0 Hz, 1 H), 4.82 (d, J = 3.0 Hz, 1 H). ^{13}C NMR: δ 17.37 (CH_3), 20.33 (CH_3), 21.53 (CH_3), 22.58 (CH_3), 27.90 (CH), 29.88 (CH_3), 30.02 (CH_3), 38.33 (C), 49.60 (CH_2), 70.60 (CH_2), 80.82 (CH), 166.90, 167.20, 200.79. IR (neat): 2959, 2870, 1742, 1715, 1645, 1471, 1408, 1375, 1360, 1314, 1250, 1170, 1150, 1105, 1031 cm^{-1}. EI-MS: m/z (rel int) 271 (1), 213 (3), 187 (22), 111 (23), 103 (28), 85 (100), 69 (18), 56 (29), 43 (96). FD-HRMS: 314.1743 (calcd for $C_{16}H_{22}O_6$ 314.1722). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.1; H, 8.3. Found: C, 61.3; H, 8.5.

2,2-Dimethyl-1,3-propanediol Bisacetoacetate (Neopentyl Glycol Bisacetoacetate) (6).[3a] Method A from 10.0 g (0.096 mol) of neopentyl glycol and 32.1 g (0.203 mol) of **1a** in 32 mL of xylene to give 22.83 g of **6** (87%) or, alternatively, by method B from 159.2 g (1.529 mol) of neopentyl glycol and 491.3 g (3.106 mol) of **1a** in 450 mL of toluene to give 337.1 g (81%) of **6**, bp 135–142 °C (0.10 mmHg). The resulting material was identical with that prepared by Clemens and Hyatt.[3a]

***cis*- and *trans*-1,4-Bis(hydroxymethyl)cyclohexane Bisacetoacetate (1,4-Cyclohexanedimethanol Bisacetoacetate) (7).**[3a] Method A from 9.8 g (0.068 mol) of 1,4-cyclohexanedimethanol (cis/trans = 28:72) and 22.1 g (0.135 mol) of **1a** in 28 mL of xylene. Analysis of the resulting crude product indicated that it consisted of a 28:72 mixture of the cis and trans acetoacetates as determined by integration of the C*H*$_2$O proton doublets at 4.08 (cis) and 3.92 (trans)[3a] ppm. Recrystallization of the crude solid from petroleum ether/acetone gave 14.7 g (69%) of crystalline product, mp 78–79 °C, which was shown by NMR analysis to be ca. 88% trans. This material was identical with that prepared by Clemens and Hyatt.[3a]

***n*-Butyl Acetoacetate (8).**[8b] Method A from 10.0 g (0.135 mol) of 1-butanol and 21.4 g (0.135 mol) of **1a** in 40 mL of xylene. The resulting crude product was short-path distilled to give 15.83 g of **8** and 3.18 g of recovered **1a** (87% based on recovered **1a**), bp 55 °C (0.1 mmHg).

***n*-Octyl Acetoacetate (9).**[8c] Method B from 13.0 g (0.10 mol) of 1-octanol and 16.6 g (0.105 mol) of **1a** in 50 mL of toluene. The resulting crude product was short-path distilled to give 17.76 g (83%) of **9**, bp 100 °C (0.9 mmHg).

Benzyl Acetoacetate (10).[8c] Method B from 10.8 g (0.10 mol) of benzyl alcohol and 16.6 g (0.105 mol) of **1a** in 50 mL of toluene. The resulting product was short-path distilled at 110–120 °C (0.9 mm) to give 19.6 g (89%) of **10**.

1-Methyl-1-cyclohexyl Acetoacetate (11).[3a] Method B by heating 11.4 g (0.141 mol) of 1-methyl-1-cyclohexanol and 16.2 g (0.110 mol) of **1a** in 50 mL of toluene at 108–130 °C for 3 h. The resulting product was distilled through an 8-in. Vigreax column to give 20.45 g of **11**, bp 57 °C (0.02 mmHg). This material was identical with an authentic sample provided by Dr. Clemens.

