[Chem. Pharm. Bull. 36(9)3354—3372(1988)]

Cycloadditions in Syntheses. XXXVII.[1] Syntheses of 6-Trifluoromethyl-1,2,4-triazines and -1,2,4-triazin-5-ones and Their Pericyclic Reactions with Olefins

NOBUYA KATAGIRI,* HIROSHI WATANABE, and CHIKARA KANEKO*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received March 11, 1988)

6-Trifluoromethyl-1,2,4-triazines and -1,2,4-triazin-5-ones were synthesized to investigate the role of the trifluoromethyl group in their thermal as well as photochemical cycloaddition reactions with olefins. In photochemical 2+2 cycloaddition using the triazin-5-ones and -3,5-diones, the activation of the imine function by the trifluoromethyl group is demonstrated and a new route to azetidine derivatives having a trifluoromethyl group is disclosed. In thermal 4+2 cycloaddition using the corresponding triazines, acceleration of the so-called inverse electron demand Diels–Alder reaction is demonstrated. Clarification of the mechanisms of these reactions and their use in the synthesis of azetidin-2-ones and pyridines having a trifluoromethyl group are also described.

Keywords——photocycloaddition; inverse electron demand Diels–Alder reaction; 6-trifluoromethyl-1,2,4-triazin-5-one; 6-trifluoromethyl-1,2,4-triazine; 4-trifluoromethylazetidin-2-one; 3-trifluoromethylpyridine; methyl trifluoropyruvate

In the previous paper in this series,[2] we have demonstrated that an introduction of a trifluoromethyl group at the C=N bond of quinoxalin- and 1,4-benzoxazin-2-ones accelerates their photoaddition to olefins. Use of ketene as the olefin in the photoaddition reaction has provided a novel synthetic route to 4-trifluoromethylazetidin-2-ones.[3] The same acceleration by the trifluoromethyl group has also been observed in quinazolin-4-one derivatives.[4]

In order to see whether the activation of the imine function by the trifluoromethyl group in 2+2 photocycloaddition reaction is a general phenomenon and exists even in monocyclic series, we have examined the photoreaction of 6-trifluoromethyl derivatives of 1,2,4-triazin-5-ones with a variety of olefins. The fact that the first experimental demonstration of the inverse electron demand Diels–Alder reaction employed perfluoroalkylated 1,2,4,5-tetrazines[5] (using the perfluoroalkyl group as an accelerator of the reaction) led us, at the same time, to examine the Diels–Alder reaction of the corresponding triazines with electron-rich olefins, in order to see if the same effect also exists.

After establishing of a facile synthetic method for 6-trifluoromethyl-1,2,4-triazines and their 5-ones, efforts have also been made to provide new synthetic routes not only to 4-trifluoromethylazetidin-2-ones through photochemical 2+2 cycloaddition of the trizainones with ketene or allene as the olefin, but also to 3-trifluoromethylpyridines by Diels–Alder reaction of the triazines with electron-rich olefins. In this paper, we describe these results in three sections.

Synthesis of Trifluoromethyl-1,2,4-triazines and Their 5-ones

Our plan for the synthesis of the title compounds was to synthesize the 1,2,4-triazin-5-ones (the substrates for the photoaddition reaction) from readily available materials at first, and convert them to the corresponding triazines (the substrates for the Diels–Alder reaction) in the next step.

We chose methyl trifluoropyruvate (**1**) as the starting material for the synthesis of the triazinones. The ester (**1**) were synthesized readily from hexafluoropropylene oxide[6] (**2**: HFPO) by methanolysis, followed by treatment with sulfuric acid.[7]

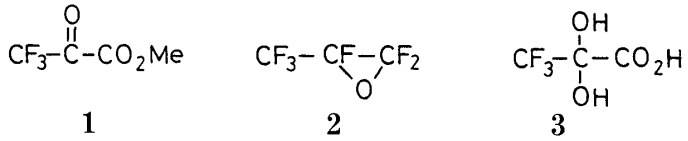
Though the ester (**1**) contains suitable functionalities for further manipulation, its chemistry has not yet been fully investigated, especially in relation to the synthesis of heterocyclic compounds having a trifluoromethyl group.

From this point of view, we were interested in studying the chemical behavior of this reagent towards amidrazones and comparing its usefulness in the synthesis of trifluoromethyl-1,2,4-triazin-5-one derivatives with that of **2** or its hydrolysis product (**3**: trifluoropyruvic acid hydrate[8]), both of which have been utilized[6] in the synthesis of trifluoromethylated heterocyclic compounds.

The reaction of **1** with benzamidrazone[9] was carried out in refluxing ethanol to give 3-phenyl-6-trifluoromethyl-1,2,4-triazin-5(2*H*)-one (**4a**) in 75% yield as the sole product. Though the formation of two isomers (**4a** and **5a**) is formally possible, it is clear that the terminal NH_2 group of the amidrazone attacks selectively the α-carbon of **1** giving an intermediate (**6a**) whose cyclization leads to the final product (**4a**). When *p*-toluamidrazone was used, the corresponding 5-one (**4b**) was obtained again as the major product. Concomitant formation of the other isomer (**5b**) in 20% yield probably reflects increased nucleophilicity of the imino group in the amidrazone due to an electron-donating effect of the tolyl group to give **7b**, whose cyclization leads to **5b**. The structures of these products (**4**—**8**) were determined by elemental analyses and acceptable spectral data.

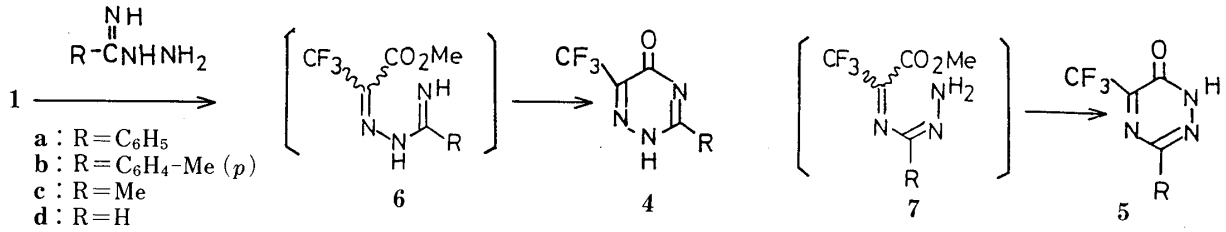
Though the yields are somewhat low, the reaction of **1** with acetamidrazone[10] and formamidrazone[11] also gave selectively the corresponding 5-one derivatives (**4c** and **4d**). The results of these reactions are summarized in Table I.

In order to compare the reactivity of **1** with that of **2** in the triazinone synthesis, **2** was



1 **2** **3**

Fig. 1



6 **4** **7** **5**

Chart 1

TABLE I. Reaction Conditions and Physical Properties of Compounds (**4** and **5**)

Compd.	R	Reaction conditions (Temp. and duration)	mp (°C)	Yield (%)
4a	C_6H_5	EtOH (Reflux, 15 min)	274—278	75
4b	C_6H_4–Me (*p*)	EtOH (Reflux, 15 min)	283—284	57
5b	C_6H_4–Me (*p*)		209—210	20
4c	Me	MeOH (Room temp., 12 h)	229—230	33
4d	H	MeOH (Room temp., 48 h)	159—160	8

reacted with benzamidrazone in ethanol (room temperature, sealed tube) to give two compounds (**4a** and **8a**) in yields of *ca.* 10%, respectively. The latter product was determined as a triazole derivative (**8a**). Since **2** is known to isomerize readily to perfluoropropionyl fluoride (**9**) in the presence of amines,[6] the formation of **8a** is reasonably explained by assuming the corresponding acylamidrazone derivative as the intermediate.

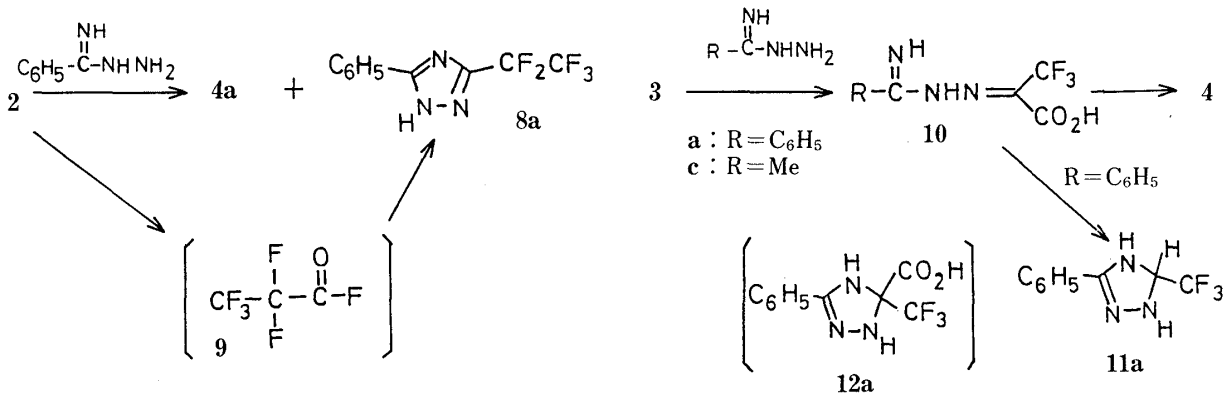


Chart 2

Use of **3** instead of **1** was then examined. When **3** was reacted with arylamidrazones, the corresponding condensation products (**10a** and **10c**) were obtained in nearly quantitative yields. While heating of **10a** in dimethylformamide (DMF) at 140 °C afforded the dihydro-1,2,4-triazole derivative (**11a**) through **12a** as the direct precursor, use of acetic acid as the solvent led to the formation of the triazinone (**4a**). The overall yields of the triazinones (**4**), though much better than those from **2**, are lower than those starting from **1**.

As is evident from the above results, the behavior of methyl trifluoropyruvate (**1**) is noteworthy, and its reactions with amidrazones are useful for the synthesis of trifluoromethyl-1,2,4-triazin-5-ones (**4**). The superiority of **1** over **2** and **3** as a synthon for **4** is attributable to its stability, ease of handling, high reactivity of the α-carbon atom due to the strongly electron-withdrawing trifluoromethyl group, and a facile and selective six-membered ring formation from the intermediate (**6**).

The triazin-5-ones (**4a—c**) thus obtained were then treated with methyl iodide in acetone in the presence of potassium carbonate to give three methylated products (**13—15**) as summarized in Table II.

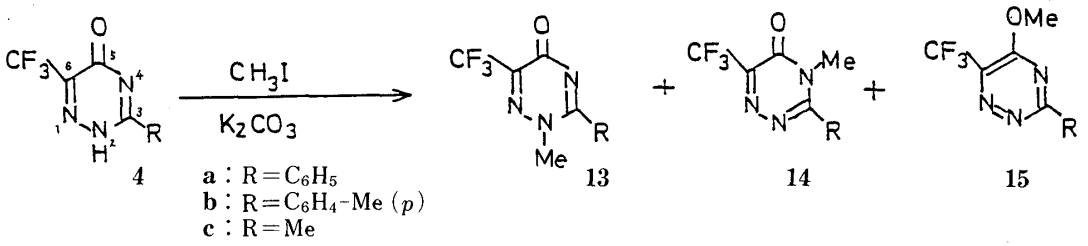


Chart 3

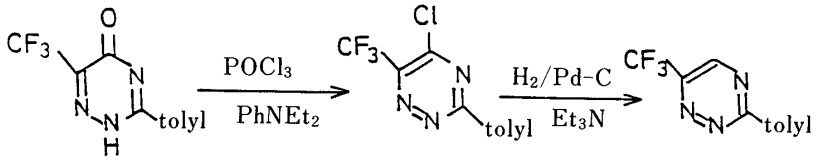
By inspection of the infrared (IR) spectra of the three products, the structures of the methoxy derivatives (**15a** and **15b**) were readily determined (absence of carbonyl absorption). Since the carbonyl absorptions of **14** appear at around 1700 cm^{-1} and the frequencies are higher than those (1675—1680 cm^{-1}) of **13**, the former compounds are assigned as the 4-methyl derivatives and the latter ones as the 2-methyl derivatives.[12] In good accordance with the above assumption, the ultraviolet (UV) spectra of **14** show their maxima in a longer-wavelength region than those of **13**.[13]

A 6-trifluoromethyl-1,2,4-triazine derivative (**17b**) was synthesized in almost quantitative

TABLE II. Physical Properties of Methylated Products (**13**—**15**)[a]

Compd.	R	**13** mp: °C (Yield: %) [λ_{max}: nm]	**14** mp: °C (Yeild: %) [λ_{max}: nm]	**15** mp: °C (Yeild: %) [λ_{max}: nm]
a	C_6H_5	138—140 (49) [206, 248]	102—104 (18) [202, 217, 294]	97—99 (27) [209, 260, 286]
b	C_6H_4–Me(*p*)	152—154 (50) [204, 246]	144—145 (14) [206, 217, 299]	123—125 (27) [211, 267, 291]
c	Me	130—132 (52) [237, 273]	82—84 (22) [215, 287]	—

a) UV spectra were measured in methanol.



