



An efficient synthesis of cycloalkane-1,3-dione-2-spirocyclopropanes from 1,3-cycloalkanediones using (1-aryl-2-bromoethyl)-dimethylsulfonium bromides: application to a one-pot synthesis of tetrahydroindol-4(5H)-one



Hisanori Nambu*, Masahiro Fukumoto, Wataru Hirota, Naoki Ono, Takayuki Yakura*

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan

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ABSTRACT

An efficient synthesis of cyclohexane- and cyclopentane-1,3-dione-2-spirocyclopropanes from 1,3-cycloalkanediones using sulfonium salts was achieved. The reaction of 1,3-cycloalkanediones with (1-aryl-2-bromoethyl)-dimethylsulfonium bromides and powdered K_2CO_3 in EtOAc provided the corresponding spirocyclopropanes in high yields. Furthermore, a one-pot synthesis of tetrahydroindol-4(5H)-one from 1,3-cyclohexanedione was achieved using the present protocol and a sequential ring-opening cyclization of spirocyclopropane with a primary amine.

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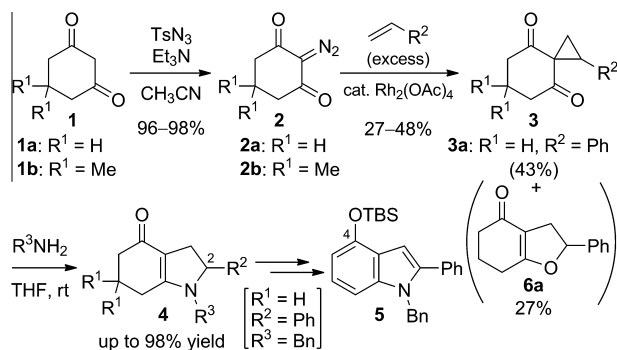
Doubly activated cyclopropanes represent versatile intermediates for the synthesis of a variety of carbo- and heterocyclic compounds.¹ In this context, a ring-opening cyclization reaction of doubly activated cyclopropanes with primary amines is one of the most powerful methods for the construction of pyrrole skeletons.² Very recently, we reported the first example of the formation of indole skeletons by employing the ring-opening cyclization of spirocyclopropanes. The reaction of cyclohexane-1,3-dione-2-spirocyclopropanes **3**, derived from 1,3-cyclohexanediones **1**, with primary amines proceeded smoothly at room temperature to give high yields of tetrahydroindol-4(5H)-ones **4**, one of which was easily converted to 4-hydroxyindole **5** (Scheme 1).³ This procedure provides a useful method for the synthesis of 4-hydroxyindoles. However, there is still a need for improvement in the yields of spirocyclopropanes **3** in Rh(II)-catalyzed cyclopropanation^{4–6} with 2-diazo-1,3-cyclohexanediones **2** (27–48% yields). The reaction of alkenes and diazo substrates derived from active methylene compounds in the presence of an Rh(II) catalyst is widely employed for the synthesis of a variety of doubly activated cyclopropanes. In the case of the preparation of spirocyclopropanes, the Rh(II)-catalyzed reaction also produced several cyclopropanes easily but in low

yields and was accompanied by a large amount of by-products. For example, the reaction of an excess amount of styrene with 2-diazo-1,3-cyclohexanedione (**2a**) using a catalytic amount of $Rh_2(OAc)_4$ gave spirocyclopropane **3a** in 43% yield and tetrahydrobenzofuran-4(5H)-one **6a**⁷ as a by-product in 27% yield (Scheme 1).⁶ Furthermore, this protocol is a two-step conversion from 1,3-cyclohexanediones **1** and requires a potentially explosive diazo compound. These drawbacks led us to develop a concise and practical route to spirocyclopropanes **3** from 1,3-cyclohexanediones **1**. Herein, we report an efficient synthesis of 1-arylspiro[2.5]octane-4,8-diones **3** using (1-aryl-2-bromoethyl)-dimethylsulfonium bromides **7** (Scheme 2).

