Diastereoselective Synthesis of Spiro and Chlorocyclopropanes from Camphorpyrazolidinone derived α,β-Unsaturated Amides

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Abstract: High diastereoselectivity are observed in the addition of gem-dichlorocarbene to an optically pure α,β-unsaturated amides derived from a chiral camphorpyrazolidinone. A novel route to the asymmetric synthesis of spiro [2,2]-pentane carboxylic acid esters derivatives *through gem*-dichlorocyclopropane is described.

Key words: diastereoselectivity, camphorpyrazolidinone, *gem*-dichlorocyclopropane, and spiro [2,2]-pentane carboxylic acid esters.

Introduction:

spiro [2,2]-pentane ring is a structural fragment of many biologically active compounds[1], including highly efficient insecticides[2,3]. In the recent years, strong physiological activity has been revealed in the series of conjugated spiro [2,2]-pentane carboxylic acid esters derivatives, and interest in these compounds has increased considerably[4]. Almost all known syntheses of such rings are based on a combination of α,β-unsaturated carbonyl derivatives and in situ generated gem-dichlorocarbene[5-7] to generate gem-dichlorocyclopropane[8,9] derivatives which further undergo annealation[10] to give

spiropentane carboxylic acid derivatives. Indeed, *gem*-dihalocyclopropane derivatives are useful synthetic intermediates because they can be readily transformed into cyclic, acyclic, heterocyclic and macrocyclic compounds including natural product precursors[11-13].

Present work:

Part-A: Use chloroform, 50% NaOH in presence TBABr. In our ongoing work for the synthesis of biologically active molecules using chiral auxiliary derived α,β-unsaturated amide that allows use for Aziridination[14] leads to hydrogenation[15,] Epoxidation[16] and cyclopropanation[17].

scheme-1

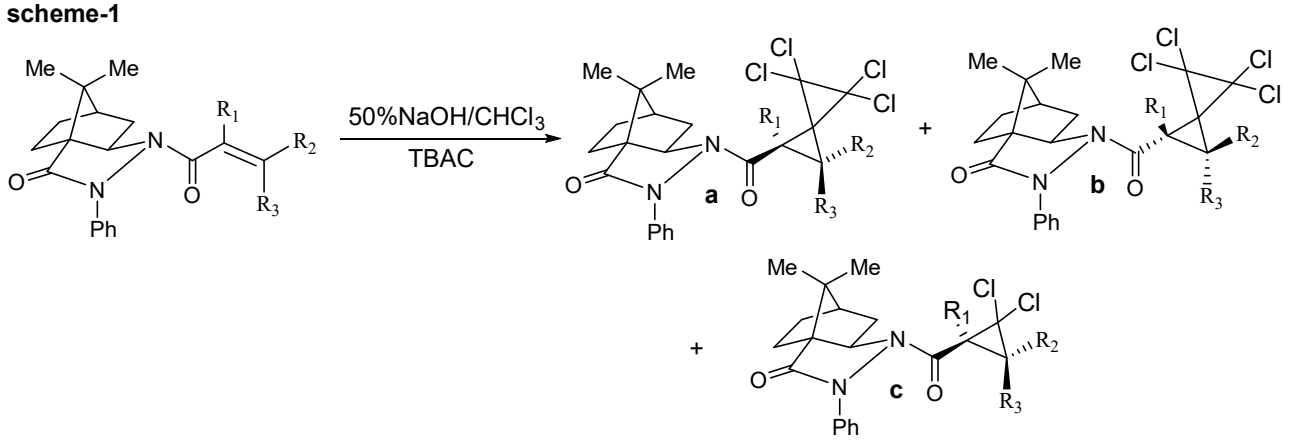


Table-1											
entry	**Substrate**	**R_1**	**R_2**	**R_3**	**Time (h)**	**Temp**	**Yield**	**spiro-a**	**spiro-b**	**cp**	**d.ratio***
1	2a	H	H	H	24	RT	68	3a	3b	0	57:43
2	2b	H	Ph	H	24	RT	62	4a	0	4b	>99.5
3	2c	H	COOEt	H	6	RT	0	0	0	0	0
4	2d	H	$C_3H_{7\text{-}n}$	H	24	RT	73	5a	0	0	>99.5
5	2e	H	CH_3	H	24	RT	61	6a	0	0	>99.5
6	2f	H	$C_3H_{7\text{-}iso}$	H	72	70°C	NR	0	0	0	0
7	2g	H	$C_4H_{9\text{-}tert}$	H	72	70°C	NR	0	0	0	0
8	2h	H	CH_3	CH_3	72	70°C	NR	0	0	0	0
9	2i	CH_3	CH_3	H	48	RT	61	0	0	7c	>99.5
10	2j	CH_3	H	H	48	70°C	12	0	0	8c	>99.5
11	2k	Br	H	H	24	70°C	0	0	0	0	0