4b **16b** **17b**

Chart 4

yield from **4b** by chlorination followed by catalytic hydrogenation.

Photochemical 2+2 Cycloaddition of 1,2,4-Triazin-5-ones and Related Compounds to Olefins

In bicyclic heteroaromatics involving an enone function in the ring system, the photoaddition to olefins proceeds by irradiation at ≥ 300 nm in a transparent solvent.[14] In the corresponding monocyclic series, however, acetone or its equivalents must be used as a sensitizer.[15] This fact indicates that the addition reaction proceeds *via* the triplet excited state (T_1) of these heteroaromatics. The need for the sensitizer in the monocyclic series simply reflects the fact that the intersystem crossing from S_1 to T_1 (the species necessary for the photoaddition reaction) is far less efficient in these compounds than in the bicyclic series.[16] Preliminary study of the photochemical behavior of the trifluoromethylated 1,2,4-triazin-5-ones, however, has shown that intersystem crossing in these compounds is an efficient process, and hence the desired photoaddition to olefins occurs smoothly by irradiation in a transparent solvent. A similar study on the corresponding 1,2,4-triazine-3,5-diones showed, on the contrary, that the desired photoaddition proceeds only in acetone due to an inefficient intersystem crossing.

Given that an efficient intersystem crossing is possible, irradiation of 1,2,4-triazin-5-one derivatives at ≥ 300 nm (high-pressure mercury lamp with a Pyrex filter) in methanol containing olefins was carried out. The reactions using the 2-methyl derivative (**13b**) gave products obviously formed by the additions across both the N_1–C_6 and C_3–N_4 bonds, irrespective of the kind of olefin. Thus, the addition to isobutene gave three products (**18**—**20**), in the respective yields of 22, 35, and 42%. The former two products (**18** and **19**) are presumably formed through the head-to-tail (H-T) adduct (**21**), formed by addition across the N_1–C_6 bond, as the primary product. Namely, **18** is formed by methanolysis of **21**, whereas **19** is formed by cycloreversion of **21** to iminoisocyanate (**22**) followed by methanolysis. The same kinds of adducts [**19** from the H-T adduct (**24**) and the head to head (H-H) adduct (**23**: 1 : 2 mixture of diastereoisomers)] were also obtained by the photoaddition of **13b** to methyl methacrylate. The structures of products **18**—**20** and **23** were determined by elemental analyses and spectral data as detailed in Experimental.

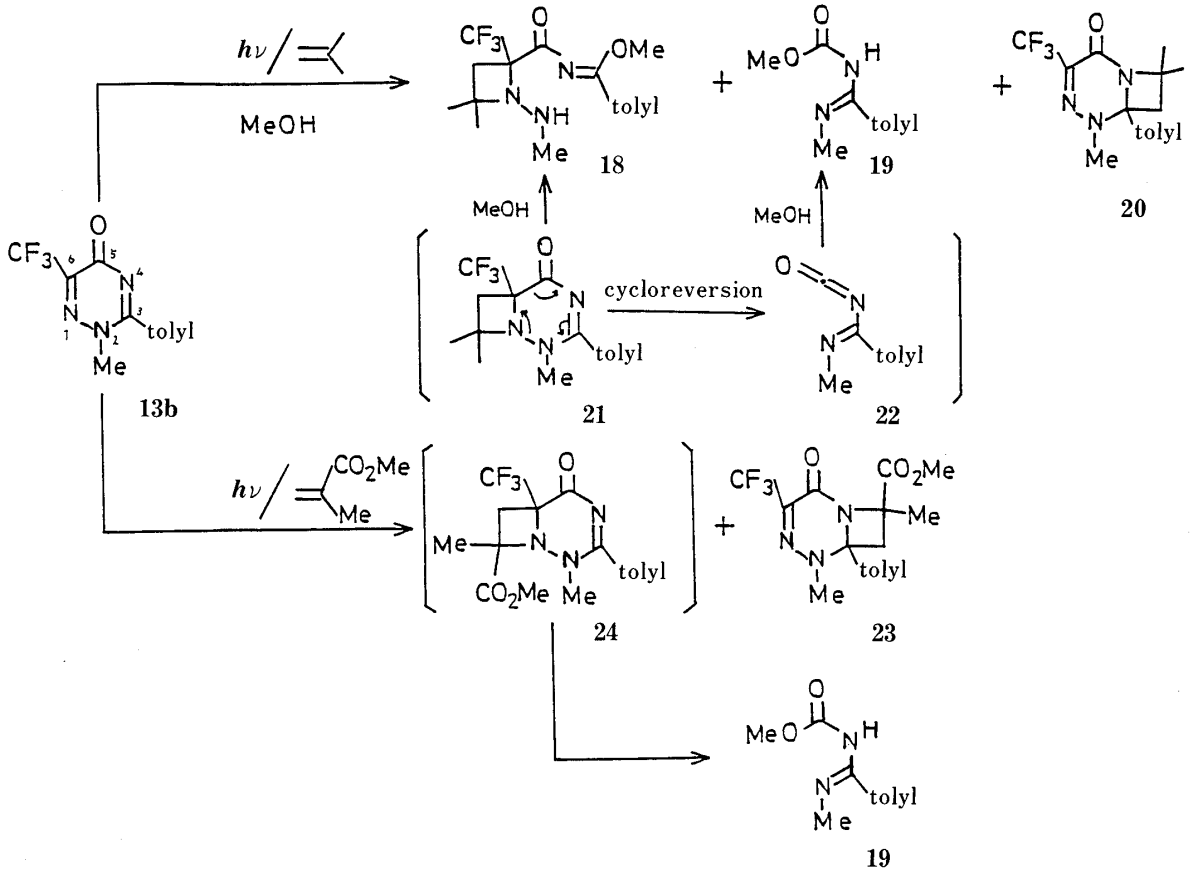


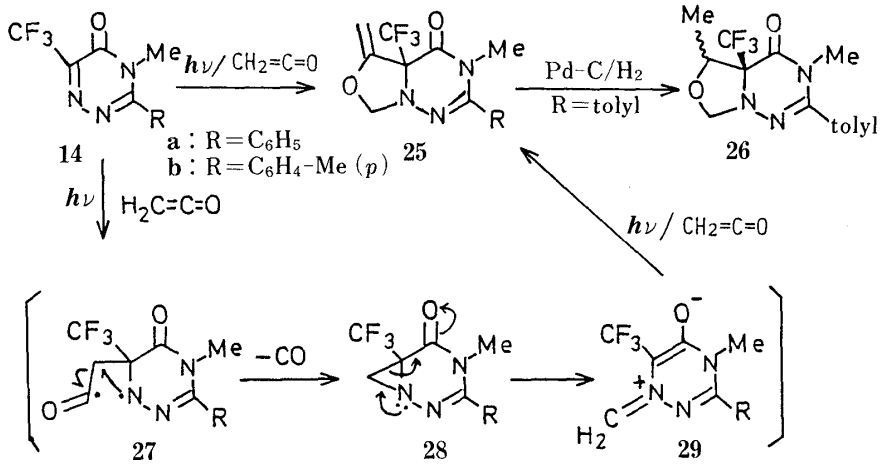
Chart 5

It is obvious that cycloaddition across the N_1–C_6 bond occurs selectively in a head-to-tail manner and that at the C_3–N_4 bond in a head-to-head manner. In these experiments, the products derived from **21** and **24** corresponding to the adducts across the N_1–C_6 bond were formed in larger amounts than those across the C_3–N_4 bond. This fact may indicate that the introduction of the trifluoromethyl group into the triazin-5-one system activates not only the directly attached C=N bond (N_1–C_6 bond), but also the remote C=N bond (C_3–N_4 bond) in these photoaddition reactions.

Though an attempted photoaddition of **13b** to ketene resulted in recovery of the starting material with partial decomposition, irradiation of **14a** and **14b** gave the addition products (**25a** and **25b**) in 41 and 33% yields, respectively. The structure of the latter product (**25b**) was determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectrum [the presence of exocyclic methylene (δ 5.60, m, 2H) and N–CH_2–O (δ 4.79, s, 2H) groups] as well as by its conversion to the dihydro derivative (**26b**) by catalytic hydrogenation. A possible mechanism for the formation of **25b** is the sequential reaction (**14**→**27**→**28**→**29**→**25**) shown in Chart 6.

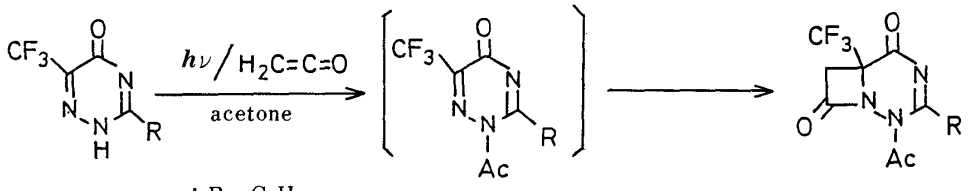
The desired 2-azetidinone formation was realized when *N*-unprotected triazin-5-ones (**4a** and **4b**) were used in the above reaction. For example, when **4a** was irradiated in acetone under bubbling of ketene, a single product (**30a**) was obtained in 61% yield. Though the same product was also obtained by the irradiation using acetonitrile as the solvent, its yield was poor (30%), probably due to low solubility of ketene in this solvent. For this reason, we have used acetone hereafter as the solvent of choice when ketene was to be used as the counterpart in the photoaddition reaction. The IR spectrum of **30a** revealed the presence of a β-lactam ring ($\nu_{C=O}$ = 1780 cm^{-1}) and the presence of an *N*-acetyl group was suggested by elemental analysis and from the ^{1}H-NMR spectrum (δ 2.62, s, 3H).

Since **13a** and **13b** did not cycloadd photochemically to ketene (*vide ante*), it is clear that



14 25 26 27 28 29

Chart 6



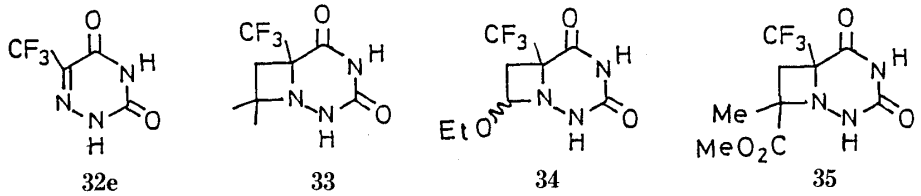
4 31 30

Chart 7

acetylation at the 2-position of **4** occurred before the photoaddition to ketene had taken place. Though actual isolation failed, a spot (less polar than **4**) corresponding to **31** was detected by thin-layer chromatography (TLC) of the reaction mixture obtained by passing ketene into an acetone solution of **4** in the dark.

In the above study, the N_1–C_6 bond in the 2-acetyl-6-trifluoromethyl-1,2,4-triazin-5-one system was found to be active enough to undergo photoaddition to ketene. We expected that the C=N bond in 6-trifluoromethyl-1,2,4-triazine-3,5-diones (**32e** and **32f**) might also participate in the same photoaddition reaction for the following reason. That is, the electronic nature of the C=N bond in **32** is almost the same as that of **31**, due to the presence of both a trifluoromethyl group at the C_6-position and an oxo function at the C_3-position.

As a preliminary test of this expectation, photoaddition of **32e** to isobutene, ethyl vinyl ether, or methyl methacrylate was examined under acetone-sensitized conditions. As expected, the adducts all having the head-to-tail structures (**33**, **34**, and **35**: 1 : 3 mixtures of diastereomers) were obtained.



32e 33 34 35

Chart 8

Though an attempted photoaddition of **32e** to ketene resulted in the formation of a complex mixture, the dimethyl derivative (**32f**) gave the expected adduct (**36f**) in 22% yield. The structure was determined unequivocally from the IR ($\nu_{C=O}$ = 1822 cm^{-1}) and ^{1}H-NMR spectra (δ 3.33 and 3.69, each d with J = 16 Hz, 2H).