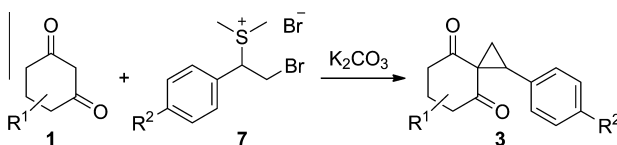
The reaction of active methylene compounds such as malonate and β -ketoester with sulfonium salts has been established^{2b,8–10} as an alternative approach to doubly activated cyclopropanes. Recently, Chandrasekaran and Gopinath reported that the reaction of 2,4-pentanedione with (2-bromo-1-phenylethyl)dimethylsulfonium bromide (**7a**) and K_2CO_3 in CH_2Cl_2/H_2O (1:1) gave the corresponding cyclopropane in 65% yield.⁹ Lu and co-workers applied this reaction to a cyclic alkanedione system, in which the reaction was conducted using DBU in DMSO, although the yield was very low.¹⁰ At the outset, we examined the reaction of 1,3-cyclohexanedione (**1a**) with sulfonium salt **7a** for the synthesis of 1-phenylspiro[2.5]octane-4,8-dione (**3a**) according to Chandrasekaran's procedure (Table 1, entry 1). The reaction of **1a** with 1.5 equiv of

* Corresponding authors. Tel.: +81 76 434 7555/7556; fax: +81 76 434 5053.

E-mail addresses: nambu@pha.u-toyama.ac.jp (H. Nambu), yakura@pha.u-toyama.ac.jp (T. Yakura).



Scheme 1. Synthesis of 4-hydroxyindole **5** employing a ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropane **3** with amine.



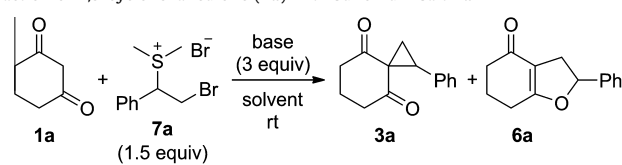
Scheme 2. Syntheses of spirocyclopropanes **3** from 1,3-cyclohexanediones **1** and sulfonium salts **7**.

7a using K₂CO₃ in CH₂Cl₂/H₂O (1:1) at room temperature provided **3a** in 30% yield. To enhance the yield of **3a**, we then screened other solvents. Switching the solvent to CH₂Cl₂ made the reaction messy to give tetrahydrobenzofuran-4(5H)-one **6a** in 6% yield without **3a** (entry 2). The use of CH₃CN, ⁱPrOH, and THF resulted in low yields of **3a** (7–14% yields, entries 3–5). We considered that the poor solubility of sulfonium salt **7a** led to low product yields. With the highly polar solvents DMF and DMSO, spirocyclopropane **3a** was obtained in 26% and 35% yields, respectively, along with **6a** in 28% and 23% yields, respectively (entries 6 and 7). Surprisingly, the reaction in EtOAc proceeded smoothly to completion within 1.5 h and gave **3a** in 81% yield (entry 8), although **7a** is almost insoluble in EtOAc. A survey of bases revealed that K₂CO₃ was the optimal base for this transformation (entry 8 vs entries 9 and 10). To our delight, the use of powdered K₂CO₃, which was finely ground in a mortar, instead of granular K₂CO₃ increased the product yield of **3a** (92% yield, entry 11).

With the optimal conditions in hand,¹¹ we investigated the scope of the reaction of a variety of 1,3-cyclohexanediones **1a–d** with several sulfonium salts **7a–c** prepared from styrene derivatives and bromodimethylsulfonium bromide^{12,13} (Table 2). The reaction of **1a** with **7b** and **7c** bearing *p*-bromo or *p*-methyl substituents on the benzene ring provided the corresponding spirocyclopropanes **3b** and **3c**¹⁴ in 92% and 74% yields, respectively. High yields of **3d–f**¹⁴ (84–94% yields) were consistently obtained in the reaction of dimedone (**1b**) with **7a–c**. The reaction of 5-methyl- and 5-phenyl-1,3-cyclohexanediones (**1c** and **1d**) with **7a** afforded diastereomeric mixtures (ca. 1:1) of spirocyclopropanes **3g** and **3h** in 89% and 81% yields, respectively. We then examined the Rh(II)-catalyzed cyclopropanation of the corresponding styrene derivatives with 2-diazo-1,3-cyclohexanediones derived from **1a–d**, and the yields are shown in square brackets in Table 2. In all cases, the yields of **3a–h** (38–47% yields) were lower than those obtained by the reactions of **1** and **7**.

