Trifluoroisopropenylzinc Reagent as a Useful α-(Trifluoromethyl)ethenyl Carbanion Synthetic Equivalent. Preparation and Palladium-Catalyzed Coupling with Aryl Halides[1]

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In recent years, trifluoromethylated organic molecules have been drawing much attention due to their unique biological properties[2] and considerable effort has been paid to the exploitation of new synthetic routes to these fluorinated compounds.[3] Trifluoromethylation,[4] fluorination,[5] and the halogen exchange reaction[6] are possible methods for introducing the trifluoromethyl group into a molecule. However, such methods are sometimes accompanied by low reactivity and low selectivity. Another approach is to prepare CF_3-containing intermediates and utilize them as building blocks.[7] The latter route is now becoming an important strategy for the construction of trifluoromethylated molecules because it usually allows access to these CF_3-substituted compounds under milder conditions and with a tolerance of functionalities. Therefore, the development of a simple method for the preparation of trifluoromethylated building blocks and their further utilization for the synthesis of desired CF_3-containing compounds are essential to organofluorine chemistry.

In exploring fluorine-containing building blocks, the following considerations are important: ease of preparation and commercial availability of the starting material and wide applicability of the fluorine-containing intermediate derived therefrom. As we know, trifluoropropene (TFP) is one of the readily available and economically feasible fluoro material. Recently, Ojima has studied in detail the carbonylation reactions of TFP catalyzed by transition metals.[8] TFP has also been used as a dienophile in Diels-Alder reaction,[9] and it underwent Friedel-Crafts reaction with aromatic compounds to afford antiinflammatory agents.[10] 2-Bromotrifluoropropene (BTFP) (1), a derivative of TFP, could be easily obtained by dehydrobromination of the dibromo compound of TFP in high yield;[11] however, its utilization as a possible precursor of α-(trifluoromethyl)ethenyl carbanion synthetic equivalent only has been rarely exploited.[7a,12]

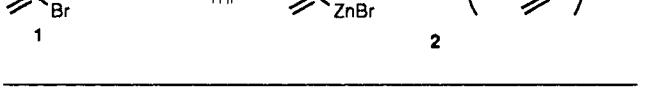
Table I. Preparation of TFPZ (2) from BTFP (1), Zn(Ag), and TMEDA

entry	TMEDA (equiv)	solvent	reaction cond[a] temp (°C)/time (h)	conversion of 1[b] (%)	yield of 2[b] (%)
1		Et_2O	40/24	0	0
2	0.5	Et_2O	40/24	50	50
3	1.0	Et_2O	40/24	100	98
4		THF	40/24	0	0
5	0.5	THF	60/9	50	47
6	1.0	THF	60/9	100	93
7	1.0	DME	67/9	100	90
8	1.0	DMF	40/3	100	30

[a] Mole ratio of BTFP and Zn (Ag) was 1:1.5; Zn(Ag) was activated by TMSCl.[14] [b] The conversion and yield were determined by ^{19}F NMR versus $C_6H_5CF_3$.

In the course of our research on the synthesis of fluorine-containing building blocks, we became interested in exploring the preparation of trifluoroisopropenylmetal reagents since it occurred to us that these reagents would be useful and versatile ones for introducing the trifluoroisopropenyl moiety into organic molecules. Drakesmith et al.[7a] have reported that trifluoroisopropenyllithium formed by the exchange metalation of BTFP with butyllithium was quite unstable; it underwent extremely facile defluorination above -90 °C and thus severely limited its use. It is known that the defluorination of α-CF_3-attached carbanion is assisted by countercations (e.g., K^+, Na^+, Li^+) with a strong affinity for the fluorine atom;[13] therefore, it could be anticipated that the use of counteractions with a weak affinity for the fluorine atom would impede the defluorination process. On the basis of this premise, we sought to prepare a trifluoroisopropenylmethyl reagent which would be stable and easy to handle. Herein, we would like to describe the successful preparation of trifluoroisopropenylzinc reagent (TFPZ) from 2-bromotrifluoropropene and the coupling reaction of this zinc reagent with aryl halides promoted by palladium.