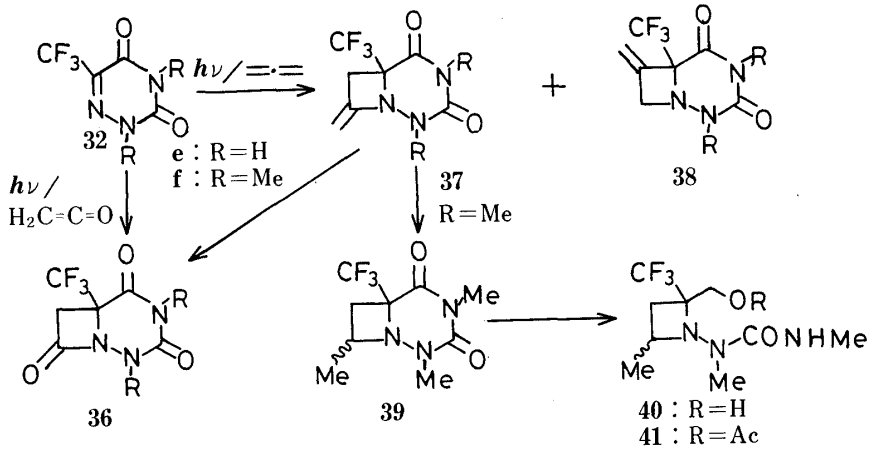


Chart 9

In order to explore an alternative route to the synthesis of the bicyclic β-lactam system (*e.g.* **36**), we then investigated the use of allene instead of ketene. Acetone-sensitized photoaddition of **32f** to allene afforded two products [H-T adduct (**37f**) and H-H adduct (**38f**)] in the respective yields of 31 and 15%. The structures of the products were determined from the ^{1}H-NMR spectra, in which methylene signals of the minor adduct (**38f**) appeared at δ 4.17 and 4.50, at far lower field than those (δ 2.91 and 3.31) of the major adduct (**37f**). The structure of **37f** was further confirmed by its conversion to **41f**, through **39f** and **40f**. The same photoaddition reaction also proceeded from **32e** to give again the H-T adduct (**37e**) as the major product. Ozonolysis of **37f** gave the azetidinone, which was identical with the adduct (**36f**) obtained from **32f** and ketene (*vide ante*). In the same manner, **37e** was also transformed to **36e** by ozonolysis.

The fact that 5-methyl-6-azauracils (**42e** and **42f**) still gave the 2+2 adducts (**43e** and **43f**) with allene shows that allene is a much better cumulene than ketene in these photoaddition reactions. As evidenced by the formation of **45e** from **43e** by ozonolysis in methanol and from the ^{1}H-NMR spectra of both adducts, the head-to-tail structures (**43e** and **43f**) are unequivocal. Hence, the addition products obtained from usual 6-azauracil derivatives (**42**) are of no use for the synthesis of the β-lactams.

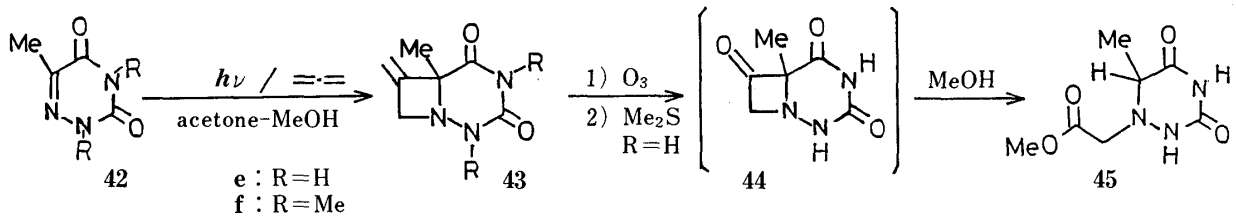


Chart 10

Thus, we have clarified that introduction of a trifluoromethyl group at the 6-position of 1,2,4-triazin-5-ones or -3,5-diones activates their C=N bonds in the photoaddition to a variety of olefins. Use of ketene as well as allene as the olefin in these reactions has opened new routes to the synthesis of β-lactams, such as **30** and **36**. In addition to the activation effect mentioned above, introduction of the trifluoromethyl group into the triazinediones has also been found to affect the regioselectivity of the photoaddition reactions, as evidenced by different regioselectivity found in the photoadditions of **32** and **42** to allene.

Based on the above experiments, the following mechanism (**A**→**B**→**C**→**D**) can be proposed in order to account for the photoreactions of 6-trifluoromethyl-1,2,4-triazin-5-ones and -3,5-diones (**A**) with olefins. Thus, the reactions proceed *via* exciplexes (**B**) which are

formed by charge transfer between excited species [A(T_1)] and olefins. The fact that an activation effect in these addition reactions exists irrespective of the kind of olefin shows that exciplexes (**B**) are formed between excited **A** as acceptors and ground state olefins as the donors. This assumption seems reasonable, because excited species (**A**) are, like their ground state species, so electron-poor that they can act as acceptors even to electron-poor olefins due to the trifluoromethyl group attached to the highly π-deficient triazine system.

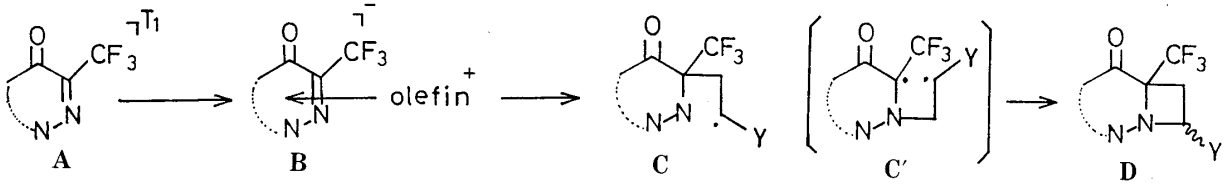


Chart 11

In photoaddition reactions of cyclic enones (**A′**) to olefins, exciplexes (**B′** and **B″**) are also assumed to act as intermediates, which determine the regioselectivity of the reactions. Thus, addition to electron-rich olefins (=–D: D designates an electron-donating substituent) gives the H-T adducts (**D′**), while addition to electron-poor ones (=–W: W designates an electron-withdrawing substituent) gives the H-H adducts (**D″**).[17]

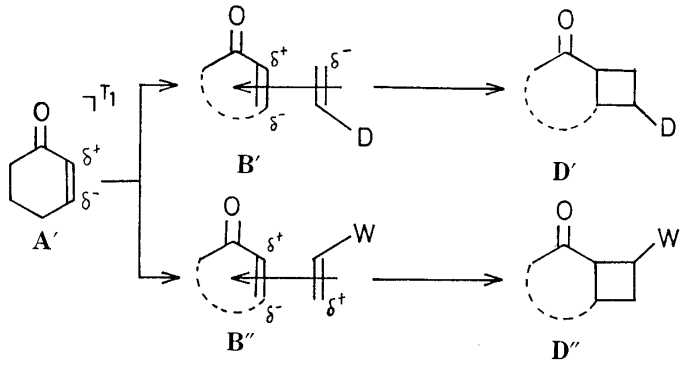


Chart 12

In the photoaddition of **A** to olefins, however, the products are always the H-T adducts (**D**) irrespective of the kind of olefin. Hence, we must assume further that, though the ease of exciplex formation determines the rate of the reaction, biradical species (**C** or **C′**) must be involved as direct precursors of the final products (**D**). It should also be noted that the charge separation (**A′**) usually believed to be present in the excited enone system[17] is improbable in **A**, because a positive charge on the α-carbon atom in the azaenone system makes such charge separation very unfavorable owing to the trifluoromethyl group. We expect that the excited species (**A**) have some radical character and differ markedly from **A′**. The same arguments can be extended to the corresponding exciplexes and predict that the orientations seen in **B′** and **B″** do not exist in **B**. The greater stability of **C** over **C′** then accounts well for the selective formation of the H-T adducts (**D**) in all cases.

It is noteworthy that all reactions so far reported concerning the photoaddition of an enone or azaenone system having strongly electron-withdrawing substituents (F or CF_3) at the α-position show an inadequacy of charge-oriented exciplexes (such as **B′** and **B″**) and the regioselectivity in these reactions fits, without exception, to the one predicted for biradical intermediates (*e.g.* **C**).[18]

Diels–Alder Reaction of 6-Trifluoromethyl-1,2,4-triazines with Olefins

Except for the derivatives substituted with strong electron-donating groups (OR, NR_2,

etc.), 1,2,4-triazine and its derivatives participate in the inverse electron demand Diels–Alder reaction.[19] This is because these triazines are ideally suited for the Diels–Alder reaction, possessing an azadiene system in a sufficiently electron-deficient triazine ring. Though introduction of perfluoroalkyl groups into the 1,2,4,5-tetrazine nucleus is known to accelerate the inverse electron demand Diels–Alder reaction,[20] the reaction using the corresponding triazine derivatives has not yet been reported.

We have examined the Diels–Alder reaction of 3-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazine (**17b**) and its derivatives (**15b** and **16b**) with a variety of olefins. The aims of the research were twofold: 1) verification of the acceleration by the trifluoromethyl group and 2) providing a new route for the synthesis of 3-trifluoromethylpyridine derivatives.

For aim 1, it is necessary to prepare the corresponding 6-methyltriazines in order to compare their reactivities with those of the corresponding trifluoromethyl derivatives. These syntheses were accomplished in the following way using 6-methyl-3-(*p*-tolyl)-1,2,4-triazin-5(2*H*)-one (**46**) as the starting material. Thus, the 6-methyltriazine (**48**)[21] was synthesized from **46** through chlorination followed by catalytic hydrogenation. Though methylation of **46** with methyl iodide in a basic medium afforded only the 2-methyl derivative (**49**), the desired 5-methoxy derivative (**50**) was obtained in 52% yield by treatment with diazomethane.

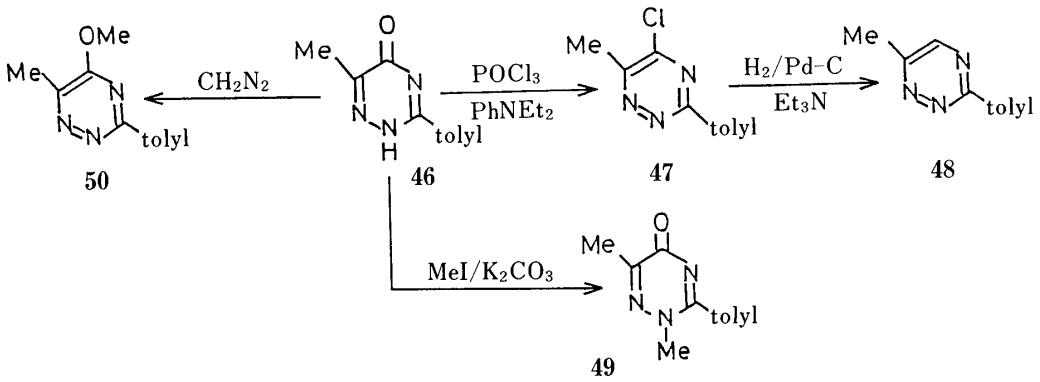


Chart 13

When 3-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazine (**17b**) was reacted with *N*-(1-cyclopenten-1-yl)-pyrrolidine (**51g**) in chloroform under reflux, two products (**52** and **53**) were obtained in 14 and 68% yields, respectively. The former product (**52**) was determined to be a cyclopenta[*c*]pyridine derivative by elemental analysis and ^{1}H-NMR spectroscopy. The structure of the major product was deduced to be **53** by elemental analysis as well as its conversion to **52** by refluxing in tetrahydrofuran (THF) containing a few drops of concentrated hydrochloric acid. Complete recovery of the starting material when we attempted to react **48** with **51g** under the same conditions shows clearly that these reactions are, as expected, inverse electron demand Diels–Alder reactions.

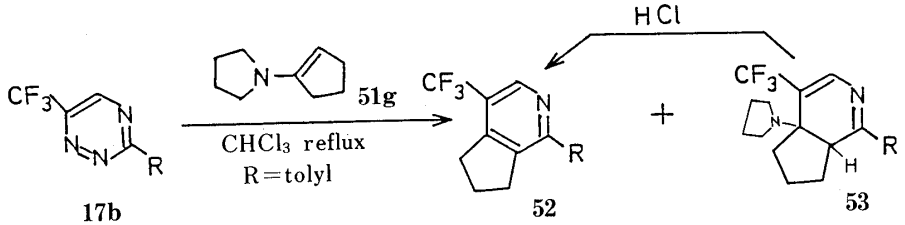


Chart 14

When the 5-chloro derivative (**16b**) was reacted with the same enamine (**51g**) in refluxing chloroform, the desired product (**54**) was obtained in only 6% yield, along with the 5-(1-pyrrolidinyl)pyridine derivative (**55**) in 26% yield. Though the yield of **54** was increased to

56% by the use of toluene (reflux) as the solvent, **55** was again formed concomitantly in an appreciable amount (40%). The results show that nucleophilic substitution of the chlorine atom in **16b** by pyrrolidine is a facile process.