3-Methyl-2-buten-1-yl Acetoacetate (12).[4d,8d] Method B from 8.6 g (0.10 mol) of 3-methyl-2-butenol and 16.2 g (0.103 mol) of **1a** in 50 mL of toluene. The resulting crude material was distilled at 63 °C (0.07 mmHg) to give 16.5 g (97%) of **12**.

2-Acetoacetoxy-2-methyl-3-butene (13).[6d,8d,e] In a flask equipped with a magnetic stirrer, thermometer, addition funnel, 11-plate Oldershaw column, still head, and nitrogen inlet was placed 30 mL of toluene. The toluene was heated to reflux, and a solution of 9.61 g (0.0608 mol) of **1a** and 8.41 g (0.0977 mol) of 2-methyl-3-buten-2-ol was rapidly added. The solution was heated at reflux for 4 h with distillative removal of the volatile byproducts. The resulting distillate was determined by GC analysis to be 47% *tert*-butyl alcohol, 22% 2-methyl-3-buten-2-ol, and 30% toluene. The resulting crude product was vacuum distilled to give 1.74 g of a forecut (bp 46–62 °C (4.9 mmHg)) which GC and ^{1}H NMR analysis showed to consist of 31% 2-methyl-6-heptanone, 5% **1a**,

(7) (a) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323. (b) Haddon, W. F.; Millington, D. S.; England, R. E.; Elliger, C. A.; Manners, G. D. Proceedings of the 36th ASMS Conference, June 5–10, 1988, 1396.

(8) (a) Leonard, D. P.; Truesdale, J. H.; Scherrer, J. H.; Wright, H. J. European Patent Appl. 227,454 (July 1, 1987); Hoy, K. L.; Milligan, C. L. U.S. Patent 3,668,183 (June 6, 1972); G. B. Patent 1,131,374 (Oct 23, 1968). (b) Soleil, J.; Loppinet, J. *Chim. Ther.* **1966**, 309. (c) Manz, O. *Justus Liebigs Ann. Chem.* **1974**, 345. (d) Cannic, G.; Linstrumelle, G.; Julia, S. *Bull. Soc. Chim. Fr.* **1968**, *12*, 4913. (e) Pogrebnoi, S. I.; Kalyan, Y. B.; Krimer, M. Z.; Smit, W. A. *Tetrahedron Lett.* **1987**, *28*, 4893. (f) Rall, K. B.; Perekalin, V. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1955**, *25*, 259. (g) Kuenstle, G.; Jung, H. German Patent 3,113,987 (April 7, 1981). (h) Beger, J.; Thielman, C. *J. Prakt. Chem.* **1981**, *323*, 337. (i) Chick, F.; Wilsmore, N. T. M. *J. Chem. Soc.* **1908**, 946.

and 65% **13**. The main distillation cut was obtained at 70–73 °C (4.4 mmHg) and consisted of 6.44 g (72%) of pure **13**.

In another run 9.86 g (0.0623 mol) of **1a**, 6.57 g of 2-methyl-3-buten-2-ol, and 21 mL of toluene were heated at reflux for 5 h with distillative removal of the volatile byproducts to give after distillation 5.08 g (48%) of pure **13**, 2.07 g of a 76:12:12 mix of **13**:**1a**:2-methyl-6-heptanone, and 0.63 g of a 13:7:80 mix of these materials. The identity of the Carroll rearrangement product was confirmed by comparison with the ^{1}H NMR spectrum of an authentic sample and by GC–MS library spectral matching techniques.

For **13**. ^{1}H NMR: δ 1.53 (s, 6 H), 2.24 (s, 3 H), 3.36 (s, 2 H), 5.10 (d, J = 10.9 Hz, 1 H), 5.19 (d, J = 17.5 Hz, 1 H), 6.08 (dd, J = 10.8 17.5 Hz, 1 H). ^{13}C NMR: δ 25.81, 29.57, 50.74, 81.77, 112.98, 141.98, 165.97, 200.98. FDMS: 170 (M^+).