Initially, we attempted to prepare the zinc reagent by the direct reaction of BTFP with activated zinc powder in a solvent such as diethyl ether, THF, and DME. However, it failed to form the desired product in any noticeable amount and the starting BTFP was recovered. After many trials, we found that the addition of tetramethylethylenediamine (TMEDA) to a mixture of BTFP and Zn(Ag) couple in THF can bring about a clean formation of the zinc reagent 2 (eq 1), which displayed a single signal in ^{19}F NMR at δ_{TFA} -16.0 ppm.



1 2 (1)

(1) Chinese Patent Appl. Serial No. CN 90 1 06105.0, Dec. 1990.
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(11) Henne, A. L.; Nager, M. *J. Am. Chem. Soc.* **1951**, *73*, 1042.
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(13) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276.
(14) On addition of trimethylchlorosilane, the Zn(Ag) couple became spongy and much more reactive. Without trimethylchlorosilane, the reaction proceeded sluggishly and the reagent 2 was found to be formed only in low yield. Knochel[15] has also noted the activation of zinc by trimethylchlorosilane in the presence of 1,2-dibromoethane.
(15) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392.

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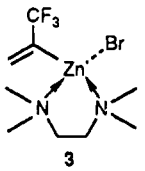
The optimum condition for the synthesis of trifluoroisopropenylzinc reagent has been examined, and the results were summarized in Table I. It reveals that the addition of TMEDA was essential to the formation of trifluoroisopropenylzinc reagent. In THF, an excellent yield (93%) of TFPZ can be achieved by the reaction of BTFP with Zn(Ag) (mole ratio, 1:1.5) in the presence of 1 mol equiv of TMEDA (Table I, entry 6). DME and diethyl ether can also be used as solvent for the preparation of TFPZ (Table I, entries 7 and 3). In DMF, however, only rather poor yield of TFPZ was obtained possibly due to the occurrence of α-defluorination (Table I, entry 8).

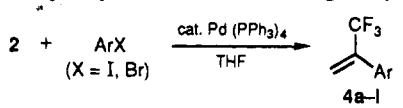
It seems reasonable to assume a chelate structure (tetracoordinated zinc) such as **3** for TFPZ. The formation



3

of a tetrahedral complex with sp^3 hybridization of the zinc atom is expected in view of its $3d^{10}4s^2$ electron configuration.[16] By the presence of a strong electron-withdrawing CF_3 group in the α-position, negative charge is being pulled away from the zinc atom causing the electron affinity of the vacant orbitals of zinc and, consequently, the tendency to form donor–acceptor complex to be increased. As a result, the covalent character of the zinc–carbon bond would be enhanced and the tendency of undergoing α-defluorination would be suppressed. Indeed, we found that this TMEDA-complexed trifluoroisopropenylzinc reagent in THF is quite thermally stable and it can be stored at room temperature over months or heated at 70 °C for a prolonged time in the absence of air and moisture showing no sign of deterioration.

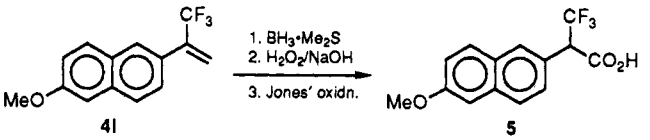
In modern organic synthesis, the cross-coupling of organometallic reagents with various electrophiles in the presence of a catalytic amount of palladium has been shown to be an efficient method for the formation of a carbon–carbon bond.[17] Recently, Burton[18] and Sauvetre[19] have reported the cross-coupling of perfluorovinylzinc reagents with aryl iodides. Encouraged by the easy preparation and remarkable stability of the TFPZ (**2**), we were interested in the feasibility of using this reagent for undergoing cross-coupling reaction with electrophiles in the presence of transition metals. Gratifyingly, we found that TFPZ (**2**) was able to undergo the coupling reaction with various aryl halides (X = I, Br) promoted by palladium with normal reactivity to afford the important α-(trifluoromethyl)styrene derivatives in good yields (eq 2).