We next turned our attention to the reaction of 5-membered carbocycles with sulfonium salt **7a** (Scheme 3). The reaction of 1,3-cyclopentanedione (**8**) with 1.5 equiv of **7a** using powdered K₂CO₃ in EtOAc provided the corresponding spirocyclopropane **9**

Table 1
Reaction of 1,3-cyclohexanedione (**1a**) with sulfonium salt **7a**^a



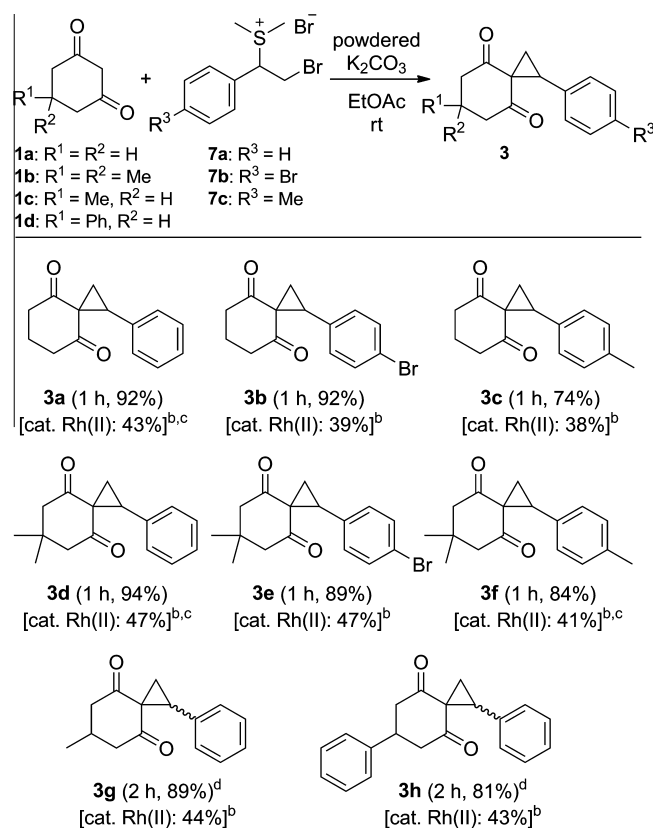
Entry	Base	Solvent	Time (h)	Yield ^b (%)	
				3a	6a
1	K ₂ CO ₃	CH ₂ Cl ₂ /H ₂ O (1:1)	8	30	Trace
2	K ₂ CO ₃	CH ₂ Cl ₂	24	Trace	6
3	K ₂ CO ₃	CH ₃ CN	9	14	Trace
4	K ₂ CO ₃	ⁱ PrOH	20	9	9
5	K ₂ CO ₃	THF	24	7	Trace
6	K ₂ CO ₃	DMF	4	26	28
7	K ₂ CO ₃	DMSO	2	35	23
8	K ₂ CO ₃	EtOAc	1.5	81	Trace
9	^t BuOK	EtOAc	24	Trace	Trace
10	DBU	EtOAc	0.5	20	7
11	K ₂ CO ₃ ^c	EtOAc	1	92	Trace

^a All reactions were performed on a 0.5 mmol scale.

^b Isolated yield.

^c Powdered K₂CO₃ was used.

Table 2
Reaction of 1,3-cyclohexanediones **1a–d** with sulfonium salts **7a–c**^a



^a All reactions were performed on a 0.5 mmol scale with 1.5 equiv of sulfonium salts **7a–c** and 3 equiv of powdered K₂CO₃ in EtOAc.

^b Yields in square brackets were obtained in the reactions of large amounts of the corresponding styrene derivatives with 2-diazo-1,3-cyclohexanediones derived from **1a–d** in the presence of 1 mol % of Rh₂(OAc)₄.

^c Ref. 3.

^d The products **3g** and **3h** were isolated as a diastereomeric mixture (ca. 1:1).

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