Knowing that **55** was stable and did not react with **51g** under these conditions, we next examined the Diels–Alder reaction of **15b** with the same enamine. Though **15b** was obtained previously from **4b** by methylation with methyl iodide in basic medium, it was prepared in a higher overall yield from the same starting material by conversion to the 5-chloro derivative (**16b**) followed by treatment with sodium methoxide in methanol. When **15b** was reacted with **51g**, **56** was obtained in 61% yield. The fact that the corresponding 6-methyltriazine (**50**) did not react with **51g** even under more drastic conditions (*e.g.* reflux in dioxane) shows again that the trifluoromethyl group in the triazine ring is important in this reaction.

In order to establish a general synthetic method for 3-trifluoromethylpyridine derivatives, we then examined the Diels–Alder reaction of **15b** with a variety of pyrrolidino-

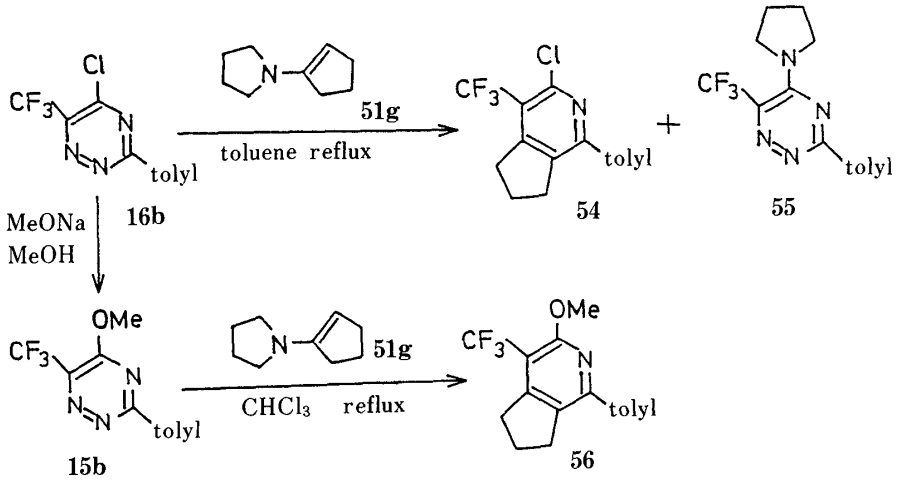
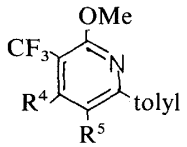


Chart 15

TABLE III. Application of Methods a and b to the Synthesis of 3-Trifluoromethylpyridines (**A**)



(**A**)

Pyrrolidinoenamine (No.) [P: $-\overset{\frown}{N}(CH_2)_4$]	Method[a]	Compd.	Pyridine (**A**) R^4, R^5	Yield (%)	**55** Yield (%)
 (**51g**)	a	**56**	$-(CH_2)_3-$	(61)	(0)
	b			(52)	(0)
 (**51h**)	a	**57**	$-(CH_2)_4-$	(31)	(0)
 (**51i**)	a	**58**	H, Me	(21)	(46)
	b			(7)	(14)
 (**51j**)	b	**59**	Me, H	(33)	(9)
 (**51k**)	b	**60**	Et, H	(14)	(16)

a) In method a, distilled enamines were used and in method b, enamines prepared *in situ* were used.

enamines (**51h—k**), which could be readily obtained by the *in situ* method originally reported by Boger *et al.*[22] Thus, a mixture containing **15b**, an appropriate ketone or aldehyde, and pyrrolidine was refluxed in chloroform in the presence of 4A-molecular sieve and the expected pyridines having the general formula **A** (Table III) were obtained.

This method (method b) gives somewhat lower yields of the desired pyridines than the ordinary method (method a: using distilled enamines), but provides a versatile synthetic route to 3-trifluoromethylpyridines by using enamines that are too unstable to isolate. The results of Diels–Alder reaction by these two methods are summarized in Table III.

As can be seen in Table III, it is evident that only one kind of pyridine is formed regioselectively even when two pyridines are formally expected (in the reactions using **51i—k**). The structures of these pyridines were readily determined from the ^{1}H-NMR spectra. For example, the ring proton of **58** appears at δ 7.73 and that of **59** at δ 7.10. Obviously, the former signal corresponds to the γ-proton and the latter signal to the β-proton of the pyridine ring. This high regioselectivity can be explained by assuming the transition state (**B**), in which the nucleophilic carbon of the enamine attacks C-3 of the 1,2,4-triazine nucleus.

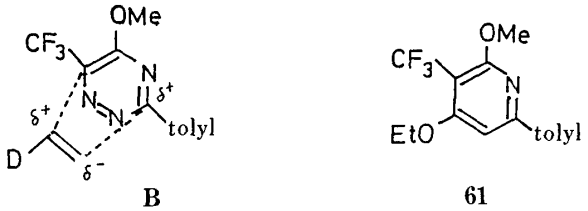
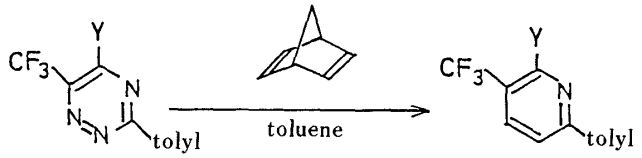


Fig. 2

In accordance with this explanation, reaction of **15b** with diethyl ketene acetal in refluxing xylene gave the pyridine (**61**), whose ring proton signal at δ 6.91 was assignable to the β-proton on the pyridine nucleus.

Finally, reaction of these triazines with norbornadiene was examined in order to see if this strained olefin[23] could behave in these reactions as an alternative to acetylene.



17b : Y=H
15b : Y=OMe

62 : Y=H
63 : Y=OMe

Chart 16

When 3-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazine (**17b**) was reacted with this diene in refluxing toluene, the expected pyridine (**62**) was obtained in 72% yield. The structure was determined from the ^{1}H-NMR spectrum. When the same reaction was carried out using **15b**, the yield of the pyridine derivative (**63**) was only 14%. The recovery (84%) of **15b** clearly shows that Diels–Alder reaction of these triazines with norbornadiene proceeds in an inverse electron demand manner.

Conclusions

Synthetic methods for 6-trifluoromethyl-1,2,4-triazines and their 5-ones from methyl trifluoropyruvate were elaborated. Using these and related compounds, cycloaddition reactions with olefins, namely photochemical 2+2 cycloaddition and Diels–Alder reactions,

were investigated. An activation by the trifluoromethyl group was demonstrated in both reactions and mechanisms have been proposed. It has become apparent that the strong electron-withdrawing nature of the trifluoromethyl group plays an important role in the acceleration of each reaction. As a result, novel synthetic methods for azetidines, azetidin-2-ones, and pyridines having a trifluoromethyl group at specified positions have been established.

Experimental

All melting points were determined on a Yanaco model MP instrument, and are uncorrected. IR spectra were measured on a JASCO A-102 spectrometer. ^{1}H-NMR spectra were recorded with JEOL JNM-PMX 60, JNM-PMX 60 si, and JEOL JNM-FX100 spectrometers using tetramethylsilane (TMS) as an internal standard. The abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad; br s, broad singlet. Low- and high-resolution mass spectra (MS) were obtained on Hitachi M-52G and JEOL JMS-01SG-2 machines, respectively. Wakogel (C-200) and activated alumina (Wako, about 300 mesh) were employed for silica gel and alumina column chromatography, respectively. Merck Kiesel-gel 60 F254 was employed for preparative TLC. The ratio of solvent mixtures for chromatography is shown as volume/volume. The irradiation source used for photoreactions was a high-pressure mercury lamp (UVL-400HA or 100HA, Pyrex filter). Yields shown in parentheses are based on the starting material, and those in square brackets are based on the consumed starting material.

3-Phenyl-6-trifluoromethyl-1,2,4-triazin-5(2*H*)-one (4a)——1) A solution of benzamidrazone (3.90 g, 28.91 mmol) and the ester (**1**) (4.51 g, 28.91 mmol) in ethanol (20 ml) was refluxed for 15 min. The solution was allowed to cool, and the resulting crystals (**4a**, 3.82 g) were collected by suction. The mother liquor was concentrated to give a further 1.41 g of **4a** as the second crop. Yield, 5.23 g (75%). Recrystallization from ethyl acetate gave pure **4a** (mp 274—278 °C, dec.) as colorless leaves. *Anal.* Calcd for $C_{10}H_6F_3N_3O$: C, 49.80; H, 2.51; N, 17.42. Found: C, 50.08; H, 2.36; N, 17.52. IR (KBr): 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD–DMSO-d_6) δ: 7.5—7.8 (3H, m), 7.9—8.5 (2H, m).

2) Trifluoropyruvic acid hydrate (**3**) (320 mg, 2 mmol) was added to a solution of benzamidrazone (270 mg, 2 mmol) in ethanol (4 ml) with stirring under ice-cooling. The mixture was allowed to stand overnight at room temperature, and the crystals (**10a**, 0.3 g) that separated were collected by suction. Ether was added to the mother liquor to give a further 0.14 g of **10a**. Total yield, 0.44 g (84%). mp 194—196 °C (dec.). Without further purification, **10a** (259 mg, 10 mmol) was heated under reflux in acetic acid (10 ml) for 30 min. The solvent was removed *in vacuo* to give a crystalline substance, which was recrystallized from ethyl acetate to afford **4a**, 126 mg (52%); this product was identical with the triazinone obtained above.

3-(*p*-Tolyl)-6-trifluoromethyl-1,2,4-triazin-5(2*H*)-one (4b) and 3-(*p*-Tolyl)-5-trifluoromethyl-1,2,4-triazin-6(1*H*)-one (5b)——A solution of *p*-toluamidrazone (13.99 g, 93.75 mmol) and the ester (**1**) (21.84 g, 140 mmol) in ethanol (50 ml) was refluxed for 15 min. The solution was allowed to cool, and the crystals that separated were collected by suction. Recrystallization from ethyl acetate gave **4b** (mp 282—284 °C, dec.) as colorless prisms. Yield, 13.64 g (57%). *Anal.* Calcd for $C_{11}H_8F_3N_3O$: C, 51.75; H, 3.16; N, 16.47. Found: C, 51.91; H, 3.04; N, 16.49. IR (KBr): 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD–DMSO-d_6) δ: 2.80 (3H, s), 7.41 (2H, d, J=8 Hz), 8.01 (2H, d, J=8 Hz). MS *m/z*: 255 (M^+). The mother liquor was concentrated *in vacuo* to give a residue, which was subjected to silica gel column chromatography. Elution with chloroform gave **5b** (mp 209—210 °C) as colorless needles ($CHCl_3$). Yield, 4.70 g (20%). *Anal.* Calcd for $C_{11}H_8F_3N_3O$: C, 51.75; H, 3.16; N, 16.47. Found: C, 51.98; H, 3.16; N, 16.25. IR ($CHCl_3$): 3370, 1687, 1598 cm^{-1}. ^{1}H-NMR ($CDCl_3$–acetone-d_6) δ: 2.39 (3H, s), 7.24 (2H, d, J=8 Hz), 7.96 (2H, d, J=8 Hz). MS *m/z*: 255 (M^+).

3-Methyl-6-trifluoromethyl-1,2,4-triazin-5(2*H*)-one (4c)——1) Triethylamine (1.01 g, 10 mmol) was added to a solution of acetamidrazone·HCl (1.09 g, 10 mmol) and the ester (**1**) (3.12 g, 20 mmol) in absolute MeOH (40 ml) under ice-cooling. The mixture was allowed to stand at room temperature for 12 h. The solvent was evaporated off *in vacuo* to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (1:2) gave **4c** (mp 229—230 °C) as colorless needles (ethyl acetate). Yield, 593 mg (33%). *Anal.* Calcd for $C_5H_4F_3N_3O$: C, 33.53; H, 2.25; N, 23.46. Found: C, 33.81; H, 2.38; N, 23.72. IR (KBr): 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 2.46 (3H, s). MS *m/z*: 179 (M^+).