d.ratio = Diastereomers ratio

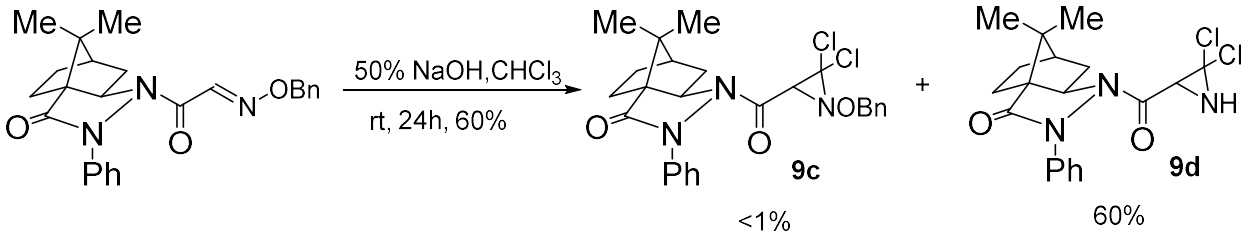
We describe here an approach to asymmetric synthesis using camphor auxiliaries derived *α*,*β*-unsaturated amide as Michael acceptors of in situ generated dichlorocarbene to gives *gem*-dichlorocyclopropane and tetrachloro spiro[2,2]pentane carboxylic acid derivatives depending upon the substitutions on α,β-unsaturated carbonyl derivatives.

The scope and generality of this addition protocol was investigated (Table 1). A wide range of *α*,*β*-unsaturated amides used tested and found that unsubstituted **2a**, gives mixture of diastereomers **3a**, **3b** respectively. the major diastereomers **3a** is **1S** based on steric grounds that carbenes like dichlorocarbene would approach the double bond from the side opposite to that of the N-phenyl substituent on chiral pyrazolidinone. The beta phenyl substituent **2b** converted to *β*-phenyl substituted esters in beta-phenyl single diastereomer **4a** with 61% yield [18,19]. The β-ester **2c** did not give the product, the n-propyl **2d** and methyl **2e** substituents gives single diastereomer **5a and 6a** in 62 and 67 % yield, respectively. Further the **6a** structure was confirmed by single x-ray crystals, where methyl group is trans to chiral amide, the trans orientations of starting material remains intact, it indicates that dichloro carbene is in singlet state and reaction proceeds in single step. The presence of additional carbons as branched chain at beta position, isopropyl **2f**, tertiary butyl **2g** and b,b-substituents **2h**, motifs did retard the desired spiro reaction (for **3f**–**3h**). The presence of a bulky *β*-aryl group that can destabilize the resulting alkyl radical intermediates was envisioned to account for the above *no reaction* selectivitively. we next turned our attention to study the reaction with *α*,*β*-substituted substrate **2i**, gives excellent yield, but product is limited to gem dichloro cyclopropane **7c** only. The product **7c** is further confirmed as 1S, 2R by ORTEP, where the beta-methyl is trans orientation with chiral amide. This method is far superior to reported method where resolution is used

to separate the required product[20]. In case of α-alkyl-substituted substrate **2j**, the product is not only limited to dichloro cyclopropane **8c** but with low yield, even after prolong reaction time. The **8c** were isolated with similar yield by resolution by reported method[21]. The product **8c** is characterized by ORTEP as 1S. The β-bromo substituents **2k** gives inseparable multiple products. This method is supervisor over reported method where direct substitution of halogen from *gem*-dihalocyclopropanes is limited[22] and dialkylation with a new 'cyclocuprate' species to yield spiro compounds is possible if the reaction is performed in the presence of a lithium acetylide[23].

In reported methods where β-Substituted acrylic esters form exclusively *gem*-dichloro cyclopropanes independently of the kind of catalyst used and *tert*-Butyl acrylate gives mixture of major, gem-dichlorocyclopropane and minor, tetrachloro spiro[2,2]-pentane derivatives[11], whereas we got exclusively tetrachloro spiro[2,2]-pentane derivative only. The α,β-disubstituted, or α–trisubstituted carbonyl derivatives gives exclusively gem-dichlorocyclopropane.

Scheme-2



Aziridines are versatile intermediates that undergo a variety of synthetically useful transformations of which nucleophilic ring opening is the most thoroughly studied[24]. The noticeable reported methods for aziridine are from imines[25,26]. The O-protected oxime, where used for C- alkylation to achieve the intermediates of biologically active molecules[27,28]. Herein we treated O-protected oxime **2l** with dichlorocarbene and

obtained the product **9a**, minor product, and major product **9b** is debenzylated, whose cyclopropane proton and NH are combined shows as mulltplet[29]. The cleavage of benzyloxy group due to excess of reagent in reaction medium, which is consistent with reported methods where unprotected oxime under similar condition gives nitrile[30].

