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Authors: Yusuke Masuda, Katsuhiko Makita, Naoki Ishida, and Masahiro Murakami

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Synthesis of Tofisopam by Way of Photoinduced CO_2 Fixation

Yusuke Masuda, Katsuhiko Makita, Naoki Ishida, and Masahiro Murakami*[a]

Abstract: Herein reported is a unique synthetic route of Tofisopam, an anxiolytic drug containing a 2,3-benzodiazepine core structure. 3,4-Dimethoxypropylbenzene and 3,4-dimethoxybenzoic acid, which are both plant-origin, and CO_2 constitute its carbon skeleton. These three renewable substances are united by two C–C bond forming reactions, i.e., a Friedel-Crafts acylation reaction and a photoinduced carboxylation reaction to construct the major carbon framework. Finally, a methyl group is introduced by a Kumada-type cross-coupling reaction to furnish Tofisopam. Various analogs of Tofisopam are readily synthesized by introducing other substituents than a methyl group at the last C–C bond forming step.

There are a number of benzodiazepines which are known to act on a γ-aminobutyric acid (GABA) receptor to generally enhance the effect of GABA, causing anxiolytic, sedative, anticonvulsant, and muscle relaxant.[1] Among them, 2,3-benzodiazepine analogs are specifically potent as the anxiolytic drug since they have no sedative, anticonvulsant, and muscle relaxant activities.[2] Tofisopam (**1a**, Figure 1) possesses a 2,3-benzodiazepine ring, to which two methoxy groups, a 3,4-dimethoxyphenyl ring, ethyl, and methyl groups are appended. The 2,3-benzodiazepine core is possibly constructed by cyclocondensation of the 1,5-dicarbonyl compound shown in Figure 1 with hydrazine. There have been various methods developed for the synthesis of the key dicarbonyl compound.[3,4] In the conventional syntheses are used a toxic chromium reagent[3] or highly energetic compounds such as aryl lithium[4] (Figure 2a).

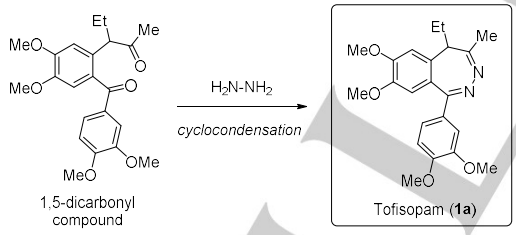


Figure 1. Structures of Tofisopam and a key 1,5-dicarbonyl intermediate.

On the other hand, it is highly desired to develop a reaction which fixes carbon dioxide (CO_2) onto organic molecules.[5,6] Since CO_2 is extraordinarily stable, most reactions which form a C–C bond with CO_2 require highly energetic nucleophiles such as carboanionic species. We have developed carboxylation reactions which fix CO_2 onto readily available and less energetic organic compounds with the aid of UV or solar light.[7] Herein, we report the synthesis of Tofisopam wherein the photoinduced carboxylation reaction fixes gaseous CO_2 into a carbon skeleton made from two plant-origin, renewable compounds (Figure 2b). Various Tofisopam analogs are readily synthesized by introducing an organyl group onto the imidoyl chloride intermediate at the last step.

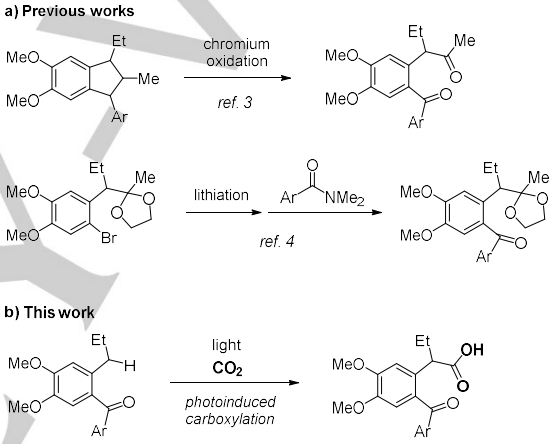
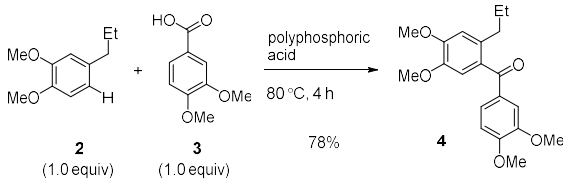


Figure 2. Syntheses of key 1,5-dicarbonyl intermediates.

We envisaged the key substrate ketone for the photoinduced carboxylation reaction would be synthesized by a Friedel-Crafts acylation reaction of propylbenzene **2**, which is readily accessible by hydrogenation of methyl eugenol,[8] with another plant-origin compound **3**.[9] Thus, a mixture of propylbenzene **2** and the carboxylic acid **3** was heated at 80 °C for 4 h in polyphosphoric acid.[10] A dehydrative Friedel-Crafts acylation reaction took place selectively at the para position of a methoxy substituent of **2** to produce ketone **4** in 78% yield.