2) Hydrazine (0.96 g, 30 mmol) was added to a solution of acetamidine·HCl (2.83 g, 30 mmol) in absolute MeOH (50 ml) under ice-cooling. The mixture was left to stand at room temperature for 20 min, then trifluoropyruvic acid hydrate (**3**) (4.80 g, 30 mmol) and triethylamine (3.03 g, 30 mmol) were added under ice-cooling. The resulting mixture was kept at room temperature for 48 h. The crystals that separated were collected by suction, and washed with $CHCl_3$. **10c** was obtained in almost quantitative yield. A solution of **10c** (1.00 g, 5.08 mol) in AcOH (10 ml) was heated at 80 °C for 15 h, then the solvent was removed *in vacuo* to give a residue, which was subjected to silica gel

(15 g) column chromatography. Elution with hexane–ethyl acetate (1 : 2→1 : 4) gave **4c**, 293 mg (32%).

6-Trifluoromethyl-1,2,4-triazin-5(2*H*)-one (4d)——Hydrazine (1.28 g, 0.04 mmol) was added to a solution of formamidine·AcOH (4.16 g, 0.04 mol) in absolute MeOH (100 ml). The mixture was left to stand at room temperature for 10 min, then **1** (6.24 g, 0.04 mol) and triethylamine (4.04 g, 0.04 mol) were added under ice-cooling. The resulting mixture was kept at room temperature for 2 d. The solvent was removed *in vacuo* to give a residue, which was subjected to silica gel (100 g) column chromatography. Elution with ethyl acetate–MeOH (100 : 1) gave **4d** (mp 159—160 °C, dec.) as pale yellow prisms (ethyl acetate–benzene). Yield, 0.51 g (8%). *Anal.* Calcd for $C_4H_2F_3N_3O$: C, 29.10; H, 1.22; N, 25.46. Found: C, 28.87; H, 1.13; N, 25.30. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$–acetone-d_6) δ: 8.63 (1H, br s), 8.83 (1H, s).

3-Pentafluoroethyl-5-phenyl-1,2,4-triazole (8a)——HFPO (6.0 g) was passed into a solution of benzamidrazone (2.7 g, 0.02 mol) in ethanol (10 ml) in a sealed glass tube under ice-salt cooling. After being stirred for 4 h, the mixture was kept overnight under ice-salt cooling. After evaporation of HFPO gas, the solvent was evaporated off *in vacuo* to give a residue, which was dissolved in ethyl acetate. The organic layer was washed with water, and dried over anhydrous Na_2SO_4. The solvent was evaporated off, and the crystalline residue was recrystallized from ethyl acetate to give **4a**, 0.4 g (8%). The mother liquor was concentrated *in vacuo* to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (4 : 1) gave **8a** (mp 142—144 °C) as colorless prisms (hexane–ether). Yield, 0.6 g (11%). *Anal.* Calcd for $C_{10}H_6F_5N_3$: C, 45.64; H, 2.30; N, 15.97. Found: C, 45.55; H, 2.21; N, 16.25. IR ($CHCl_3$): 1612, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.15—8.10 (5H, m), 12.89 (1H, br s). MS *m/z*: 263 (M^+).

3-Phenyl-5-trifluoromethyl-1,2,4-triazoline (11a)——A suspension of **10a** (0.10 g, 0.37 mmol) in DMF (3 ml) was heated at 140 °C for 30 min. The solvent was evaporated off *in vacuo*, and the crystalline residue obtained was recrystallized from hexane to give **11a** (mp 86—87 °C) as colorless needles. Yield, 70 mg (88%). *Anal.* Calcd for $C_9H_8F_3N_3$: C, 50.24; H, 3.75; N, 19.53. Found: C, 50.52; H, 3.76; N, 19.70. IR ($CHCl_3$): 3520, 3400, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.1—6.7 (2H, br s), 7.36—8.09 (6H, m).

2-Methyl-3-phenyl-6-trifluoromethyl-1,2-4-triazin-5(2*H*)-one (13a), 4-Methyl-3-phenyl-6-trifluoromethyl-1,2,4-triazin-5(4*H*)-one (14a), and 5-Methoxy-3-phenyl-6-trifluoromethyl-1,2,4-triazine (15a)——A suspension of **4a** (482 mg, 2.0 mmol), CH_3I (1136 mg, 8 mmol), and K_2CO_3 (414 mg, 3 mmol) in acetone (20 ml) was heated under reflux with stirring for 2 h. The solvent was evaporated off, and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, and dried over anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was subjected to silica gel (40 g) column chromatography. Elution with hexane–ethyl acetate (5 : 1→3 : 1) gave **15a**, **14a**, and **13a**, successively.

15a: mp 97—99 °C, colorless needles (hexane–ether). Yield, 141 mg (27%). *Anal.* Calcd for $C_{11}H_8F_3N_3O$: C, 51.77; H, 3.16; N, 16.47. Found: C, 51.60; H, 3.00; N, 16.45. IR ($CHCl_3$): 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.25 (3H, s), 7.4—7.7 (3H, m), 8.40—8.65 (3H, m). MS *m/z*: 255 (M^+).

14a: mp 102—104 °C, colorless needles (hexane–ether). Yield, 91 mg (18%). *Anal.* Calcd for $C_{11}H_8F_3N_3O$: C, 51.77; H, 3.16; N, 16.47. Found: C, 52.02; H, 3.03; N, 16.44. IR ($CHCl_3$): 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.54 (3H, s), 7.61 (5H, s). MS *m/z*: 255 (M^+).

13a: mp 138—140 °C, colorless plates (benzene). Yield, 248 mg (49%). *Anal.* Calcd for $C_{11}H_8F_3N_3O$: C, 51.77; H, 3.16; N, 16.47. Found: C, 52.05; H, 3.00; N, 16.44. IR ($CHCl_3$): 1682, 1598 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s), 7.60 (5H, s). MS *m/z*: 255 (M^+).

2-Methyl-3-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazin-5(2*H*)-one (13b), 4-Methyl-3-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazin-5(4*H*)-one (14b), and 5-Methoxy-3-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazine (15b)——A suspension of **4b** (3.20 g, 12.5 mmol), CH_3I (5.68 g, 40 mmol), and K_2CO_3 (2.48 mg, 18 mmol) in acetone (150 ml) was heated under reflux with stirring for 2.5 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, and dried over anhydrous Na_2SO_4. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel (60 g) column chromatography. Elution with hexane–ethyl acetate (5 : 1→3 : 1→1 : 1) gave **15b**, **14b**, and **13b**, successively.

15b: mp 123—125 °C, pale yellow needles (ether). Yield, 901 mg (27%). *Anal.* Calcd for $C_{12}H_{10}F_3N_3O$: C, 53.54; H, 3.74; N, 15.61. Found: C, 53.54; H, 3.74; N, 15.63. IR ($CHCl_3$): 1548 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 4.25 (3H, s), 7.32 (2H, d, J=8 Hz), 8.42 (2H, d, J=8 Hz). MS *m/z*: 269 (M^+).

14b: mp 144—145 °C, pale yellow plates (benzene). Yield, 482 mg (14%). *Anal.* Calcd for $C_{12}H_{10}F_3N_3O$: C, 53.54; H, 3.74; N, 15.61. Found: C, 53.73; H, 3.70; N, 15.68. IR ($CHCl_3$): 1700, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 3.54 (3H, s), 7.35 (2H, d, J=8 Hz), 7.54 (2H, d, J=8 Hz). MS *m/z*: 269 (M^+).

13b: mp 152—154 °C, colorless needles (benzene). Yield, 1671 mg (50%). *Anal.* Calcd for $C_{12}H_{10}F_3N_3O$: C, 53.54; H, 3.74; N, 15.61. Found: C, 53.62; H, 3.63; N, 15.68. IR ($CHCl_3$): 1674, 1612, 1597 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.88 (3H, s), 7.28 (2H, d, J=8 Hz), 7.51 (2H, d, J=8 Hz). MS *m/z*: 269 (M^+).

2,3-Dimethyl-6-trifluoromethyl-1,2,4-triazin-5(2*H*)-one (13c) and 3,4-Dimethyl-6-trifluoromethyl-1,2,4-triazin-5(4*H*)-one (14c)——A suspension of **4c** (198 mg, 1.1 mmol), CH_3I (426 mg, 3 mmol), and K_2CO_3 (248 mg, 1.8 mmol) in acetone (10 ml) was heated under reflux with stirring for 30 min. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated *in vacuo*, and the residue was subjected to silica gel (5 g)

column chromatography. Elution with hexane–ethyl acetate (1 : 1→1 : 2) gave **14c** and **13c**, successively.

14c: mp 82—84 °C, colorless prisms (hexane–ether). Yield, 47 mg (22%). *Anal.* Calcd for $C_6H_6F_3N_3O$: C, 37.32; H, 3.13; N, 21.76. Found: C, 37.16; H, 3.05; N, 21.94. IR ($CHCl_3$): 1700, 1502 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 3.54 (3H, s).

13c: mp 130—132 °C, colorless plates (benzene). Yield, 111 mg (52%). *Anal.* Calcd for $C_6H_6F_3N_3O$: C, 37.32; H, 3.13; N, 21.76. Found: C, 37.60; H, 3.08; N, 21.55. IR ($CHCl_3$): 1678, 1604, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s), 3.92 (3H, s).

5-Chloro-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazine (16b)——*N*,*N*-Diethylaniline (1.49 g, 10 mmol) was added to a suspension of **4b** (2.55 g, 10 mmol) in $POCl_3$ (10 ml). The mixture was stirred at room temperature for 2 h, and diluted with benzene (30 ml). The solution was washed with chilled water, chilled NH_4OH, and brine, successively. The oragnic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to alumina (45 g) column chromatography. Elution with benzene gave **16b** (mp 106 °C) as colorless leaves (hexane). Yield, 2.31 g (84%). *Anal.* Calcd for $C_{11}H_7ClF_3N_3$: C, 48.28; H, 2.58; Cl, 12.96; N, 15.36. Found: C, 48.61; H, 2.81; Cl, 12.91; N, 15.34. IR ($CHCl_3$): 1618 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 7.37 (2H, d, J=8 Hz), 8.47 (2H, d, J=8 Hz). MS *m/z*: 273 (M^+).

3-(*p*-Tolyl)-6-trifluoromethyl-1,2,4-triazine (17b)——A mixture of **16b** (1.092 g, 4 mmol), Et_3N (0.808 g, 8 mmol), and Pd–C (60 mg) in benzene (30 ml) was shaken in a hydrogen atmosphere until one equivalent of hydrogen was consumed. The precipitate and catalyst were filtered off, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel (30 g) column chromatography. Elutions with hexane–ether (10 : 1) gave **17b** (mp 94—97 °C, dec.) as yellow prisms (hexane). Yield, 868 mg (91%). *Anal.* Calcd for $C_{11}H_8F_3N_3$: C, 55.23; H, 3.37; N, 17.57. Found: C, 55.36; H, 3.26; N, 17.69. ^{1}H-NMR (CCl_4) δ: 2.45 (3H, s), 7.90 (2H, d, J=8 Hz), 8.47 (2H, d, J=8 Hz), 8.82 (1H, s). MS *m/z*: 293 (M^+).

Photoreaction of 13b with Isobutene——A solution of **13b** (269 mg, 1 mmol) in methanol (200 ml) was irradiated at ≥300 nm under bubbling of isobutene with ice-cooling for 1.5 h. The solvent was evaporated off and the residue was chromatographed on silica gel (8 g). Elution with hexane–ethyl acetate (3 : 1→2 : 1→1 : 1) gave methyl *N*-(4,4-dimethyl-1-methylamino-2-trifluoromethyl-2-azetidinoyl)toluimidate (**18**), 1,1,3-trimethyl-6-oxo-2a-(*p*-tolyl)-5-trifluoromethyl-1,2,2a,3-tetrahydro-6*H*-azeto[2,1-*c*][1,2,4]triazine (**20**), and *N*-methoxycarbonyl-*N'*-methyl-*p*-toluamidine (**19**), successively.

18: mp 107—108 °C, colorless prisms (hexane). Yield, 78 mg (22%). *Anal.* Calcd for $C_{17}H_{22}F_3N_3O_2$: C, 57.14; H, 6.20; N, 11.76. Found: C, 57.47; H, 6.21; N, 11.74. IR ($CHCl_3$): 3350, 1620, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s), 1.49 (3H, s), 2.31—2.64 (8H, m), 3.60 (3H, s), 7.26 (2H, d, J=8 Hz), 7.64 (2H, d, J=8 Hz). MS *m/z*: 357 (M^+).