Allyl Acetoacetate (14).[8c,d] Method C from 6.30 g (0.11 mol) of allyl alchol, 12.9 g (0.082 mol) of **1a**, and 12 mL of xylene. The solution was heated to reflux (103 °C) and maintained at that temperature for 2 h. The resulting crude material was concentrated in vacuo and distilled at 77 °C (8.5 mmHg) to give 8.6 g (74%) of allyl acetoacetate.

Isopinocampheol Acetoacetate (15).[3a] Method B by heating 7.71 g (48.7 mol) of **1a** and 7.45 g (48.3 mmol) of isopinocampheol in 13.2 mL of toluene for 3 h with distillative removal of the volatile byproducts. The resulting crude material was concentrated and distilled to give 10.34 g (90%) of isopinocampheol acetoacetate, bp 82 °C (0.05 mmHg). This product was identical with a sample provided by Dr. Clemens.

1-(Diethylamino)-2-acetoacetoxypropane (16). Method B by addition of 32.40 g (0.205 mol) of *tert*-butyl acetoacetate to a solution of 30 mL (26.67g, 0.203 mol) of 1-(diethylamino)-2-propanol and 30 mL of toluene which had been preheated to 100 °C. The solution was heated at reflux (120–130 °C) for a total of 3.5 h, after which time GC analysis indicated complete reaction. The reaction mixture was concentrated in vacuo and distilled to give 36.73 g (84%) of acetoacetate **16**, bp 74 °C (0.07 mmHg). ^{1}H NMR: δ 0.95 (t, J = 7.15 Hz, 6 H), 1.20 (d, J = 6.29 Hz, 3 H), 2.25 (s, 3 H), 2.34 (dd, J = 5.40, 13.6 Hz, 1 H), 2.47–2.63 (m, 5 H), 3.42 (s, 2 H), 5.01–5.12 (m, 1 H). ^{13}C NMR: δ 11.58, 17.85, 29.65, 47.47, 50.27, 57.64, 70.18, 166.88, 201.02 ppm. IR (neat): 2978, 2818, 1740, 1715, 1648, 1452, 1412, 1361, 1315, 1240, 1205, 1154, 1059 cm^{-1}. EI-MS: m/z (rel int) 215 (2), 114 (7), 87 (14), 86 (100), 58 (15), 42 (19). HRMS: 215.1534 (calcd for $C_{11}H_{21}NO_3$ 215.1521).

Phenyl Acetoacetate (17).[8f] This material was prepared from a modification of method B. In a flask equipped with a magnetic stirrer, a thermometer, a nitrogen inlet, an addition funnel, an 18-in. Vigreux column, and a still head was placed 30.1 g of phenol, 33.5 g of **1a**, 100 mL of xylene, and 110 mL of cyclohexane. The solution was warmed to reflux (100–135 °C) for 8 h and the *tert*-butyl alcohol/cyclohexane azeotrope was collected by distillation (bp 70–74 °C). The crude product was vacuum distilled to give 7.3 g of recovered **1a** and 21.9 g of **17** (74% based on recovered **1a**).

Glycidyl Acetoacetate (18).[8g] Method B by addition of a solution of 39.0 g (0.526 mol) of glycidol and 10 mL of toluene to a solution of 67.9 g (0.429 mol) of **1a** in 60 mL of toluene which had been heated to 120 °C. The solution was heated at reflux for 2 h and distilled at 76 °C (0.2 mmHg) to give 49.9 g (73%) of **18**. ^{1}H NMR: δ 2.22 (s, 3 H), 2.61 (dd, J = 2.61, 4.81 Hz, 1 H), 2.78 (dd, J = 1.08, 4.62 Hz, 1 H), 3.14–3.19 (m, 1 H), 3.46 (s, 2 H), 3.91 (dd, J = 6.25, 12.30 Hz, 1 H), 4.42 (dd, J = 1.91, 12.33 Hz, 1 H). ^{13}C NMR: δ 29.84, 44.30, 48.83, 49.46, 65.44, 166.99, 200.53. IR (neat): 3070, 3004, 2961, 2939, 1755, 1719, 1659, 1638, 1418, 1370, 1326, 1266, 1161, 1044 cm^{-1}. CI-MS: (NH_4^+ – CI), 159 (MH^+), 176 ($M + NH_4^+$). HRMS: 158.0601 (calcd for $C_7H_{10}O_4$ 158.0576).