Part-B: Use of Trichloro acetic acid sodium salt, chloroform in presence TBAC: After getting the variable products by using chloroform/NaOH in presence of TBAC, our goal was to versatile intermediate, gem-dichlorocyclopropane by following the reported methods such as trichloro acetic acid sodium salt in chloroform in presence of n-butylammonium salts[31-33] to our surprise we obtained conjugate Michael addition

Scheme-3

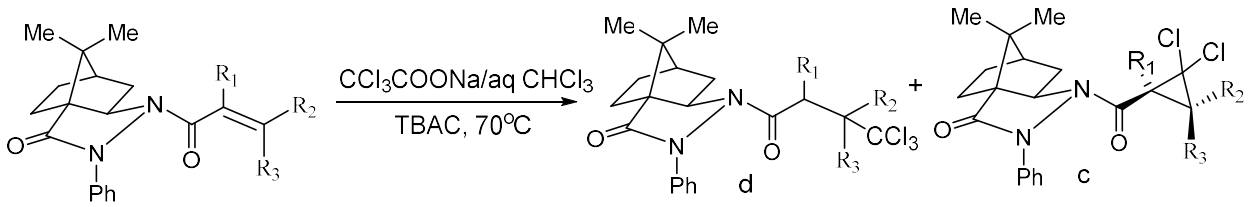


Table-2

Entry	Substrate	R_1	R_2	R_3	Time(h)	Yield	Chloro	CP	d.ratio*
1	2a	H	H	H	24	65	11d	0	0
2	2b	H	Ph	H	48	NR	0	0	0
3	2c	H	COOEt	H	3	12	11d	10d	0
4	2d	H	$C_3H_{7\text{-}n}$	H	48	NR	0	0	0
5	2e	H	CH_3	H	48	NR	0	0	0
6	2f	H	$C_3H_{7\text{-}iso}$	H	72	NR	0	0	0
7	2g	H	$C_4H_{9\text{-}tert}$	H	72	NR	0	0	0
8	2h	H	CH_3	CH_3	72	NR	0	0	0
9	2i	CH_3	CH_3	H	72	NR	0	0	0
10	2j	CH_3	H	H	48	5	0	8c	>99.5
11	2k	Br	H	H	24	0	0	0	0

d.ratio = Diastereomers ratio

product **10d** which are valuable as it involved formation of C-C bond under simple reaction, in contrast to reported where low temperature reaction condition are needed[34]. The product **10d** is further confirmed by single crystal data. The β-ester **2b** substituent

gives products with 12% yield, along with decarboxylated product **9d** in 55% yield. The β-, β,β- and α,β-substituents did not react due to steric addition of trichlorocarbene. In case of α-substituents only 5% yield of product **8c** where isolated. Overall, the use of trichloro acetate in combination with TBAC is limited to olefin and β- ester and to some extent to α-substituents only.

Application:

The present method allowed for the construction of a series of sprio[2,2]-pentane as well as gem-dichlorocyclopropane molecules. Beta-phenyl as used for spiro[2,2]-pentane as insecticide[35], α,β-dimethyl used as pesticides[20], cereblon binders[36] and fungicide[37], α-methyl dichlorocyclopropane is used as herbicides[38], bromodomain inhibitors[39], GSK inhibitors[40], microcides[41], ALX and FPRL2 receptor agonists[42].

Conclusion:

we have developed a stereoselective reaction for synthesizing the gem-dichlorocyclopropane and its annulated products, tetrachloro spiro[2,2] pentane carboxylic acid derivatives, by using α,β-unsaturated amides and O-protected oxime **2a-l** derived from a chiral camphorpyrazolidinone as a acceptor of in situ generated dichlorocarbene, depending on the substituents and its position on unsaturated carbonyl substrates, β-substituents forms selectively spiro[2,2] pentane whereas α-substituents and α,β-substituents shows gem-dichlorocyclopropane. The O-protected give dichloro-aziridine after cleavage of benzyloxy group. This efficiency was demonstrated without using any metals and non-anhydrous reactions conditions.

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■ **Competing interests:**

There is no Competing Interests pending

Data and materials availability: Crystallographic model data is available through the CCDC under identifier **2040634**, (3a*S*,6*R*,7a*R*)-8,8-dimethyl-1-((E)-4-methylpent-2-enoyl)-2-phenylhexahydro-3a,6-methanoindazol-3(2H)-one (**2f**); **2040633**, (3a*S*,6*R*,7a*R*)-1-((E)-4,4-dimethylpent-2-enoyl)-8,8-dimethyl-2-phenylhexahydro-3a,6-methanoindazol-3(2H)-one (**2g**): **2040637,** (E)-2-((6R,7aR)-8,8-dimethyl-3-oxo-2-phenylhexahydro-3a,6-methanoindazol-1(4H)-yl)-2-oxoacetaldehyde O-benzyl oxime (**2l**); **2040635,** (3a*S*,6R,7aR)-8,8-dimethyl-2-phenyl-1-((1R,2R)-4,4,5,5-tetrachloro-2-methylspiro[2.2]pentane-1-carbonyl)hexahydro-3a,6-methanoindazol-3(2H)-one (**6a**); **2040632,** (3As,6R,7aR)-1-((S)-2,2-dichloro-1-methylcyclopropane-1-carbonyl)-8,8-dimethyl-2-phenylhexahydro-3a,6-methanoindazol-3(2H)-one (**8c**); **2040636,** (3a*S*,6R,7aR)-8,8-dimethyl-2-phenyl-1-(4,4,4-trichlorobutanoyl)hexahydro-3a,6-methanoindazol-3(2H)-one (**10d**). See Fig. S1 for crystals data details.

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