4a–l

The experimental results were summarized in Table II. With aryl iodides, the coupling reaction of **2** (2 mol equiv) proceeded smoothly in the presence of 2 mol % $Pd(PPh_3)_4$ at 45–50 °C in THF. Reactions were completed in less than 6 h, and the corresponding coupling products were obtained in high yields (Table II, entries 1–4). In the case of 4-bromoiodobenzene, the bromine substituent in the benzene ring remained intact under the given conditions and 4-bromotrifluoromethylstyrene (**4d**) was obtained as the sole product in 92% yield (Table II, entry 4). Nevertheless, the coupling reaction with **2** could be extended to aryl bromides by carrying out the reaction at THF refluxing temperature for a prolonged time (16–20 h) and the corresponding coupling products were formed in satisfactory yields[20] (Table II, entries 5–11). Aryl bromides bearing a nitro or formyl group in the ortho position were found to be somewhat sluggish toward the coupling reaction with **2**, possibly due to steric reasons, and an incremental addition of another 2 mol % of palladium catalyst was required at the end of 10 h during the course of reaction (Table II, entries 8–10). In addition, 1-naphthyl iodide, 2-naphthyl bromide, and 6-methoxy-2-naphthyl bromide also underwent the palladium-catalyzed coupling reaction with **2** to give the corresponding coupling products **4j–l** in nearly quantitative yields (Table II, entries 12–14). However, *o*-amino- and acetylamino-substituted bromobenzene failed to react with **2** under our reaction conditions.

A lot of α-methylarylacetic acids, including Naproxen, are known to possess good antiinflammatory and analgesic properties. Among these, a fluorine containing analogue, Flurbiprofen ((3-fluorobiphenylyl)-1-α-methylacetic acid) is a very effective antiinflammatory agent with few side effects.[21] The ready availability of α-(trifluoromethyl)-styrene derivatives by the abovementioned coupling reaction of **2** with aryl halides led us to exploit the synthesis of trifluoro analogues of α-methylarylacetic acid therefrom. Thus, 6-methoxy-2-(α-(trifluoromethyl)ethenyl)-naphthalene (**4l**) was allowed to react with borane followed by treatment with alkaline hydrogen peroxide; the resultant alcohol without isolation was directly subjected to Jones' oxidation to afford the trifluoro analogue of Naproxen (**5**) in 69% yield (eq 3).



4l **5**

In conclusion, we have succeeded in preparing the trifluoroisopropenylzinc reagent from readily available 2-bromotrifluoropropene. This zinc reagent acts as an α-(trifluoromethyl)ethenyl carbanion synthetic equivalent without the occurrence of defluorination and can undergo palladium-catalyzed coupling reactions with aryl halides to afford a series of useful α-(trifluoromethyl)styrene derivatives in good yields. As a demonstration of the utility of these trifluoro-containing intermediates, compound **41** has been transformed to the trifluoro analogue of Naproxen (**5**). The biological property of **5** is under investigation.

Experimental Section

^1H NMR spectra were recorded on a Varian EM-360A spectra with TMS as an internal standard. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid (δ 0.00) as an external standard; downfield shifts were designated negative. IR spectra were taken on a Shimadzu 440-IR spectrometer, and mass spectra were done on a Finnigan 4021 GC/MS/DC intrument. All reactions as well as column chromatography were monitored routinely with the aid of TLC or ^{19}F NMR spectroscopy.

THF was distilled from $LiAlH_4$. Zn(Ag) was prepared according to the method described by Conia.[22] $Pd(PPh_3)_4$ was obtained

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Table II. Palladium-Catalyzed Cross-Coupling of TFPZ (2) with Aryl Halides