***N*,*N*-Dibutylacetoacetamide (19).**[8h] Method A from 7.7 g (0.0596 mol) of dibutylamine and 9.2 g (0.058 mol) of **1a** in 25 mL of xylene. The resulting crude product was short-path distilled to give 11.92 g (96%) of **19**, bp 88–89 °C (0.1 mmHg).

Acetoacetanilide (20).[8i] Method A in 83% yield from 10.0 g (0.107 mol) of aniline and 17.2 g (0.109 mol) of **1a** in 25 mL of xylene. The resulting product crystallized upon cooling and was recrystallized from acetone to give 15.84 g (83%) of **20**, mp 83 °C (lit.[8i] mp 84 °C).

4-Nitroacetoacetanilide (21).[3a] Method B from 13.8 g (0.10 mol) of *p*-nitroaniline and 16.2 g (0.105 mol) of **1a** in 50 mL of toluene. The resulting product solidified on cooling to give 19.0 g (86%) of **21**, mp 115–120 °C (lit.[3a] mp 120–122 °C).

Method D: *N*-Heptylacetoacetamide (22).[3a] In a flask equipped with a Vigreux column, a temperature controller, an addition funnel, and a nitrogen inlet was placed 33.4 g (0.211 mol) of **1a**, and 500 mL of toluene. The solution was warmed to 105 °C, and a solution of 16.82 g (0.146 mol) of *n*-heptylamine in 100 mL of toluene was slowly added over 50 min while the volatile byproduct was recovered by distillation. The solution was heated for 25 min, cooled to room temperature, and concentrated in vacuo, and the solid product was filtered and recrystallized from petroleum ether/acetone to give 22.4 g (77%) of **22**.

In another run a solution of 15.9 g (0.101 mol) of *t*-BAA and 126 mL of xylene was warmed to 110 °C, and 8.2 g (0.071 mol) of *n*-heptylamine in 50 mL of xylene was added dropwise over 45 min during which time the reaction was allowed to warm to 120 °C. The solution was heated for 20 additional min, and the resulting crude material was purified as before to give 7.54 g (54%) of product.

When preparation of **22** was attempted according to method B from 64.5 g (0.408 mol) of **1a** and 46.6 g (0.405 mol) of *n*-heptylamine in 100 mL of toluene a 7.7:27.8:57.1:7.3 mixture of **1a**:**22**:**24**:**25** was obtained. Reaction of 15.7 g (0.099 mol) of **1a** and 11.54 g (0.100 mol) of amine in 190 mL of toluene gave **22** in 37% isolated yield and a GC proportion of **1a**:**22**:**25** of 1:3.6:1.45, with no **24** being detected by GC analysis. For **22**.[3a] ^{1}H NMR: δ 0.84–0.91 (m, 3 H), 1.26–1.32 (m, 8 H), 1.44–1.54 (m, 2 H), 2.27 (s, 3 H), 3.22–3.28 (m, 2 H), 3.41 (s, 2 H), 7.12–7.27 (br s, 1 H, NH). ^{13}C NMR: δ 13.59, 22.15, 24.47, 28.54, 28.99, 30.44, 31.34, 39.26, 49.72, 165.76, 204.81.

