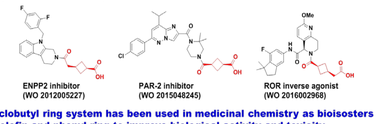
27O-ISMS32

Rapid and efficient synthesis of deuterated cyclobutane derivatives using continuous photo flow chemistry

Toshiro Yamashita, Hitoaki Nishikawa, Tetsuji Kawamoto.
Chemistry, Research Division, Axcelead Drug Discovery Partners, Inc.

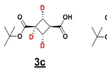
Background

Representative compounds



Cyclobutyl ring system has been used in medicinal chemistry as bioisosters of olefin and phenyl ring to improve biological activity and toxicity.

Target D labeled compounds (New compounds)

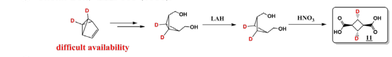


①Internal standard compounds in non-clinical / clinical pharmacokinetic studies.
・No d0 compound must be contained.
・Introduction of more than three or four D atoms are essential.

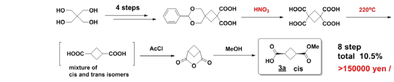
②Introduction of D atom at metabolic position to improve pharmacokinetic properties.

Conventional synthetic methods

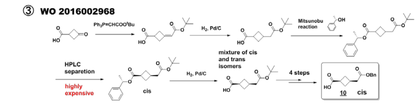
① Chem. Ber., 116 669 (1983).



② J. Org. Chem., 30 1945 (1965).

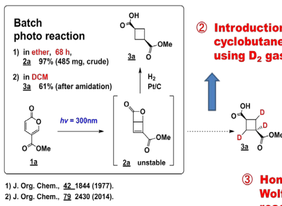


③ WO 2016002968



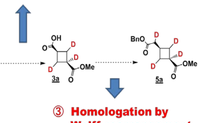
No effective synthetic method for 3c and 5

Synthetic strategy



1) J. Org. Chem., 42 1844 (1977).
2) J. Org. Chem., 79 2430 (2014).

② Introduction of D atom on cyclobutane ring system using D_2 gas

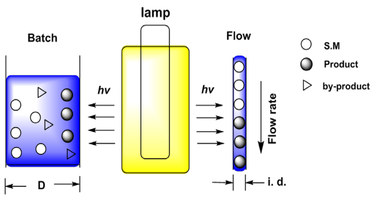


③ Homologation by Wolff rearrangement reaction in BnOD.

① Raise up the efficacy of photo reaction in safer solvent using photo flow chemistry.

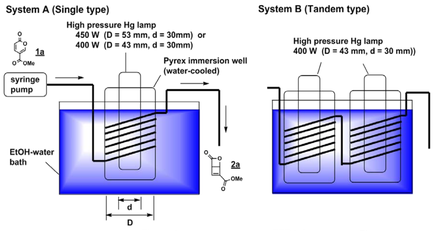
Photo flow chemistry

Photo flow reaction is more efficient than batch reaction.



・Specific surface area of irradiation was larger than batch reaction due to short i.d. of flow tube.
・Smaller amount of by-product was formed because product was immediately flowed out before degradation.

Photo flow reaction system



FEP tube 1/16" i.d. 0.75 mm length 800 cm
Flow rate 0.2-0.5 mL/min (Rt = 17.7-12.9 min)

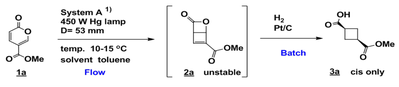
FEP tube 1/16" i.d. 0.75 mm length 1700 cm
Flow rate 0.75 mL/min (Rt = 10.0 min)

Photo flow reaction system A

Immersion well (water-cooled)

Whole picture of photo flow system

Initial study of photo flow chemistry using methyl ester 1a



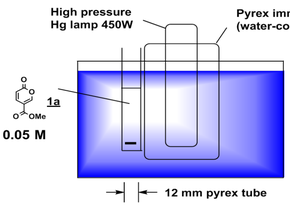
entry	1a (M)	Flow rate (ml/min)	Rt (min) 2)	Conversion (% HPLC) 2a	Conversion (% HPLC) 1a	Comment
1	0.1	0.5	7.1	24	76	
2	0.1	0.3	11.8	40	60	
3	0.1	0.2	17.7	66	34	
4	0.1	0.1	35.3	100	0	by-product
5	0.05	0.2	17.7	100	0	best condition
6	0.05	0.3	11.8	100	trace	
7	0.06	0.2	17.7	100	trace	
8 3)	0.05 (616 mg)	0.2	17.7	100	0	3a, quant.(crude, 640mg)
9 4)	0.05 (154 mg)	Batch reaction		100	0	by-product

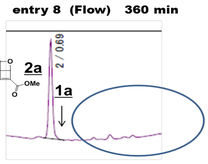
1) Reaction resulted in messy when quarz filter was used. 2) Residence time 3) Flow time 400 min.
4) Batch reaction in Pyrex tube (i.d. 12 mm), reaction time 120 min.

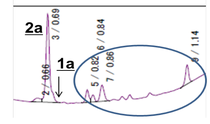
The condition used in entry 5 was found to be proper for this reaction.

Batch photo reaction

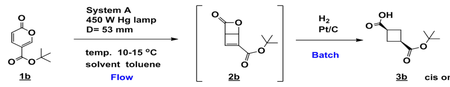
Photo flow reaction was cleaner than photo batch reaction.
Batch reaction gave a lot of by-products (entry 9).