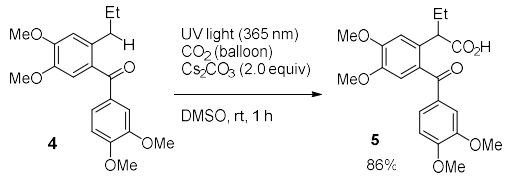
Scheme 1. Dehydrative Friedel-Crafts acylation.

With the substrate ketone **4** in hand, we tried the key photoinduced carboxylation reaction of **4**; a dimethyl sulfoxide (DMSO) solution of ketone **4** under an atmospheric pressure of

[a] Dr. Y. Masuda, K. Makita, Dr. N. Ishida, Prof. Dr. M. Murakami
Department of Synthetic Chemistry and Biological Chemistry
Kyoto University, Katsura, Kyoto 615-8510 (Japan)
E-mail: murakami@sbchem.kyoto-u.ac.jp

Supporting information and the ORCID identification numbers for the authors of this article can be found under:

CO_2 was irradiated with UV light. No carboxylated compound was formed under the conditions we previously reported, *i.e.*, in the absence of a base,[7b] although **4** was gradually consumed.[11] On the other hand, the desired carboxylic acid **5** was produced in 86% yield when the photoinduced carboxylation reaction of **4** was carried out in the presence of Cs_2CO_3 (Scheme 2).[12] A [4 + 2] cycloaddition step between *o*-quinodimethane[13] generated from **4** and CO_2 might be accelerated under the basic conditions, although we have no theoretical or experimental evidence to support this explanation. The reaction was scalable; when 5 mmol (1.7 g) of **4** was used, **5** was produced in 67% yield (1.3 g).

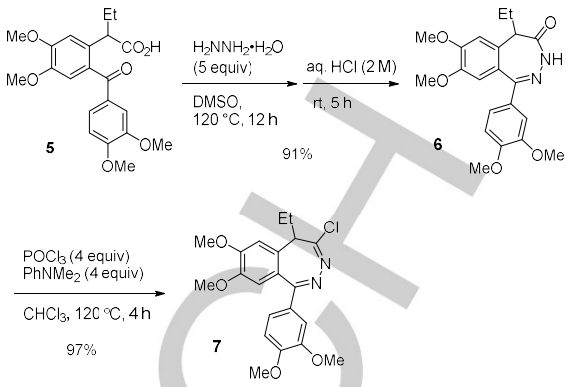


Scheme 2. Photoinduced carboxylation of ketone **4** with CO_2.

Next, the carboxylic acid **5** was treated with hydrazine in DMSO to form the corresponding hydrazone (Scheme 4). After heating the mixture at 120 °C for 12 h, an aq. HCl solution was added directly to the reaction mixture at room temperature to promote the subsequent seven-membered ring formation.[7b,14] Benzodiazepine **6** was isolated in 91% yield by silica gel chromatography. Next, the benzodiazepine **6** was converted to imidoyl chloride **7** almost quantitatively by treatment with phosphoryl chloride in the presence of *N,N*-dimethylaniline.[15]

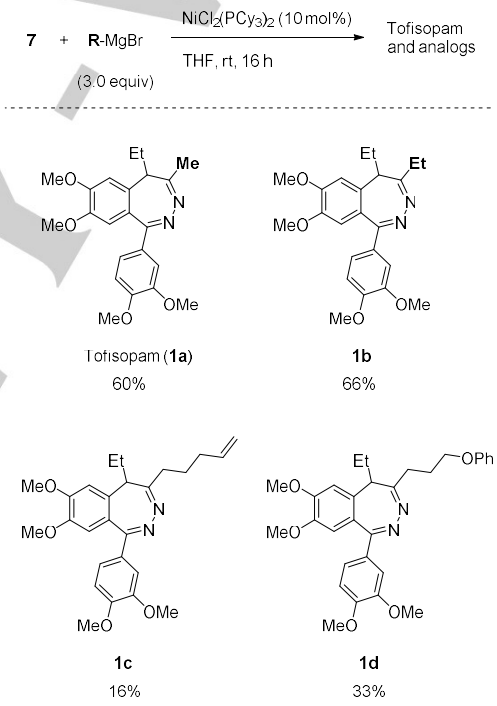
The last manipulation was substitution of the chloro substituent with a methyl substituent. No reaction occurred when the imidoyl chloride **7** was treated with methylmagnesium bromide at room temperature. Next, the reaction with methylmagnesium bromide was carried out in the presence of bis(tricyclohexylphosphine)nickel(II) dichloride [$NiCl_2(PCy_3)_2$, 10 mol%].[16] To our delight, a desired substitution reaction took place to afford Tofisopam (**1a**) in 60% isolated yield (Table 1). The structure of the obtained material was confirmed by comparison of its spectral data (IR[3a] and NMR[17]) and melting-point[17] with those reported in literatures (See Supporting Information).