An authentic sample of **24** was prepared by heating 14.1 g (0.089 mol) of **1a**, 19.5 g (0.169 mol) of *n*-heptylamine, and 5 mg of *p*-toluenesulfonic acid monohydrate in 25 mL of toluene at reflux for 40 min. The crude product was distilled to give 12.3 g (54%) of **24**, bp 92 °C (0.04 mmHg). ^{1}H NMR: δ 0.87 (m, 3 H), 1.21–1.39 (m, 8 H), 1.45 (s, 9 H), 1.49–1.60 (m, 2 H), 1.87 (s, 3 H), 3.15 (q, J = 7.7 Hz, 2 H), 4.35 (s, 1 H), 8.45 (br s, 1 H, N*H*). ^{13}C NMR: δ 13.74 (CH_3), 19.02 (CH_3), 22.30 (CH_2), 26.59 (CH_2), 28.42 (CH_3), 28.73 (CH_2), 30.35 (CH_2), 31.45 (CH_2), 42.87 (CH_2), 77.57 (C), 83.41 (CH), 161.38, 171.00. IR: 3280, 2945, 2919, 2845, 1649, 1616, 1499, 1441, 1363, 1280, 1250, 1152 cm^{-1}. EI-MS: m/z (rel int) 255 (10), 199 (10), 184 (22), 182 (25), 156 (41), 140 (64), 128 (38), 115 (100), 96 (72), 84 (36), 57 (47), 41 (63). HRMS: 255.2198 (calcd for $C_{15}H_{29}NO_2$ 255.2209). Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.5; H, 11.5; N, 5.5. Found: C, 70.2; H, 11.9; N, 6.0.

An authentic sample of **25** was prepared by heating 5.69 g (0.029 mol) of **22** and 3.89 g (0.034 mol) of *n*-heptylamine in 50 mL of toluene for 1.5 h with distillative removal of the water with a Dean–Stark trap. The resulting oil was unstable to either flash chromatography or distillation and was thus characterized spectroscopically without further purification. ^{1}H NMR: δ 0.84–0.91 (m, 6 H), 1.22–1.41 (m, 12 H), 1.42–1.59 (m, 4 H), 1.86 (s, 3 H), 3.10–3.23 (m, 4 H), 4.25 (s, 1 H), 4.92 (br s, 1 H, NH), 9.02 (br s, 1 H, NH). ^{13}C NMR: δ 13.70 (2 C, CH_3), 19.05 (CH_3), 22.28 (2 C, CH_2), 26.61 (CH_2), 26.70 (CH_2), 28.76 (2C, CH_2), 29.95 (CH_2), 30.36 (CH_2), 31.42 (CH_2), 31.52 (CH_2), 38.57 (CH_2), 42.66 (CH_2), 84.20 (CH), 158.55 (C), 171.24. IR: 3295, 2950, 2920, 2848, 1630, 1593, 1540, 1488, 1465, 1439, 1278, 1209 cm^{-1}. MS (EI): 296 (23), 281 (9), 267 (18), 253 (26), 239 (19), 225 (19), 211 (20), 197 (7), 182 (100), 154 (29), 140 (32), 96 (39), 84 (57), 43 (59), 41 (80). GC–HRMS: 296.2845 (calcd for $C_{18}H_{36}N_2O$ 296.2828).

In a separate control experiment, 0.71 g (0.0028 mol) of **25** and 1.554 g (0.0135 mol) of *n*-heptylamine were heated in 10 mL of xylene at reflux (T = 131 °C). GC analysis of the reaction mixture showed less than 10% conversion to **24** after 2 h. After 40 h at reflux NMR analysis of the crude mixture showed it to be a 1.27:1 mixture of **25** and **24**. Thus this process is presumed to be negligible under the conditions used for preparation of **22**.

***tert*-Amylacetoacetamide (23).** Method D by addition of 12.68 g (0.145 mol) of *tert*-amylamine in 100 mL of toluene over 45 min to a preheated solution of 29.80 g (0.188 mol) of **1a** in 250 mL of toluene. The solution was heated at reflux for an additional 1.5 h, concentrated, and distilled to give 19.91 g (80%) of **23**, bp 91 °C (0.75 mmHg). This material could also be prepared in 70%

isolated yield by method C from 42.93 g (0.271 mol) of **1a** and 31.33 g (0.359 mol) of *tert*-amylamine in 50 mL of toluene. ^{1}H NMR: δ 0.76 (t, J = 7.45 Hz, 3 H), 1.21 (s, 6 H), 1.62 (q, J = 7.45 Hz, 2 H), 2.18 (s, 3 H), 3.26 (s, 2 H), 6.69 (br s, 1 H, NH). ^{13}C NMR: δ 7.96 (CH_3), 25.99 (2 C, CH_3), 30.72 (CH_3), 32.57 (CH_2), 50.72 (CH_2), 53.96 (C), 164.70, 205.49. IR: 3340, 3080, 2980, 2940, 2890, 1730, 1665, 1560, 1468, 1420, 1370, 1340, 1208, 1169 cm^{-1}. EI-MS: m/z (rel int) 171 (1), 156 (3), 142 (35), 72 (43), 58 (100), 43 (43). HRMS: 171.1260 (calcd for $C_9H_{17}NO_2$ 171.1259).