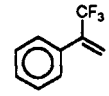
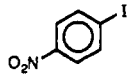
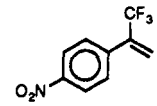
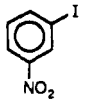
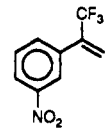
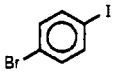
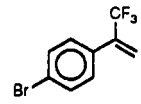
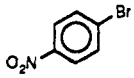
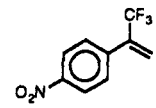
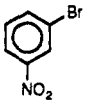
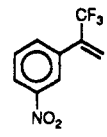
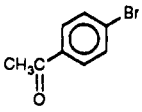
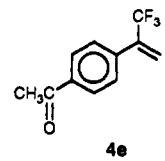
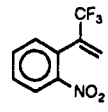
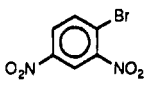
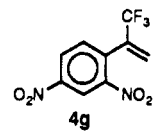
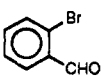
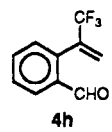
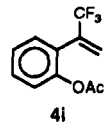
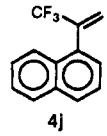
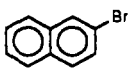
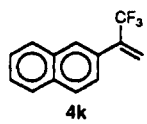
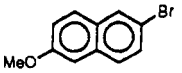
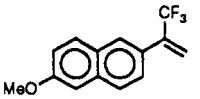
entry	ArX	reaction cond[a,b] temp (°C)/time (h)	products[d]	yields[e] (%)
1		45/6	 **4a**	96
2		45/6	 **4b**	95
3		50/5	 **4c**	92
4		50/5.5	 **4d**	92
5		67/16	 **4b**	93
6		67/16	 **4c**	88
7		67/18	 **4e**	90
8		67/20[c]	 **4f**	80
9		67/19[c]	 **4g**	81
10		67/20[c]	 **4h**	85
11		67/20	 **4i**	83
12		67/6	 **4j**	99
13		67/8	 **4k**	98

Table II (Continued)

entry	ArX	reaction cond[a,b] temp (°C)/time (h)	products[d]	yields[e] (%)
14		67/16	 41	96

[a] Mole ratio of aryl halide to 2 was 1:2. [b] 2 mol % of $Pd(PPh_3)_4$ based on aryl halide was used as catalyst unless otherwise stated. [c] Another 2 mol % of $Pd(PPh_3)_4$ was added at the end of 10 h. [d] All products were fully characterized by ^1H NMR, ^{19}F NMR, IR, MS, and C, H, F elemental analyses. [e] Isolated product yield based on aryl halide.

by the method of Coulson.[23] All reactions were carried out under nitrogen atmosphere.

Trifluoroisopropenylzinc Reagent (2). To a suspension of Zn(Ag) (2.5 g, 38 mmol) in THF (20 mL) was added trimethylchlorosilane (0.5 mL) during stirring. After 10 min, tetramethylethylenediamine (6 mL, 25 mmol) was added and then 2-bromotrifluoropropene (4.4 g, 25 mmol) was added dropwise at room temperature. After addition, the mixture was heated at 60 °C for 9 h. After being cooled to room temperature, the resulting solution of 2 in THF was transferred to a bottle with a septum under nitrogen and stored as such. The yield of 2 was shown to be 93% as determined by ^{19}F NMR versus $PhCF_3$. 2 displayed a single peak at δ −16.0 in ^{19}F NMR.

General Procedure for the Coupling of 2 with Aryl Halides. To the abovementioned zinc reagent 2 in THF (20 mL, ca. 20 mmol) was added $Pd(PPh_3)_4$ (0.2 mmol) and aryl halide (10 mmol). The mixture was then allowed to heat at 45–67 °C for 5–20 h (see Table II). After being cooled, the reaction mixture was poured into *n*-hexane (100 mL), and the solid which precipitated was triturated and filtered. The filtrate was concentrated in vacuo, and the residue thus obtained was purified by short-path distillation under reduced pressure (for compounds **4a**, **4c**) or by flash column chromatography on silica gel using a 100:1 mixture of petroleum ether (60–90 °C) and ethyl acetate as the eluent.

In the case where the aryl halide used was 2-nitrobromobenzene, 2,4-dinitrobromobenzene, or 2-bromobenzaldehyde, another 2 mol % of $Pd(PPh_3)_4$ was added at the end of 10 h during the course of the reaction.