20: mp 115—116 °C, colorless prisms (hexane–ether). Yield, 136 mg (42%). *Anal.* Calcd for $C_{16}H_{18}F_3N_3O$: C, 59.07; H, 5.58; N, 12.92. Found: C, 59.14; H, 5.63; N, 12.60. IR ($CHCl_3$): 1665, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, s), 1.50 (3H, s), 2.40 (3H, s), 2.57 (1H, d, J=11 Hz), 2.81 (1H, d, J=11 Hz), 3.24 (3H, s), 7.22 (2H, d, J=8 Hz), 7.40 (2H, d, J=8 Hz). MS *m/z*: 325 (M^+).

19: mp 116—117 °C, colorless prisms (hexane–ether). Yield, 72 mg (35%). *Anal.* Calcd for $C_{11}H_{14}FN_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.86; H, 7.00; N, 13.40. IR ($CHCl_3$): 3450, 1676, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.99 (3H, s), 3.66 (3H, s), 7.16 (2H, d, J=8 Hz), 7.36 (2H, d, J=8 Hz). MS *m/z*: 206 (M^+).

Photoreaction of 13b with Methyl Methacrylate——A solution of **13b** (135 mg, 0.5 mmol) and methyl methacrylate (10 ml) in MeOH (200 ml) was irradiated at ≥300 nm under an argon atmosphere for 80 min. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (2 g). Elution with hexane–ethyl acetate (5 : 1→3 : 1→1 : 1) gave **13b** (48 mg, 36%) and a mixture of **19** and **23**, successively. The mixture of **19** and **23** was subjected to preparative TLC. Development with hexane–ethyl acetate (9 : 1) gave **23** (less polar) and **19** (more polar, 31 mg, 30%). 1-Methoxycarbonyl-1,3-dimethyl-2a-(*p*-tolyl)-5-trifluoromethyl-1,2,2a,3-tetrahydro-6*H*-azeto[2,1-*c*]triazine (**23**): colorless oil. Yield, 57 mg (31%). High-resolution MS *m/z*: M^++1 Calcd for $C_{17}H_{18}F_3N_3O_3$: 370.1377. Found: 370.1403. IR ($CHCl_3$): 1732, 1672 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H × 1/3, s), 1.72 (3H × 2/3, s), 2.39 (3H, s), 2.60—3.70 (2H, m), 3.26 (3H × 2/3, s), 3.36 (3H × 1/3, s), 3.75 (3H × 2/3, s), 3.80 (3H × 1/3, s).

5-Methyl-3-methylene-4-oxo-6-phenyl-3a-trifluoromethyl-3,3a,4,5-tetrahydro-1*H*-oxazolo[4,3-*f*][1,2,4]triazine (25a)——A solution of **14a** (52 mg, 0.204 mmol) in acetone (50 ml) was irradiated at ≥300 nm under bubbling of ketene with ice-cooling for 30 min. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (5 : 1) gave **25a** as a colorless oil. Yield, 26 mg (41%) [64%]. IR ($CHCl_3$): 1700, 1655, 1630 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.10 (3H, s), 4.79 (2H, s), 5.05—5.60 (2H, m), 7.45 (5H, s). MS *m/z*: 311 (M^+). Further elution with the same solvent gave the starting material (19 mg, 37%).

5-Methyl-3-methylene-4-oxo-6-(*p*-tolyl)-3a-trifluoromethyl-3,3a,4,5-tetrahydro-1*H*-oxazolo[4,3-*f*][1,2,4]triazine (25b)——Employing the same procedure as described above, **25b** was obtained by the photoreaction of **14b** (136 mg, 0.5 mmol) and ketene, together with recovery of **14b** (75 mg, 55%). Yield, 53 mg (33%) [72%]. *Anal.* Calcd for $C_{15}H_{14}F_3N_3O_2$: C, 55.39; H, 4.34; N, 12.92. Found: C, 55.31; H, 4.43; N, 12.84. IR ($CHCl_3$): 1710, 1660, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.08 (3H, s), 4.76 (2H, s), 5.0—5.6 (2H, m), 7.24 (4H, s).

3,5-Dimethyl-4-oxo-6-(*p*-tolyl)-3a-trifluoromethyl-3,3a,4,5-tetrahydro-1*H*-oxazolo[4,3-*f*][1,2,4]triazine (26)——A suspension of **2b** (30 mg) and Pd–C (18 mg) in methanol (5 ml) was shaken in a hydrogen atmosphere for 1.5 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (20 : 1) gave **26** (30 mg) as a colorless oil. IR ($CHCl_3$): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.81 (3H, m), 2.39 (3H, s), 3.11 (3H, s), 4.08—4.61 (1H, m), 4.79—4.93 (1H, m), 5.23 (1H, d, J=3 Hz), 7.25 (4H, s). MS *m/z*: 327 (M^+).

6-Acetyl-1,3-dioxo-5-(*p*-tolyl)-2a-trifluoromethyl-1,2,2a,3-tetrahydro-6*H*-azeto[2,1-*f*][1,2,4]triazine (30a)——A solution of **4a** (0.1 g, 0.41 mmol) in acetone (40 ml) was irradiated at ≥300 nm under bubbling of ketene with ice-cooling for 1 h. After evaporation of the solvent *in vacuo*, the crystalline residue was recrystallized from ethyl acetate to give **30a** (mp 217 °C, dec.) as colorless prisms. Yield, 82 mg (61%). *Anal.* Calcd for $C_{14}H_{10}F_3N_3O_3$: C, 51.70; H, 3.09; N, 12.92. Found: C, 51.15; H, 3.14; N, 13.19. IR (KBr): 1758, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s), 3.82 (2H, br s), 7.37 (5H, s).

6-Acetyl-1,3-dioxo-5-phenyl-2a-trifluoromethyl-1,2,2a,3-tetrahydro-6*H*-azeto[2,1-*f*][1,2,4]triazine (30b)——A solution of **4b** (538 mg, 2.11 mmol) in acetone (50 ml) was irradiated at ≥300 nm under bubbling of ketene with ice-cooling for 30 min. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (10 g). Elution with hexane–ethyl acetate (5 : 1) gave **30b** (mp 221 °C, dec.) as colorless prisms (ethyl acetate). Yield, 70 mg (10%). *Anal.* Calcd for $C_{15}H_{12}F_3N_3O_3$: C, 53.10; H, 3.56; N, 12.39. Found: C, 53.05; H, 3.60; N, 12.62. IR ($CHCl_3$): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$–acetone-d_6) δ: 2.35 (3H, s), 2.61 (3H, s), 3.82 (2H, br s), 7.26 (4H, s).

1,1-Dimethyl-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (33)——A solution of **32e** (102 mg, 0.567 mmol) and isobutene (10 g) in CH_3CN (200 ml) and acetone (10 ml) was irradiated at ≥300 nm with ice-cooling for 1 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (5 g). Elution with hexane–ethyl acetate (3 : 1) gave **33** (mp 144—146 °C) as colorless prisms (hexane–ether). Yield, 110 mg (82%). *Anal.* Calcd for $C_8H_{10}F_3N_3O_2$: C, 40.51; H, 4.25; N, 17.72. Found: C, 40.48; H, 4.41; N, 17.43. IR (Nujol): 3300, 3000, 1730, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.13 (3H, s), 1.36 (3H, s), 2.41 (2H, s).

1-Ethoxy-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (34)——A solution of **32e** (90 mg, 0.5 mmol) and ethyl vinyl ether (10 ml) in CH_3CN (200 ml) and acetone (10 ml) was irradiated at ≥300 nm for 1 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (6 g). Elution with hexane–ethyl acetate (3 : 1) gave **34** (mp 161 °C, dec.) as colorless prisms (ethyl acetate). Yield, 88 mg (70%). *Anal.* Calcd for $C_8H_{10}F_3N_3O_3$: C, 37.95; H, 3.98; N, 16.60. Found: C, 37.77; H, 4.03; N, 16.36. IR (Nujol): 3210, 3100, 1720, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.22 (3H, t, J=6 Hz), 2.27 (1H, d, J=12 Hz), 2.91 (1H, dd, J=12, 5 Hz), 3.74 (2H, m), 4.97 (1H, d, J=5 Hz). MS *m/z*: 253 (M^+).

1-Methoxycarbonyl-1-methyl-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (35)——A solution of **32e** (180 mg, 1.0 mmol) and methyl methacrylate (10 ml) was irradiated at ≥300 nm for 4.5 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (5 g). Elution with hexane–ethyl acetate (5 : 1→1 : 1) gave a mixture of **35** and the starting material (**32e**). Due to difficulty in the isolation of **35**, the elemental analysis and mass spectrum could not be obtained. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s), 2.40 (1H × 3/4, d, J=12 Hz), 2.48 (1H × 1/4, d, J=12 Hz), 3.04 (1H × 1/4, d, J=12 Hz), 3.14 (1H × 3/4, d, J=12 Hz), 3.76 (3H, s).

4,6-Dimethyl-1,3,5-trioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (36f)——1) A solution of **32f** (105 mg, 0.5 mmol) in acetone (150 ml) was irradiated at ≥300 nm under bubbling of ketene with ice-cooling for 1.5 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (10 g). Elution with hexane–ethyl acetate (5 : 1) gave **36f** as a colorless oil. Yield, 28 mg (22%) [57%]. High-resolution MS *m/z*: M^+ Calcd for $C_8H_8F_3N_3O_3$: 251.0517. Found: 251.0473. IR ($CHCl_3$): 1822, 1734, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.26 (3H, s), 3.33 (1H, d, J=16 Hz), 3.34 (3H, s), 3.69 (1H, d, J=16 Hz). Further elution with the same solvent gave the starting material (**32f**) (64 mg, 61%).

2) Ozone gas was passed over a solution of **37f** (50 mg, 0.2 mmol) in methanol (5 ml) at −78 °C for 3 min. Me_2S (0.5 ml) was added to the mixture, and the whole was stirred at room temperature for 30 min. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (5 g). Elution with hexane–ethyl acetate (8 : 1→3 : 1) gave **36f**, 19 mg (38%), as a colorless oil, which was identical with the β-lactam obtained above.

1-Methylene-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (37e) and 2-Methylene-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (38e)——A solution of **32e** (169 mg, 0.93 mmol) in MeOH (200 ml) and acetone (20 ml) was irradiated at ≥300 nm under bubbling of allene for 30 min. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (15 g). Elution with hexane–ethyl acetate (3 : 1) gave **37e** (mp 147—148 °C) as colorless prisms (hexane–ether). Yield, 69 mg (34%). High-resolution MS *m/z*: M^+ Calcd for $C_7H_6F_3N_3O_2$: 221.0412. Found: 221.0405. *Anal.* Calcd for $C_7H_6F_3N_3O_2$: C, 38.02; H, 2.73; N, 19.00. Found: C, 38.14; H, 2.83; N, 18.79. IR (KBr): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 2.94 (1H, m), 3.33 (1H, m), 4.38 (1H, m), 4.63 (1H, m). Further elution with hexane–ethyl acetate (1 : 1) gave **38e** (mp 187—198 °C, sublim.) as colorless needles (hexane–ethyl acetate). Yield, 10 mg (5%). *Anal.* Calcd for $C_7H_6F_3N_3O_2$: C, 38.02; H, 2.73; N, 19.00. Found: C, 38.04; H, 2.96; N, 18.81. IR (Nujol): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$–acetone-d_6) δ: 4.42 (2H, t, J=2 Hz), 5.30 (1H, m), 5.47 (1H, m). MS *m/z*: 221 (M^+).

1,3,5-Trioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (36e)——Ozone gas was bubbled in the solution of **37e** (20 mg, 0.09 mmol) in ethyl acetate (5 ml) with ice-salt cooling for 30 min. Me_2S was added to the reaction mixture, and the reaction temperature was allowed to rise to room temperature. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (1 : 1) gave **36e** (mp 200—203 °C) as colorless prisms (hexane–ethyl acetate). Yield, 11 mg (52%). High-resolution MS *m/z*: M^+ Calcd $C_6H_4F_3N_3O_3$: 223.0204. Found: 223.0225. IR (KBr): 1830, 1748, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 3.30 (1H, d, J=15 Hz), 3.67 (1H, d, J=15 Hz).

4,6-Dimethyl-1-methylene-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (37f) and 4,6-Dimethyl-2-methylene-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]-triazine (38f)——By means of the same procedure as described above, **37f** and **38f** were obtained by the photoreaction of **32f** (350 mg, 1.675 mmol) with allene.

