Tetrahedron 69 (2013) 4953–4963

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis, characterization and applications of densely functionalized pyridazines and fulvene-type compounds containing azulene moiety

Badugu Devendar [a], Chi-Phi Wu [a,*], Chi-Yuan Chen [a], Hung-Chang Chen [a], Chung-Hao Chang [a], Chien-Kuo Ku [b,*], Cheng-Yin Tsai [b], Chieh-Yuan Ku [b]

[a] Department of Chemistry, Chung Yuan Christian University, Chungli 32023, Taiwan
[b] Department of Applied Physics and Chemistry, Taipei Municipal University of Education, Taipei 10042, Taiwan

ARTICLE INFO

Article history:
Received 28 June 2012
Received in revised form 28 March 2013
Accepted 8 April 2013
Available online 12 April 2013

Keywords:
Azulene
Vilsmeier–Haack formylation
Friedel–Crafts reaction
Michael addition reaction
Intramolecular cyclization

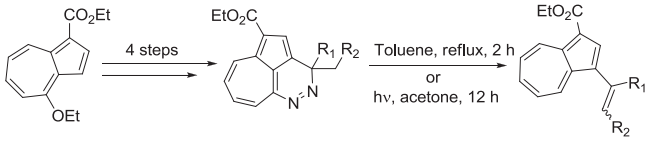
ABSTRACT

Ethyl 4-ethoxyazulene-1-carboxylate (**1**) is highly efficient and novel substrate for electrophilic substitution reactions. These derivatives (**2**–**4**) were treated with NH_2NH_2/$PhNHNH_2$ in ethanol to produce pyridazine, and fulvene derivatives with azulene frameworks (**5**, **6**, **17**, **19**) via intramolecular cyclization. The substrates **5**–**8**, **11**, and **19** were effectively converted into densely functionalized heterocyclic molecules via Vilsmeier–Haack, Friedel–Crafts, and Michael addition reactions.

1. Introduction

Azulene and its derivatives are interesting and structurally challenging carbocyclic moieties[1] because of the presence of azulene ring system as a centerpiece of number of bioactive natural products, such as orientalol F,[2a] purbinernoid,[2b] guaiane,[2c] pseudolaric acids A, B, F, and H,[2d] guanacastepene A, and heptemerone G,[2e] englerin A,[2f] (−)-9-deoxyenglerin A.[2g] Several azulene derivatives, in fact, have been known to exhibit various biological activities, such as insect anti-feeding agent,[3a] anti-fungal infections of skin and nails,[2d] anti-inflammatory agents,[3b] anti-oxidant therapeutics,[3c] and anti-microbial agents.[3d,e] Subsequently, azulenes and their derivatives have attracted the attention of chemists'[5a–c] due its abnormal properties and interesting modern applications.

The electrophilic substitution method is one of the most important methodologies for the functionalization of aromatic compounds.[4] There are several reports of electrophilic substitution reactions for functionalizing azulenes these including Vilsmeier–Haack formylations[6a–f] and Friedel–Crafts acylations,[7a,b] of azulene derivatives at 1- and/or 3-positions. Recently, we have reported the highly efficient intramolecular Friedel–Crafts type cyclization methodology on azulene derivatives at 3-position, and the applications of corresponding derivatives toward thermal and photo-chemical reactions (Scheme 1).[7b] In continuing of our research program[7b,8] in carbo- and heterocyclic molecules with azulene framework, we herein report the synthesis of pyridazine, and fulvene type of products with azulene moiety.