α-(Trifluoromethyl)styrene (4a): colorless oil; ^1H NMR ($CDCl_3$) δ 5.72 (s, 1 H), 5.92 (s, 1 H), 7.42 (s, 5 H); ^{19}F NMR ($CDCl_3$) δ −11.0 (s); IR (neat) 1580, 1500, 1380 cm^{-1}; MS *m/z* (relative intensity) 172 (M, 37), 103 (62), 78 (100). Anal. Calcd for $C_9H_7F_3$: C, 62.79; H, 4.10; F, 33.11. Found: C, 62.27; H, 4.25; F, 33.18.

4-Nitro-α-(trifluoromethyl)styrene (4b): pale yellow oil; ^1H NMR ($CDCl_3$) δ 5.90 (s, 1 H), 6.20 (s, 1 H), 7.12–7.60, centered at 7.39 (A_2B_2, J = 4 Hz, 4 H); ^{19}F NMR ($CDCl_3$) δ −12.0 (s); IR (neat) 1600, 1540, 1500, 1380 cm^{-1}; MS *m/z* (relative intensity) 217 (M, 100), 171 (28), 151 (32); Anal. Calcd for $C_9H_6F_3NO_2$: C, 49.78; H, 2.79; N, 6.45; F, 26.25. Found: C, 49.98; H, 2.71; N, 6.41; F, 26.57.

3-Nitro-α-(trifluoromethyl)styrene (4c): pale yellow oil; ^1H NMR ($CDCl_3$) δ 5.92 (s, 1 H), 6.15 (s, 1 H), 7.10–7.80 (m, 3 H), 8.34 (s, 1 H); ^{19}F NMR ($CDCl_3$) δ −11.0 (s); IR (neat) 1620, 1580, 1540, 1500, 1358 cm^{-1}; MS *m/z* (relative intensity) 217 (M, 100), 171 (33), 151 (35). Anal. Calcd for $C_9H_6F_3NO_2$: C, 49.78; H, 2.79; N, 6.45; F, 26.25. Found: C, 49.80; H, 2.51; N, 6.14; F, 26.30.

4-Bromo-α-(trifluoromethyl)styrene (4d): colorless oil; ^1H NMR ($CDCl_3$) δ 5.73 (s, 1 H), 5.95 (s, 1 H), 7.10–7.58, centered at 7.36 (A_2B_2, J = 4 Hz, 4 H); ^{19}F NMR ($CDCl_3$) δ −12.0 (s); IR (neat) 1600, 1500, 1359 cm^{-1}; MS *m/z* (relative intensity) 252 (M + 1, 100), 231 (14), 182 (49), 102 (38). Anal. Calcd for $C_9H_6BrF_3$: C, 43.06; H, 2.41; F, 22.70; Found: C, 43.41; H, 2.31; F, 22.79.

4-Acetyl-α-(trifluoromethyl)styrene (4e): colorless oil; ^1H NMR ($CDCl_3$) δ 2.50 (s, 3 H), 5.72 (s, 1 H), 6.00 (s, 1 H), 7.12–7.60, centered at 7.37 (A_2B_2, J = 4 Hz, 4 H); ^{19}F NMR ($CDCl_3$) δ −11.5 (s); IR (neat) 1690, 1600, 1500, 1358 cm^{-1}; MS *m/z* (relative intensity) 214 (M, 100). Anal. Calcd for $C_{11}H_9F_3O$: C, 61.60; H, 4.23; F, 26.61; Found: C, 61.67; H, 4.60; F, 26.83.

2-Nitro-α-(trifluoromethyl)styrene (4f): pale yellow oil; ^1H NMR ($CDCl_3$) δ 5.76 (s, 1 H), 6.21 (s, 1 H), 7.20–7.40 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −11.8 (s); IR (neat), 1610, 1540, 1500, 1360 cm^{-1}; MS *m/z* (relative intensity) 217 (M, 100), 171 (30), 151 (41), 102 (25). Anal. Calcd for $C_9H_6F_3NO_2$: C, 49.78; H, 2.79; N, 6.45; F, 26.25. Found: C, 49.89; H, 2.51; N, 6.90; F, 26.30.