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Supplementary Material Available: A listing of additional spectral data for compounds **6**, **8–12**, **14**, and **15** as well as ^{1}H and ^{13}C spectra for compounds **5**, **16**, **23**, **24**, and **25** (12 pages). Ordering information is given on any current masthead page.

Construction of Trifluoromethylated Quarternary Carbons via Diels–Alder Reactions of 2-(Trifluoromethyl)propenoic Acid Derivatives: Application to the Synthesis of 16,16,16-Trifluororetinal[1]

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Diels–Alder reactions of 2-(trifluoromethyl)propenoic acid (**1**) and its 2,2,2-trifluoroethyl ester **2** with various dienes gave adducts in good yields. In Lewis acid catalyzed Diels–Alder reactions of **2**, the combination of the Lewis acid and solvent proved to be crucial. For example, polymerization occurred in the case of $TiCl_4$–CH_2Cl_2 and adduct formation was observed with $TiCl_4$–toluene and $TiCl_2$(O-*i*-Pr)$_2$–CH_2Cl_2. In the $TiCl_4$-catalyzed Diels–Alder reaction of the 2-(trifluoromethyl)propenoate ester **3** of D-pantolactone with butadiene, the formation of the *R* configurational quaternary carbon bearing the trifluoromethyl group was confirmed by X-ray crystallographic analysis of the adduct **20**. No polymerization of ester **3** could be detected in the presence of $TiCl_4$ in CH_2Cl_2. The reactivity difference between **2** and **3** in $TiCl_4$-catalyzed Diels–Alder reactions may possibly be attributable to the stabilization of the **3**–$TiCl_4$ complex or weakening of Lewis acidity by coordination of the bidentate ester group of **3**. The synthesis of *all-trans*-16,16,16-trifluororetinal (**4**), which is considered to be an important analogue for the study of retinal-binding protein, was conducted on the basis of these results. Comparison of the absorption maximum (362 nm) of **4** with other trifluororetinals **34** (362 nm) and **35** (382 nm) reported previously suggests the possibility of a large torsion of the conjugated system between the ring and the polyenal side chain in **4**.

Introduction

The introduction of fluoro substituents into biochemically important molecules has attracted much attention in organic, biological, and medicinal chemistry for studying the biochemical process of the parent molecule and/or enhanced or altered activity of the fluoro analogue.[2] For this purpose, new and/or more effective methods for the selective introduction of fluoro substituents into organic molecules should be developed. The growing number of fluorinated compounds, commercially available, should serve as starting materials for preparing functionalized fluoro molecules. It is also interesting to compare the reactivity of the fluorinated molecule with the related hydrocarbon during reactions. In recent examinations of the reactivity of fluorinated compounds, the electronic effect of the fluoroalkyl group had been found to considerably affect the stereochemical results in the asymmetric reduction of fluoroalkyl ketones with binaphthol-mediated aluminum hydride reagent,[3] in nucleophilic attack on trifluoromethylated cyclohexanone derivatives,[4] in the α-hydroxylation of the enolate prepared from γ,γ,γ-trifluoroester derivative,[5] and in Pd(0)-mediated intramolecular lactonization.[6] We describe herein the results of Diels–Alder reactions of 2-(trifluoromethyl)propenoic acid (**1**) and esters **2** and **3** for construction of quaternary carbons bearing a trifluoromethyl group and the preparation of 16,16,16-trifluororetinal (**4**).[7]

Results and Discussion

2-(Trifluoromethyl)propenoic acid (**1**) and its derivatives are strong acceptors in the Michael reaction and have been utilized in the synthesis of the fluoro analogues of nucleoside bases and amino acid derivatives.[8] The cyclo-

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