Finally, we synthesized analogs of Tofisopam simply by varying the Grignard reagent for the last substitution reaction. The use of ethylmagnesium bromide afforded the ethyl analog **1b** in 66% yield. Functional groups such as alkenyl (**1c**) and phenoxy (**1d**) groups were successfully introduced onto a benzodiazepine pharmacophore, albeit in lower yields. Such late-stage diversification demonstrates the advantage of the present route introducing a C–C bond at the last step, and is promising for the pharmaceutical discoveries.[18]



Scheme 3. Synthesis of imidoyl chloride **7**.

Table 1. Synthesis of Tofisopam (**1a**) and its analogs.



To summarize, we synthesized Tofisopam in 5 steps and 36% overall yield starting from readily available plant-origin renewable compounds. The key 1,5-dicarbonyl intermediate was synthesized by a photoinduced carboxylation reaction, in which CO_2 was successfully incorporated at the benzylic C–H bond in a site-selective manner. Furthermore, the present strategy renders it possible to diversify the imidoyl chloride intermediate into various analogs of Tofisopam through a cross-coupling reaction with a range of Grignard reagents.

Experimental Section

Synthesis of ketone 4: A mixture of **2** (1.8 g, 10 mmol), **3** (1.8 g, 10 mmol), and poly phosphoric acid (15 mL) was stirred at 80 °C for 4 h. After the reaction mixture was cooled to room temperature, water was added. The resulting aqueous solution was extracted with EtOAc (3 times). The combined organic layer was washed with water, a sat. aq. NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc = 3:1) to afford ketone **4** as white solids (2.7 g, 7.8 mmol, 78%).

Synthesis of carboxylic acid 5: A DMSO (5 mL) solution of **4** (68.9 mg, 0.20 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol) was irradiated by UV light (365 nm) under an atmospheric pressure of CO_2 for 1 h. An aq. HCl solution (1 M) was added to the reaction mixture. The resulting mixture was extracted with Et_2O (3 times). The combined organic layer was washed with water (3 times) and extracted with an aq. NaOH solution (2 M) (3 times). The combined aqueous layer was acidified with an aq. HCl solution (2 M), and extracted with Et_2O (3 times). The organic layer was washed with a sat. aq. NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to afford the carboxylic acid **5** as white solids (67.0 mg, 0.17 mmol, 86% yield).

Synthesis of amide 6: A DMSO (1 mL) solution of **5** (77.7 mg, 0.20 mmol) and hydrazine monohydrate (100 mg, 1.0 mmol) was stirred at 120 °C for 12 h. After the reaction mixture was cooled to room temperature, an aq. HCl solution (2 M, 4 mL) was added. After stirring at room temperature for 5 h, a sat. aq. $NaHCO_3$ solution was added to the reaction mixture, which was subjected to extraction with dichloromethane (3 times). The combined organic layer was washed with water, a sat. aq. NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (dichloromethane/EtOAc = 2:1) to afford amide **6** as white solids (70.2 mg, 0.18 mmol, 91%).

Synthesis of imidoyl chloride 7: A $CHCl_3$ (2 mL) solution of amide **6** (115 mg, 0.30 mmol), *N,N'*-dimethylaniline (123 mg, 1.20 mmol), and phosphoryl chloride (123 mg, 1.20 mmol) was stirred at 120 °C for 4 h. After the reaction mixture was cooled to room temperature, volatiles were removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (dichloromethane/EtOAc = 20:1) to afford imidoyl chloride **7** as pale yellow solids (117 mg, 0.28 mmol, 97%).

Typical procedure for synthesis of Tofisopam 1a: A THF (2 mL) solution of **7** (40.6 mg, 0.10 mmol), $NiCl_2(PCy_3)_2$ (13.8 mg, 0.02 mmol), and methylmagnesium bromide (3.0 M in THF, 0.10 mL, 0.30 mmol) was stirred at 80 °C for 12 h. After cooling to room temperature, a sat. aq. NH_4Cl solution was carefully added to the reaction mixture, which was subjected to extraction with EtOAc (3 times). The combined organic layer was washed with water, a sat. aq. NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 1:2) to afford Tofisopam **1a** as yellow solids (22.8 mg, 0.060 mmol, 60%).

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Keywords: tofisopam • photoreaction • carbon dioxide • C–H carboxylation • 2,3-benzodiazepine

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[11] Significantly different reactivities were previously observed between ortho methyl-substituted and ethyl-substituted benzophenones.[7b] This is explained by assuming a steric factor operating at the [4+2] cycloaddition step of the intermediate quinodimethane with CO_2. A similar steric retardation would explain the low reactivity of the ortho propyl-substituted benzophenone derivative **4**.

[12] Although the carboxylation reaction was also promoted by other inorganic bases, Cs_2CO_3 gave the best result, probably because of its high basicity and solubility in DMSO. See Supporting Information for the effect of bases.

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