2,4-Dinitro-α-(trifluoromethyl)styrene (4g): yellow oil; ^1H NMR ($CDCl_3$) δ 5.78 (s, 1 H), 6.20 (s, 1 H), 7.70 (d, J = 4 Hz, 1 H), 8.58 (dd, J = 4 and 1.5 Hz, 1 H); ^{19}F NMR ($CDCl_3$) δ −11.0 (s); IR (neat) 1610, 1550, 1540, 1510, 1358 cm^{-1}; MS *m/z* (relative intensity) 263 (M + 1, 15), 243 (34), 215 (42), 186 (100). Anal. Calcd for $C_9H_5F_3N_2O_4$: C, 41.24; H, 1.92; N, 10.69; F, 21.74; Found: C, 41.55; H, 1.77; N, 10.42; F, 21.79.

2-Formyl-α-(trifluoromethyl)styrene (4h): colorless oil; ^1H NMR ($CDCl_3$) δ 5.54 (s, 1 H), 6.15 (s, 1 H), 7.20–7.80 (m, 4 H), 10.00 (s, 1 H); ^{19}F NMR ($CDCl_3$) δ −10.0 (s); IR (neat) 1710, 1610, 1600, 1500 cm^{-1}; MS *m/z* (relative intensity) 201 (M + 1, 98), 181 (37), 151 (77), 132 (100). Anal. Calcd for $C_{10}H_7F_3O$: C, 60.01; H, 3.53; F, 28.47; Found: C, 60.30; H, 3.39; F, 28.42.

2-Acetoxy-α-(trifluoromethyl)styrene (4i): colorless oil; ^1H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 5.60 (s, 1 H), 6.18 (s, 1 H), 7.20–7.80 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −12.0 (s); IR (neat) 1720, 1610, 1500, 1358 cm^{-1}; MS *m/z* (relative intensity) 230 (M, 100), 211 (37), 187 (40). Anal. Calcd for $C_{11}H_9F_3O_2$: C, 57.40; H, 3.94; F, 24.76. Found: C, 57.31; H, 4.26; F, 24.57.

1-(α-(Trifluoromethyl)ethenyl)naphthalene (4j): colorless oil; ^1H NMR ($CDCl_3$) δ 5.83 (s, 1 H), 6.02 (s, 1 H), 7.45 (m, 7 H); ^{19}F NMR ($CDCl_3$) δ −12.4 (s); IR (neat) 1610, 1580, 1510, 1358 cm^{-1}; MS *m/z* (relative intensity) 222 (M, 100), 153 (60), 128 (13). Anal. Calcd for $C_{13}H_9F_3$: C, 70.27; H, 4.08; F, 25.05. Found: C, 70.36; H, 4.16; F, 25.46.

2-(α-(Trifluoromethyl)ethenyl)naphthalene (4k): colorless oil; ^1H NMR ($CDCl_3$) δ 5.86 (s, 1 H), 6.06 (s, 1 H), 7.50 (m, 7 H); ^{19}F NMR ($CDCl_3$) δ −12.6 (s); IR (neat) 1610, 1580, 1500, 1358 cm^{-1}; MS *m/z* (relative intensity) 222 (M, 100), 153 (57), 128 (20). Anal. Calcd for $C_{13}H_9F_3$: C, 70.27; H, 4.08; F, 25.05. Found: C, 70.11; H, 4.24; F, 25.33.

6-Methoxy-2-(α-(trifluoromethyl)ethenyl)naphthalene (41): white solid; mp 68–69 °C; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 5.82 (s, 1 H), 6.01 (s, 1 H), 7.50 (m, 6 H); ^{19}F NMR ($CDCl_3$) δ −13.0 (s); IR (KCl) 1600, 1580, 1500, 1358 cm^{-1}; MS *m/z* (relative intensity) 252 (M, 100), 209 (71), 183 (17), 139 (35). Anal. Calcd for $C_{14}H_{11}F_3O$: C, 66.66; H, 4.40; F, 22.60. Found: C, 66.42; H, 4.23; F, 22.42.