37f: Eluent, hexane–ethyl acetate (3 : 1), colorless oil. Yield, 128 mg (31%). High-resolution MS *m/z*: M^+ Calcd for $C_9H_{10}F_3N_3O_2$: 249.0724. Found: 249.0708. IR ($CHCl_3$): 1722, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.91 (1H, m), 3.24 (3H, s), 3.27 (3H, s), 3.31 (1H, m), 4.33 (1H, m), 4.54 (1H, m).

38f: Eluent, hexane–ethyl acetate (3 : 1), colorless oil. Yield, 64 mg (15%). High-resolution MS *m/z*: M^+ Calcd for $C_9H_{10}F_3N_3O_2$: 249.0724. Found: 249.0716. IR ($CHCl_3$): 1724, 1678 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.14 (3H, s), 3.24 (3H, s), 4.17 (1H, m), 4.50 (1H, m), 5.27 (1H, m), 5.60 (1H, m).

1,4,6-Trimethyl-3,5-dioxo-2a-trifluoromethyl-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (39)——A mixture of **37f** (109 mg, 0.438 mmol) and Pd–C (15 mg) in MeOH (25 ml) was shaken in a hydrogen atmosphere for 30 min. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give **39**, 110 mg (100%), as a colorless oil. High-resolution MS *m/z*: M^+ Calcd for $C_9H_{12}F_3N_3O_2$: 251.0881. Found: 251.0890. IR ($CHCl_3$): 1720, 1672 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H × 1/2, d, J=6 Hz), 1.38 (3H × 1/2, d, J=6 Hz), 1.91—3.04 (2H, m), 3.12 (3H × 1/2, s), 3.19 (3H × 1/2, s), 3.28 (3H, s), 3.54—4.48 (1H, m).

1-(1,3-Dimethylureido)-2-hydroxymethyl-4-methyl-2-trifluoromethylazetidine (40)——$NaBH_4$ (0.2 g) was added to a solution of **39** (100 mg) in EtOH (5 ml). The mixture was stirred for 12 h, and the insoluble material (excess $NaBH_4$) was filtered off. The filtrate was neutralized with ion exchange resin (Dowex 50), and concentrated *in vacuo*. The residue was chromatographed on silica gel (8 g). Elution with hexane–ethyl acetate (5 : 1→3 : 1) gave **40** as a colorless oil. Yield, 30 mg (27%). IR ($CHCl_3$): 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H × 1/2, d, J=6 Hz), 1.17 (3H × 1/2, d, J=6 Hz), 1.47—2.57 (2H, m), 2.72 (3H × 1/2, s), 2.80 (3H × 1/2, s), 2.98 (3H × 1/2, s), 3.13 (3H × 1/2, s), 3.27—4.03 (1H, br s), 3.60 (1H, s), 3.94 (1H, s), 6.30 (1H, br s).

2-Acetoxymethyl-1-(1,3-dimethylureido)-4-methyl-2-trifluoromethylazetidine (41)——Pyridine (three drops) was added to a solution of **40** (30 mg) in acetic anhydride (2 ml) with ice-cooling. The mixture was allowed to stand at room temperature for 3 h. The resulting mixture was concentrated *in vacuo* to give **41** as a colorless oil. High-resolution MS *m/z*: M^+ Calcd for $C_{11}H_{18}F_3N_3O_3$: 297.1299. Found: 297.1318. IR ($CHCl_3$): 1752, 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H × 1/2, d, J=6 Hz), 1.24 (3H × 1/2, d, J=6 Hz), 1.51—2.62 (2H, m), 2.14 (3H × 1/2, s), 2.20 (3H × 1/2, s), 2.76 (3H × 1/2, d, J=6 Hz), 2.78 (3H × 1/2, d, J=6 Hz), 3.00 (3H, s), 3.81—4.74 (3H, m), 6.34 (1H, br s).

2a-Methyl-2-methylene-3,5-dioxo-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,3]triazine (43e)——A solution of 6-azathymine (**42e**) (254 mg, 2.0 mmol) in MeOH (200 ml) and acetone (20 ml) was irradiated at ≥300 nm under bubbling of allene for 30 min. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel. Elution with $CHCl_3$ containing MeOH (3% v/v) gave **43e** (mp 195 °C, sublim.) as colorless prisms (ethyl acetate). Yield, 110 mg (33%). *Anal.* Calcd for $C_7H_9N_3O_2$: C, 50.30; H, 5.43; N, 25.14. Found: C, 50.57; H, 5.50; N, 24.83. IR (Nujol): 1727, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.54 (1H, s), 4.24 (2H, m), 5.10 (1H, m), 5.28 (1H, m). MS *m/z*: 167 (M^+). Further elution with the same solvent gave the starting material (137 mg, 54%).

2a,4,6-Trimethyl-2-methylene-3,5-dioxo-1,2,2a,3,5,6-hexahydro-4*H*-azeto[2,1-*f*][1,2,4]triazine (43f)——By means of the same procedure as described above, **43f** was obtained by the photoreaction of 1,3-dimethyl-6-azathymine (**42f**) (106 mg, 0.684 mmol) with allene.

43f: Eluent, hexane–ethyl acetate (5 : 1→3 : 1). mp 91—92 °C, colorless prisms (hexane). Yield, 50 mg (37%). *Anal.* Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.59; H, 6.55; N, 21.54. IR ($CHCl_3$): 1710, 1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, s), 3.11 (3H, s), 3.19 (3H, s), 4.23 (2H, m), 5.06 (1H, m), 5.30 (1H, m). MS *m/z*: 195 (M^+).

1-Methoxycarbonylmethyl-6-methyl-1,6-dihydro-1,2,4-triazine-3,5-dione (45)——Ozone gas was bubbled into a solution of **43e** (32 mg, 0.2 mmol) in MeOH (5 ml) at −78 °C for 5 min. Me_2S (0.5 ml) was added, and the resulting mixture was stirred at room temperature for 1 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (7 g). Elution with hexane–ethyl acetate (3 : 1→1 : 1) gave **45** (mp 169 °C) as colorless prisms (MeOH). Yield, 20 mg (52%). *Anal.* Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.49; H, 5.52; N, 20.80. IR ($CHCl_3$): 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$–acetone-d_6–CD_3OD) δ: 1.39 (3H, d, J=7 Hz), 3.63 (1H, q, J=7 Hz), 3.67 (2H, s), 3.72 (3H, s). MS *m/z*: 201 (M^+).

6-Methyl-3-(*p*-tolyl)-1,2,4-triazin-5(2*H*)-one (46)——Anhydrous hydrazine (1.60 g, 50 mmol) was added to a solution of ethyl toluimidate (8.15 g, 50 mmol) in EtOH (40 ml). The mixture was heated under reflux for 1.5 h. After cooling, methyl pyruvate (7.14 g, 70 mmol) was added to the reaction mixture. The resulting mixture was heated again

under reflux for 15 min. The crystals that separated were collected by suction, and washed with ether. The mother liquor and washings were concentrated *in vacuo* to give the second crop. The combined crystals were recrystallized from MeOH to give **46** (mp 253—254 °C, dec.) as pale yellow prisms. Yield, 4.61 g (41%). High-resolution MS *m/z*: M^+ Calcd for $C_{11}H_{11}NO$: 201.0901. Found: 201.0897. IR (Nujol): 1610 cm^{-1}. ^{1}H-NMR (CD_3OD–$CDCl_3$) δ: 2.37 (3H, s), 2.47 (3H, s), 7.43 (2H, d, J=8 Hz), 7.96 (2H, d, J=8 Hz).

5-Chloro-6-methyl-3-(*p*-tolyl)-1,2,4-triazine (47)——*N*,*N*-Diethylaniline (411 mg, 2.76 mmol) was added to a suspension of **46** (554 mg, 2.76 mmol) in $POCl_3$ (2 ml) with ice-cooling. The mixture was stirred at room temperature for 30 min, and then diluted with benzene. The solution was successively washed with chilled water, chilled diluted NH_4OH, and brine, and dried over anhydrous Na_2SO_4, then the solvent was evaporated off. The residue was chromatographed on alumina (10 g). Elution with benzene gave **47** (99—101 °C, dec.) as pale yellow prisms (hexane). Yield, 419 mg (69%). High-resolution MS *m/z*: M^+ Calcd for $C_{11}H_{10}N_3Cl$: 219.0563. Found: 219.0552. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.77 (2H, s), 7.27 (2H, d, J=8 Hz), 8.35 (2H, d, J=8 Hz).

6-Methyl-3-(*p*-tolyl)-1,2,4-triazine (48)——A mixture of **47** (419 mg, 1.91 mmol), Et_3N (423 mg, 3.82 mmol), and Pd–C (30 mg) in benzene (10 ml) was shaken in a hydrogen atmosphere at room temperature until an equimolar amount of hydrogen was consumed. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (12 g). Elution with hexane–ethyl acetate (1 : 1) gave **48** (mp 81—82 °C) as pale yellow leaves (hexane). Yield, 191 mg (54%). High-resolution MS *m/z*: M^+ Calcd for $C_{11}H_{11}N_3$: 185.0952. Found: 185.0947. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.70 (3H, s), 7.31 (2H, d, J=8 Hz), 8.39 (2H, d, J=8 Hz), 8.50 (1H, s). Further elution with the same solvent gave **47**, 131 mg (31%).

2,6-Dimethyl-3-(*p*-tolyl)-1,2,4-triazin-5(2*H*)-one (49)——A mixture of **46** (4.17 g, 20.7 mmol), CH_3I (8.52 g, 60 mmol), and K_2CO_3 (4.14 g, 30 mmol) in acetone (200 ml) was heated under reflux for 2 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g). Elution with hexane–ethyl acetate (1 : 1) gave **49** (mp 151—152 °C) as pale yellow prisms (ether). Yield, 516 mg (12%). High-resolution MS *m/z*: M^+ Calcd for $C_{12}H_{13}N_3O$: 215.1058. Found: 215.1049. IR ($CHCl_3$): 1660, 1592 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.60 (3H, s), 3.80 (3H, s), 7.29 (2H, d, J=8 Hz), 8.07 (2H, d, J=8 Hz).

5-Methoxy-6-methyl-3-(*p*-tolyl)-1,2,4-triazine (50)——A solution of excess CH_2N_2 in ether was added dropwise to a solution of **46** (1.89 g, 9.4 mmol) in dioxane (15 ml) with ice-cooling. After being allowed to stand at room temperature for 5 h, the mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel (60 g). Elution with hexane–ethyl acetate (3 : 1) gave **50** (mp 118—119 °C) as pale yellow prisms (ethyl acetate). Yield, 1.01 g (52%). High-resolution MS *m/z*: Calcd for $C_{12}H_{13}N_3O$: 215.1058. Found: 215.1048. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.53 (3H, s), 4.13 (3H, s), 7.25 (2H, d, J=8 Hz), 8.21 (2H, d, J=8 Hz). Further elution with hexane–ethyl acetate (1 : 1) gave **46**, 851 mg (45%).

1-(*p*-Tolyl)-4-trifluoromethyl-6,7-dihydro-5*H*-2-pyrindine (52) and 4a-(1-Pyrrolidinyl)-1-(*p*-tolyl)-4-trifluoromethyl-4a,6,7,7a-tetrahydro-5*H*-2-pyrindine (53)——A solution of **17b** (90 mg, 0.38 mmol) and **51g** (96 mg, 0.7 mmol) in $CHCl_3$ (1 ml) was heated under reflux for 2 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (10 g). Elution with hexane–ether (10 : 1) gave **52** as a colorless oil. Yield, 15 mg (14%). High-resolution MS *m/z*: M^+ Calcd for $C_{16}H_{14}F_3N$: 277.1078. Found: 277.1053. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (2H, t, J=7 Hz), 2.44 (3H, s), 3.17 (4H, t, J=7 Hz), 7.27 (2H, d, J=8 Hz), 7.69 (2H, d, J=8 Hz), 8.71 (1H, s). Further elution with the same solvent gave **53** (mp 94 °C) as yellow prisms (MeOH). Yield, 87 mg (66%). *Anal.* Calcd for $C_{20}H_{23}F_3N_2$: C, 68.95; H, 6.65; N, 8.04. Found: C, 68.78; H, 6.81; N, 8.07. ^{1}H-NMR ($CDCl_3$) δ: 0.85—1.95 (10H, m), 2.24—2.81 (5H, m), 2.24 (3H, s), 7.16 (2H, d, J=8 Hz), 7.38 (1H, q, J=2 Hz), 8.10 (2H, d, J=8 Hz). MS *m/z*: 348 (M^+).