Optimization of photo flow chemistry using tert-Bu ester 1b

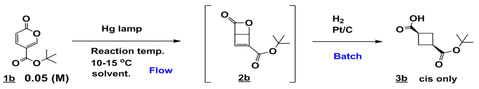


entry	1b (M)	Flow rate (mL/min)	Flow time (min)	Rt (min)	HPLC 2b	HPLC 1b	3b Isolated	3b productivity (g / 10 hr)
10	0.05 (780 mg)	0.2	400	17.7	92	8	678 mg (85%)	1.0
11	0.05	0.2	-	49.7 1)	91	9		
12	0.05	0.2	-	59.7 2)	94	6	by-product	
13	0.05 (13.5 g)	0.3	4560	39.8 2)	86	14	11.1 g (81%)	1.5

1) FEP tube (i.d. 1.59 mm, L 500 cm) was used.
2) FEP tube (i.d. 0.75 mm, L 2700 cm, wound with two layers) was used.

・Thicker tube (i.d. 1.59 mm, L 500 cm) gave the same potency (entry 11).
・Increase in tube length enhanced the conversion to some extent concomitant with increasing the amount of by-product (entry 12).
・11.1 g of tert-Bu ester 3b was successfully obtained (entry 13).

Optimization of photo flow chemistry using tert-Bu ester 1b

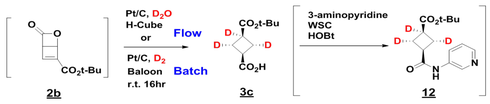


entry	system	d 1)	solvent	Flow rate (ml/min)	Rt (min)	HPLC 2b	HPLC 1b	3b productivity (g / 10 hr)
10	A	53	toluene	0.2	17.7	92	8	1.0
14	A	43 2)	toluene	0.4	16.1	92	8	2.0
15	A	43	toluene	0.5	12.9	76	24	-
16	A	43	CH_3CN 3)	0.5	12.9	86	14	2.4
17	B	43	CH_3CN	0.75	10.0	86	14	3.6

1) d: light tube diameter. 2) 400 W Hg lamp (pyrex filter).
3) Low conversion was found in THF, AcOEt, n-hexane and DMF.

・Productivity raised up to 2 .0 g per 10 hr when the immersion well with shorter diameter (D) was used (entry 14).
・Productivity raised up to 2.4 g per 10 hr when CH_3CN was used as solvent (entry 16).
・Productivity raised up to 3.6 g per 10 hr when flow system B was used (entry 17).

Introduction of D atoms to cyclobutane ring system

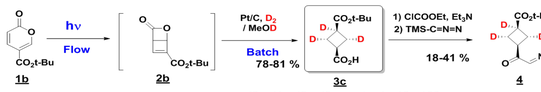


entry		solvent	$d_0 : d_1 : d_2 : d_3$ 1)	3c Isolated (%)
1	H-Cube 2) (D_2O)	THF	2 : 11 : 49 : 100	73
2		Toluene	1 : 7 : 44 : 100	93
3		EtOD	messy	
4	Baloon (D_2 gas) 3)	THF	38 : 62 :100 : 96	88
5 3)		Toluene	1 : 3 : 17 : 100	96
6 3)		MeOD	n.d. : 1 : 19 : 100	55 ⇒ up to 81%

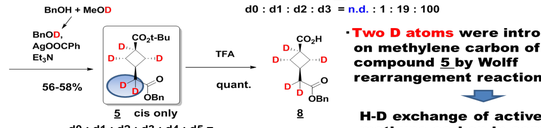
1) D content of 3c was determined by LCMS analysis of amide 12
2) 0.025-0.075 M, Flow rate 0.4 mLmin
3) 2b was used after azeotropical distillation with MeOD.

d0 compound was not detected (entry 6).

Preparation of new D labeled compounds 3c and 5



d0 : d1 : d2 : d3 = n.d. : 1 : 19 : 100



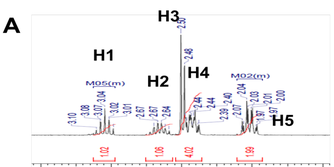
d0 : d1 : d2 : d3 : d4 : d5 = n.d. : n.d. : 0.7 : 9 : 47 : 100

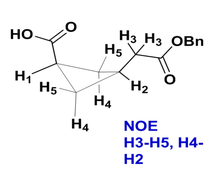
・Two D atoms were introduced on methylene carbon of compound 5 by Wolff rearrangement reaction in BnOD.

H-D exchange of active methyne carbon in compound 4 was proposed.

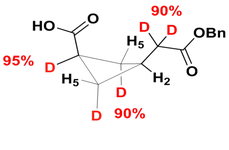
Proposed mechanism

^{1}H NMR analysis of D labeled compound 8





compound 8



Summary and Future plan

Summary

・More efficient method to synthesize compounds 3a and 3b using photo flow chemistry in safer solvent was established.
  ・Photo flow reaction was cleaner than photo batch reaction.
  ・The distance between lamp and reactor tube is relevant to the efficacy.
  ・Productivity was raised up to 3.6 g / 10 hr using system B.
・Introduction of D atoms to cyclobutane ring system with high deuterium content was successfully achieved. No d0 compound was contained.
・Two D atoms could be introduced on methylene carbon of compound 5 by the Wolff rearrangement reaction in BnOD.

Future Plan

・Further optimization of the photoreaction conditions to improve productivity (numbering up etc.).
・Further contribution to Medchem. (Synthesis of D compounds, metabolite, unique library etc.).
・Fully deuterization of cyclobutane ring system.

AXCELEAD Drug Discovery Partners