6-Methoxy-α-(trifluoromethyl)-2-naphthaleneacetic acid (5). To a solution of **41** (504 mg, 2 mmol) in DME (5 mL) was added BH_3·Me_2S (10 M, 0.3 mL, 3 mmol), and the reaction mixture was refluxed for 8 h. After the mixture was cooled to 0 °C, 50% aqueous NaOH solution (0.5 mL), ethanol (1 mL), and 30% H_2O_2 (0.4 mL) were added successively. The mixture was then stirred for 30 min and diluted with ethyl acetate (15 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2 × 5 mL) and brine (2 × 5 mL) and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo, and the residue thus obtained was dissolved in acetone (5 mL) at 0 °C and treated with Jones' reagent[24] (0.5 mL) for 1 h. After being quenched with 2-propanol (0.5 mL), the mixture was extracted with ethyl ether (3 × 5 mL) and the ethereal extract then was washed with 1 N

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NaOH (3 × 5 mL). The alkaline solution was acidified with 2 N H_2SO_4, and the solid which precipitated was extracted with ethyl ether (3 × 5 mL). The ethereal solution was washed with brine (3 × 5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography on silica gel using petroleum ether (60–90 °C)/ethyl acetate (7:3) as the eluent to afford **5** (390 mg, 69% yield): a white solid, mp 140–142 °C; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H), 4.49 (q, J_{H-F} = 8.5 Hz, 1 H), 7.50 (m, 6 H); ^{19}F NMR ($CDCl_3$) δ −7.0 (d, J_{H-F} = 8.5 Hz); IR (KCl) 3500, 1710, 1600, 1500, 1358 cm^{-1}; MS *m/z* (relative intensity) 284 (M, 62), 239 (100). Anal. Calcd for $C_{14}H_{11}F_3O_3$: C, 59.16; H, 3.90; F, 20.05. Found: C, 59.27; H, 4.29; F, 20.17.

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Registry No. 1, 1514-82-5; 2, 136476-22-7; 4a, 384-64-5; 4b, 136476-18-1; 4c, 136476-19-2; 4d, 136476-20-5; 4e, 136476-23-8; 4f, 136476-24-9; 4g, 136476-25-0; 4h, 136476-26-1; 4i, 136476-27-2; 4j, 136476-28-3; 4k, 136476-29-4; 4l, 136476-30-7; 5, 87406-13-1; iodobenzene, 591-50-4; *p*-iodonitrobenzene, 636-98-6; *m*-iodonitrobenzene, 645-00-1; *p*-bromoiodobenzene, 589-87-7; *p*-bromonitrobenzene, 586-78-7; *m*-bromonitrobenzene, 585-79-5; *p*-bromoacetophenone, 99-90-1; *o*-bromonitrobenzene, 577-19-5; 2,4-dinitrobromobenzene, 584-48-5; *o*-bromobenzaldehyde, 6630-33-7; *o*-bromophenyl acetate, 1829-37-4; 1-iodonaphthalene, 90-14-2; 2-bromonaphthalene, 580-13-2; 2-bromo-6-methoxynaphthalene, 5111-65-9; silver–zinc couple, 12041-17-7.

Mechanistic Studies on DNA Photolyase. 4. The Enthalpy of Cleavage of a Model Photodimer

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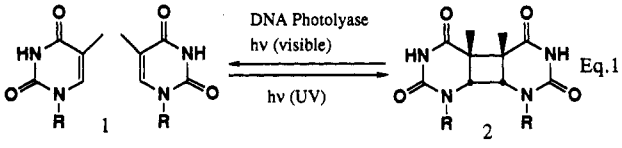
Cyclobutane pyrimidine photodimers constitute the highest quantum yield lethal damage caused to DNA by ultraviolet light.[1] In the cell this lesion can be efficiently repaired by DNA photolyase in a light-dependent reaction (350–450 nm, eq 1).[2] While model studies using quinones



and indoles as sensitizers have demonstrated that both the photodimer radical cation and anion undergo facile fragmentation reactions,[3] the mechanism of this interesting reaction has not yet been clearly established.[4,5]

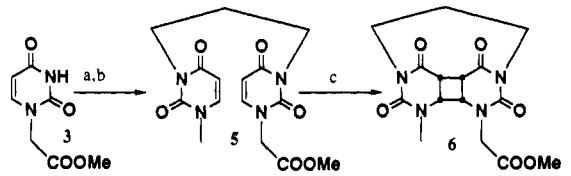
In this paper, we report the enthalpy of cleavage of a model uracil photodimer.[6]

Experimental Section

Melting points were uncorrected. Microanalyses were performed by Guelph Chemical Laboratories. Chromatography was carried out on silica gel.