Scheme 1. Syntheses of vinyl azulene derivatives.[7b]

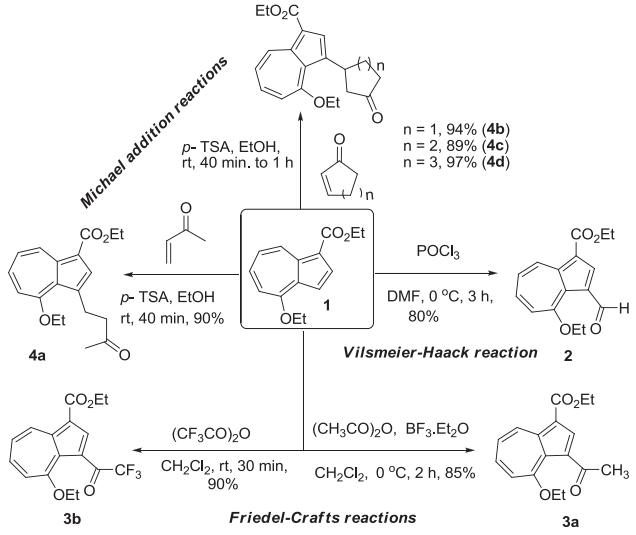
2. Results and discussion

Ethyl 4-ethoxyazulene-1-carboxylate (**1**) was prepared from commercially available tropolone in four steps.[8] Compound **1** was subjected to Vilsmeier–Haack formylation conditions ($POCl_3$/DMF, 0 °C, 3 h) to obtain ethyl 4-ethoxy-3-formylazulene-1-carboxylate (**2**), and with Friedel–Crafts acylation methodology (Ac_2O, $BF_3 \cdot Et_2O$, 0 °C, 2 h and $(CF_3CO)_2O/CH_2Cl_2$, room temperature,

* Corresponding authors. Tel.: +886 32653333; fax: +886 32653399; e-mail addresses: bdevendar@yahoo.com (B. Devendar), chiphi@cycu.edu.tw (C.-P. Wu), Kuo@tmue.edu.tw (C.-K. Ku).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.04.034

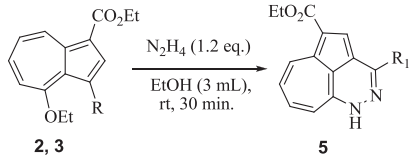
30 min) to produce ethyl 3-acetyl-4-ethoxyazulene-1-carboxylate (**3a**), and ethyl 4-ethoxy-3-(2,2,2-trifluoroacetyl)azulene-1-carboxylate (**3b**) with excellent yields (Scheme 2). We also extended our synthetic strategy toward the applications of Michael addition reactions.[9] The best results in this approach were obtained when ethyl 4-ethoxyazulene-1-carboxylate (**1**) was treated with methyl vinyl ketone (MVK) in the presence of *p*-toluenesulfonic acid (*p*-TSA) in ethanol at room temperature for 40 min, thus providing the desired ethyl 4-ethoxy-3-(3-oxobutyl)-azulene-1-carboxylate (**4a**), in 90% isolated yield (Scheme 2); the reaction proceeds more selectively at 3-position, which was confirmed from spectral analysis. To examine the scope of this reaction, we employed various activated cyclic enones, i.e., cyclopentenone, cyclohexenone, and cycloheptenone with the compound **1** (Scheme 2). A variety of cyclic enones have been proved to be very efficient substrates under these conditions.



Scheme 2. Selective Vilsmeier–Haack, Friedel–Crafts, and Michael addition reactions on ethyl 4-ethoxyazulene-1-carboxylate (**1**).

After successful syntheses of Vilsmeier–Haack and Friedel–-Crafts products, we found that ethyl 1*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (**5a**) was readily prepared in excellent yield (95%) from **2** and hydrazine in ethanol at room temperature for 30 min; the reaction presumably proceeded via a substitution reaction and a subsequent intramolecular condensation (Table 1, entry 1). Encouraged by these results, we successfully transformed representative Friedel–Crafts products **3a**,**b** into the desired ethyl 3-methyl-1*H*-azuleno[8,1-*cd*]pyridazine-5-carbo-xylate (**5b**) and ethyl 3-(trifluoromethyl)-1*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (**5c**) in excellent yields after purification by column chromatography (Table 1). The reactions apparently produced via a substitution

Table 1
Syntheses of azuleno[8,1-*cd*]pyridazine-5-carboxylate derivatives (**5**)[a]