Transformation of 53 into 52——A solution of **53** (15 mg, 0.043 mmol) and concentrated HCl (two drops) in THF (3 ml) was heated under reflux for 5 min. The mixture was neutralized with aqueous $NaHCO_3$ solution. The THF layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to preparative TLC. Development with hexane–ethyl acetate (40 : 1) gave **52**, 3 mg (25%), which was identical with the pyrindine obtained above.

3-Chloro-1-(*p*-tolyl)-4-trifluoromethyl-6,7-dihydro-5*H*-2-pyrindine (54) and 5-(1-Pyrrolidinyl)-3-(*p*-tolyl)-6-trifluoromethyl-1,2,4-triazine (55)——Compound **51g** (69 mg, 0.5 mmol) was added to a solution of **16b** (136 mg, 0.5 mmol) in toluene (2 ml) with ice-cooling. The mixture was heated at 100 °C for 2 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (10 g). Elution with hexane–ether (10 : 1) gave **54** (mp 84—85 °C) as colorless prisms (MeOH). Yield, 87 mg (56%). High-resolution MS *m/z*: M^+ Calcd for $C_{16}H_{13}ClF_3N$: 311.0688. Found: 311.0659. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (2H, t, J=7 Hz), 2.41 (3H, s), 3.10 (4H, t, J=7 Hz), 7.26 (2H, d, J=8 Hz), 7.70 (2H, d, J=8 Hz). Further elution with the same solvent gave **55**, 62 mg (40%). *Anal.* Calcd for $C_{15}H_{15}F_3N_4$: C, 58.44; H, 4.90; N, 18.17. Found: C, 58.56; H, 4.84; N, 18.12. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.20 (4H, m), 2.41 (3H, s), 3.55—4.95 (4H, m), 7.27 (2H, d, J=8 Hz), 8.36 (2H, d, J=8 Hz).

General Procedure for the Reaction of Triazines (15b) with Enamines (51g—k)——Method a: A solution of **15b** (135 mg, 0.5 mmol) and an enamine (**51g—i**) (1.0 mmol) in $CHCl_3$ (1—2 ml) was heated under reflux for 8—36 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (10 g). Elution with the solvent gave the corresponding trifluoromethylpyridine (**56—58**). The yields are given in Table III.

Method b: A mixture of **15b** (135 mg, 0.5 mmol), a carbonyl compound (0.5 mmol), pyrrolidine (36 mg, 0.5 mmol), and 4A molecular sieve (0.2 g) was heated under reflux with stirring for 7—36 h. The insoluble material was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (10 g) to give the corresponding trifluoromethylpyridine (**56** and **58—60**).

56: Eluent, hexane–$CHCl_3$ (5 : 1). mp 91—92 °C, colorless prisms (MeOH). *Anal.* Clacd for $C_{17}H_{16}F_3NO$: C, 66.44; H, 5.25; N, 4.56. Found: C, 66.18; H, 5.39; N, 4.50. ^{1}H-NMR ($CDCl_3$) δ: 1.73—2.37 (2H, m), 2.41 (3H, s), 2.87—3.33 (4H, m), 4.04 (3H, s), 7.29 (2H, d, J=8 Hz), 7.76 (2H, d, J=8 Hz). MS *m/z*: 307 (M^+).

57: Eluent, hexane–$CHCl_3$ (5 : 1). mp 63—64 °C, colorless prisms (hexane). High-resolution MS *m/z*: Calcd for $C_{18}H_{18}F_3NO$: 321.1339. Found: 321.1352. ^{1}H-NMR ($CDCl_3$) δ: 1.49—2.07 (4H, m), 2.40 (3H, s), 2.52—3.27 (4H, m), 3.94 (3H, s), 7.23 (2H, d, J=8 Hz), 7.41 (2H, d, J=8 Hz). MS *m/z*: 321 (M^+).

58: Eluent, hexane–$CHCl_3$ (5 : 1→1 : 1). mp 105—107 °C, colorless prisms (MeOH). *Anal.* Calcd for $C_{15}H_{15}F_3NO$: C, 63.82; H, 5.36; N, 4.96. Found: C, 63.54; H, 5.10; N, 4.81. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.43 (3H, s), 4.03 (3H, s), 7.25 (2H, d, J=8 Hz), 7.52 (2H, d, J=8 Hz), 7.73 (1H, s). MS *m/z*: 282 (M^+).

59: Eluent, hexane–ethyl acetate (40 : 1→20 : 1). mp 92—93 °C, pale green prisms (MeOH). *Anal.* Calcd for $C_{15}H_{14}F_3NO$: C, 64.05; H, 5.02; N, 4.98. Found: C, 63.80; H, 5.29; N, 4.87. ^{1}H-NMR (CCl_4) δ: 2.41 (3H, s), 2.52 (3H, q, J=3 Hz), 4.08 (3H, s), 7.10 (1H, s), 7.17 (2H, d, J=8 Hz), 7.87 (2H, d, J=8 Hz). MS *m/z*: 281 (M^+).

60: Eluent, hexane–ethyl acetate (15 : 1), yellow oil. High-resolution MS *m/z*: M^+ Calcd for $C_{16}H_{16}F_3NO$: 295.1183. Found: 295.1176. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 2.39 (3H, s), 2.84 (2H, qq, J=7, 2 Hz), 4.03 (3H, s), 7.06—7.39 (3H, m), 7.89 (2H, d, J=8 Hz).

4-Ethoxy-2-methoxy-6-(*p*-tolyl)-3-trifluoromethylpyridine (61)——A solution of **15b** (135 mg, 0.5 mmol) and diethyl ketene acetal (232 mg, 2.0 mmol) in xylene (2 ml) was heated under reflux for 48 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (5 g). Elution with hexane–ethyl acetate (25 : 1) gave **61**, which was purified by preparative TLC using hexane–ethyl acetate (25 : 1) as a developing solvent.

61: Colorless oil. Yield, 20 mg (13%). High-resolution MS *m/z*: M^+ Calcd for $C_{16}H_{16}F_3NO_2$: 311.1132. Found: 311.1150. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, t, J=7 Hz), 2.40 (3H, s), 4.06 (3H, s), 4.21 (2H, q, J=7 Hz), 6.21 (1H, q, J=1 Hz), 7.24 (2H, d, J=8 Hz), 7.89 (2H, d, J=8 Hz). Further elution with the same solvent gave the starting material (**15b**), 99 mg (73%).

2-(*p*-Tolyl)-5-trifluoromethylpyridine (62)——A solution of **17b** (120 mg, 0.5 mmol) and norbornadiene (0.5 ml) in toluene (2 ml) was heated under reflux for 4 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (5 g). Elution with hexane gave **62** (mp 130—131 °C) as colorless needles (hexane). Yield, 85 mg (72%). *Anal.* Calcd for $C_{13}H_{10}F_3N$: C, 65.82; H, 4.25; N, 5.90. Found: C, 65.90; H, 4.48; N, 5.83. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 7.20 (2H, d, J=8 Hz), 7.68—7.99 (4H, m), 8.80 (1H, q, J=2 Hz).

2-Methoxy-6-(*p*-tolyl)-3-trifluoromethylpyridine (63)——By means of the same procedure as described above, **63** was obtained from **15b** (135 mg, 0.5 mmol) and norbornadiene (0.5 ml).

63: Eluent, hexane–ethyl acetate (15 : 1). mp 77 °C, colorless needles (MeOH). Yield, 19 mg (14%). High-resolution MS *m/z*: M^+ Calcd for $C_{14}H_{12}F_3NO$: 267.0870. Found: 267.0848. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 4.11 (3H, s), 7.27 (2H, d, J=8 Hz), 7.37 (1H, d, J=6 Hz), 7.87 (1H, d, J=6 Hz), 7.97 (2H, d, J=8 Hz). Further elution with the same solvent gave the starting material **15b**, 113 mg (84%).

Acknowledgements This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. The authors thank the Research and Development Division, Asahi Glass Co., Ltd., for the gift of hexafluoropropylene oxide (HFPO).

References and Notes

1) Part XXXVI: M. Sato, K. Kawakami, T. Suzuki, H. Morisawa, S. Nishimura, and C. Kaneko, *Steroids*, in press.
2) C. Kaneko, K. Kasai, H. Watanabe, and N. Katagiri, *Chem. Pharm. Bull.*, **34**, 4955 (1986).
3) N. Katagiri, K. Kasai, and C. Kaneko, *Chem. Pharm. Bull.*, **34**, 4429 (1986).
4) C. Kaneko, K. Kasai, N. Katagiri, and T. Chiba, *Chem. Pharm. Bull.*, **34**, 3672 (1986).
5) R. A. Carboni and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **81**, 4342 (1959); J. Sauer and H. Wiest, *Angew. Chem. Int. Ed. Engl.*, **1**, 269 (1962).
6) H. Millauer, W. Schertgeger, and G. Siegemund, *Angew. Chem. Int. Ed. Engl.*, **24**, 161 (1985); N. Ishikawa, *Yuki Gosei Kyokai Shi*, **35**, 131 (1977).
7) I. L. Kunyants, V. V. Shokina, and B. B. Chulenda, *Angew. Chem. Int. Ed. Engl.*, **24**, 161 (1977); I. L. Knunyants and G. G. Yakobson, "Syntheses of Fluoroorganic Compounds," Springer-Verlag, Berlin, 1985.
8) M. E.-S. Mustafa, A. Takaoka, and N. Ishikawa, *Bull. Soc. Chem. Fr.*, **1986**, 944.
9) D. G. Neilson, R. Roger, J. W. M. Heatlie, and L. M. R. Newlands, *Chem. Rev.*, **70**, 151 (1970).
10) W. Oberhummer, *Monatsh.*, **63**, 285 (1933).
11) H. Neunhoeffer and H. Henning, *Chem. Ber.*, **101**, 3947 (1968).

12) The IR spectra of 2-pyridone, 4-pyridone, and their N-substituted derivatives were investigated by Katritzky *et al.* The IR absorptions of the 2-pyridone series appear at a higher frequency than those of the latter compounds. A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, **1960**, 2947. See also, "Physical Methods in Heterocyclic Chemistry," ed. by A. R. Katritzky, Academic Press, New York, 1963, p. 259.
13) It is well known that 2-pyridone and its *N*-alkyl derivatives show their absorption maxima in a longer wavelength region than those of the corresponding 4-pyridones. S. F. Mason, *J. Chem. Soc.*, **1959**, 1253. See also, A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, New York, 1964, p. 178.
14) C. Kaneko and T. Naito, *Chem. Pharm. Bull.*, **27**, 2254 (1979); T. Naito and C. Kaneko, *Tetrahedron Lett.*, **22**, 2671 (1981).
15) C. Kaneko, K. Shiba, H. Fujii, and Y. Momose, *J. Chem. Soc., Chem. Commun.*, **1980**, 1177.
16) Reviews on this topic: C. Kaneko and T. Naito, *Heterocycles*, **19**, 2183 (1982); T. Naito and C. Kaneko, *Yuki Gosei Kyokai Shi*, **42**, 51 (1984).
17) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964).
18) A. Wexler, R. J. Balchunis, and J. S. Swenton, *J. Chem. Soc., Chem. Commun.*, **1975**, 601; A. Wexler and J. S. Swenton, *J. Am. Chem. Soc.*, **98**, 1602 (1976).
19) D. L. Boger, *Chem. Rev.*, **86**, 781 (1986); D. L. Boger and J. S. Panek, *J. Org. Chem.*, **46**, 2179 (1981); H. J. Metz and H. Neunhoeffer, *Chem. Ber.*, **114**, 2807 (1982).
20) R. A. Carboni and R. V. Lindsey, *J. Am. Chem. Soc.*, **81**, 4342 (1959).
21) H. Neunhoeffer, L. Motits, H. Hennig, and K. Ostheimer *Justus Liebigs Ann. Chem.*, **760**, 88 (1972).
22) D. L. Boger, J. S. Panek, and M. M. Meier, *J. Org. Chem.*, **47**, 895 (1982).
23) It is well known that additional substitution of the heterocyclic azadiene system with electron-withdrawing groups increases the electron-deficient nature of the heterodiene and, hence, permits the use of strained alkenes as dienophiles in the corresponding Diels-Alder reactions. For examples, see: J. A. Elix, W. S. Wilson, R. N. Warrener, and I. C. Calder, *Aust. J. Chem.*, **25**, 268 (1972); M. G. Barlow, R. G. Barlow, R. H. Haszerdine, and D. J. Simpkin, *J. Chem. Soc., Chem. Commun.*, **1979**, 658.