3-(3-Bromopropyl)-1-(carbomethoxymethyl)uracil (4). Three grams (0.016 mol) of **3**[7] was combined with 6.5 mL (13 g, 0.064 mol) of 1,3-dibromopropane and 6.63 g (0.048 mol) of dry finely ground K_2CO_3 in 30 mL of dry DMF and heated at 60 °C for 1.5 h. The reaction mixture was cooled to room temperature and filtered, and the solvent was removed. Chromatography (0.5% CH_3OH in CH_2Cl_2) gave 3.7 g (75%) of **4**: ^1H NMR δ 7.65 (d, J = 9 Hz, 1 H), 5.75 (d, J = 9 Hz, 1 H), 4.6 (s, 2 H), 3.9 (t, J = 6 Hz, 2 H), 3.65 (s, 3 H), 3.5 (t, J = 6 Hz, 2 H), 1.9–2.1 (m, 2 H); HRMS calcd for $C_{10}H_{14}N_2O_4Br$ 305.0143, found 305.0137.

Scheme I[a]



[a] (a) 1,3-Dibromopropane; (b) 1-methyluracil; (c) *hv*.

Bisuracil (5). **4** (2.6 g, 8.5 mmol), 1.0 g (8.5 mmol) of 1-methyluracil,[8] and 3.5 g (25.5 mmol) of K_2CO_3 in 40 mL of dry DMF were heated at 60 °C for 1.5 h. The reaction mixture was filtered, and the solvent was removed. Chromatography (1% CH_3OH in CH_2Cl_2) gave 2.3 g (78%) of **5**: mp 176–178 °C; ^1H NMR δ 7.6 (d, J = 9 Hz, 2 H), 5.75 (d, J = 9 Hz, 1 H), 5.65 (d, J = 9 Hz, 1 H), 4.6 (s, 2 H), 3.75 (t, J = 6 Hz, 4 H), 3.65 (s, 3 H), 3.3 (s, 3 H), 1.6–1.8 (m, 2 H). Anal. Calcd for $C_{15}H_{18}O_6N_4$: C, 51.43; H, 5.18; N, 15.99. Found: C, 51.28; H, 4.91; N, 15.75.

Cis-Syn Photodimer 6. One gram of **5** was dissolved in 500 mL of CH_3CN and degassed by purging with argon for 15 min; 50 mL of acetone was added, and the solution was irradiated in a Rayonet reactor (λ_{max} = 300 nm) for 10 h. The solvent was removed, and the photodimer was purified by chromatography (1% CH_3OH in CH_2Cl_2) to give 0.63 g (63%) of **6**: mp 253–255 °C; ^1H NMR δ 3.65–4.45 (multiplet, 10 H), 3.63 (s, 3 H), 2.8 (s, 3 H), 2.0–2.2 (m, 1 H), 1.4–1.6 (m, 1 H). Anal. Calcd for $C_{15}H_{18}O_6N_4$: C, 51.43; H, 5.18; N, 15.99. Found: C, 51.81; H, 5.35; N, 16.09.

Combustion Calorimetry. The standard enthalpies of formation of bisuracil **5** and its photodimer **6** were measured using a mini rotating-bomb combustion calorimeter suitable for samples of ca. 10–50 mg.[9] The compounds were burned as pellets (ca. 20 mg) under 30 atm of oxygen using *n*-hexadecane (ca. 4 mg) as combustion aid. The bomb was not rotated during the experiments. The HNO_3 formed was determined as NO_3^- using a Dionex 4000*i* ion chromatography apparatus.

Results and Discussion

The model photodimer was synthesized as outlined in Scheme I. The trimethylene linker ensured that only the syn-cis isomer resulted from the photodimerization reaction.[10]

The standard enthalpy of formation of bisuracil **5** and its photodimer **6** were found to be −1116.6 ± 3.7 kJ/mol

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