Entry	Reactants **2**, **3**	R	Products **5**	R_1	Yield[b] (%)
1	**2**	CHO	**5a**	H	95
2	**3a**	$COCH_3$	**5b**	CH_3	92
3	**3b**	$COCF_3$	**5c**	CF_3	85

[a] All the reactions were carried out with 1 mmol scale of **2**, and **3**.
[b] Isolated yields after silica gel column chromatography.

followed by intramolecular condensation reactions. The structures of **5a**–**c** were confirmed from ^{1}H NMR, ^{13}C NMR, IR, and MS data analyses, while that of **5b** was further confirmed with single-crystal X-ray diffraction analysis (CCDC # 882109),[10] see Fig. 1 for the ORTEP diagram.

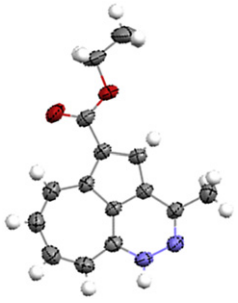
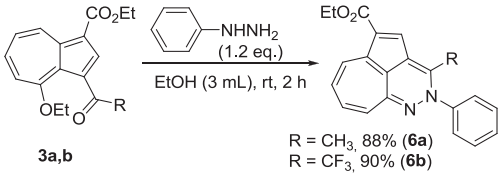


Fig. 1. ORTEP diagram of compound **5b**.

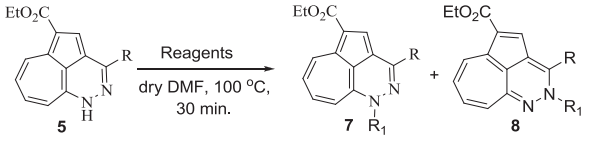
With a view to understand the generality of this methodology, we further investigated the reactions of **3a** and **3b** with phenyl hydrazine at room temperature for 2 h. Interestingly we obtained fulvene type products (**6a** and **6b**) with the π-electron delocalization within the ring system, in 88% and 90% yields, respectively (Scheme 3). All these products were well characterized from spectral analysis.



Scheme 3. Syntheses of fulvene type of products (**6a**, **b**).

Encouraged by these promising and interesting results, we further transformed **5a** and **5b**, by treatment with methyl/ethyl iodide with and/or without a base, into a mixture of *N*-alkylated pyridazines and/or fulvene type of products (**7a**–**d**, **8a**–**d**). We noticed that the compound **5c** did not convert to *N*-methylated or fulvene type of products (**7e**, **8e**) in the presence of methyl iodide in the absence of a base. Interestingly, with methyl iodide/ethyl iodide and NaH, we obtained exclusively the compounds **7e** (96%), and **7f** in 90% yield (Table 2); all these products were well characterized from the analysis of their spectral data. Particularly, with the help of

Table 2
N-Alkylation of azuleno[8,1-*cd*]pyridazine-5-caboxylate derivatives (**5**)[a]



Entry	Reactants **5**	Reagents (1.2 equiv)	R_1	Products **7**/yield[b] (%)	Products **8**/yield[b] (%)
1	**5a**	CH_3I	CH_3	**7a**/15	**8a**/56
2	**5a**	CH_3CH_2I	CH_3CH_2	**7b**/–	**8b**/39
3	**5a**	CH_3CH_2I/NaH	CH_3CH_2	**7b**/35	**8b**/54
4	**5b**	CH_3I	CH_3	**7c**/13	**8c**/37
5	**5b**	CH_3CH_2I	CH_3CH_2	**7d**/14	**8d**/41
6	**5c**	CH_3I	CH_3	**7e**/–	**8e**/–
7	**5c**	CH_3I/NaH	CH_3	**7e**/96	**8e**/–
8	**5c**	CH_3CH_2I/NaH	CH_3CH_2	**7f**/90	**8f**/–

[a] All the reactions were carried out with 1 mmol scale of **5**.
[b] Isolated yields after silica gel column chromatography.