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A multicomponent synthesis of cyclopropanes

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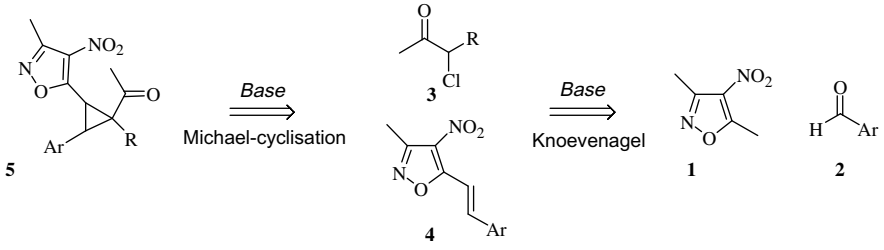
ABSTRACT

A multicomponent synthesis of cyclopropanes is described. The title compounds were obtained in high yields from commercially available materials.

The cyclopropane subunit is an important structural motif present in bioactive compounds of natural[1,2] and synthetic origin.[3,4] Additionally, cyclopropanes are versatile building blocks for the synthesis of functionalised cycloalkanes[5,6] and acyclic compounds.[7] While several investigators have focused on the development of enantioselective preparations of cyclopropanes,[8] a one-pot multicomponent approach to the preparation of the cyclopropane core is unexplored.

As a part of our ongoing efforts in developing multicomponent syntheses to access potentially bioactive scaffolds, we envisaged a novel synthesis of cyclopropanes from commercially available 3,5-dimethyl-4-nitroisoxazole **1**, an aromatic aldehyde **2** and a suitable chloroketone **3** (Scheme 1).

We have recently reported some applications of 3,5-dimethyl-4-nitroisoxazole **1** in which spiroisoxazolines,[9] 3-arylpropionic acids,[10] indole propionic acids[11] or arylglutaric acids[12] were obtained in one-pot from commercially available materials. These syntheses were based on the ability of compound **1** to undergo sequential Knoevenagel–Michael tandem reactions, when reacted with an aromatic aldehyde and a suitable Michael donor in the presence of catalytic amounts of base.[9–12] Similarly, the cyclopropanation of electron-poor olefins with chloroketones has been repeatedly reported to run under the catalysis of amines.[13] Based on this information, it was anticipated that isoxazole **1**, an aldehyde **2** and a suitable chloroketone **3** would react in a sequential Knoevenagel–Michael-cyclisation process in the presence of an amine catalyst. Data collected on the reactivity of 3-methyl-4-nitro-5-styrylisoxazoles **4** indicated these compounds as soft Michael acceptors;[9–12] for this reason, ethyl-2-chloroacetylacetate **3** (R = CO_2Et) was selected for its ability to generate a soft stabilised



Scheme 1.

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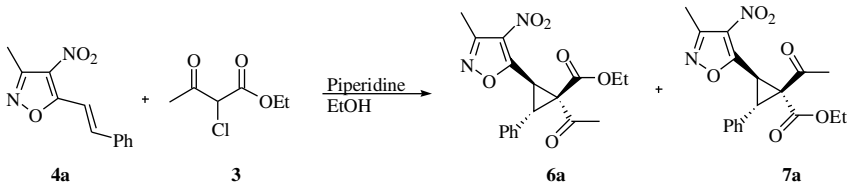


Scheme 2. Synthesis of cyclopropanes **6a** and **7a** from styryl isoxazole **4a**.

chloroenolate. The planned synthesis is modular in nature, as each of the three components employed contributes one carbon to the cyclopropane core (Scheme 1).

To test this hypothesis, we reacted 3-methyl-4-nitro-5-styrylisoxazole **4a** with ethyl 2-chloroacetoacetate **3** at room temperature in the presence of an equimolar amount of piperidine (Scheme 2). We were delighted to observe that under these conditions, starting material **4a** was converted quantitatively, and diastereoisomeric cyclopropanes **6a** and **7a** were obtained in over 80% combined yields.

The stereochemistry of cyclopropanes **6** and **7** was established by X-ray analysis carried out on compound **6d** (Table 1, Fig. 1).[14] Compounds **6a** and **7a** were also obtained by reacting **1**, benzaldehyde **2a** and chloroketone **3** in one-pot (Table 1). Isoxazole **1** and benzaldehyde **2a** were firstly reacted in the presence of 1.0 equiv of piperidine at 60 °C for 2 h, then 1.0 equiv of **3** was added and the mixture was stirred at room temperature for a further 12 h.

The one-pot procedure was employed to generate a small family of compounds **6**–**7a–f** by variation of the aldehyde components **2a–f**. Compounds **6**–**7a–f** were obtained in high combined yields with the exception of the reaction involving the electron-rich aldehyde *p*-anisaldehyde (Table 1, entry 3) which gave only a moderate yield.

Reaction using 2-furaldehyde was disappointing, yielding only the ethenyl furyl isoxazole intermediate. It is possible that the electron-rich furyl group deactivates the styryl double bond to such an extent that cyclopropanation using soft chloroenolates became very slow.

Diastereoisomeric cyclopropanes **6a–f** and **7a–f** were isolated by means of column chromatography, and could be employed as stereo-defined starting materials for further transformations.

The reaction of **4a** and ethyl 2-chloroacetoacetate **3** was studied in the presence of organic and inorganic bases. The use of inorganic bases such as NaOH, Na_2CO_3 and $NaHCO_3$ or the use of sodium alkoxides led to rapid decomposition of chloroacetate **3**. Secondary amines such as piperidine, pyrrolidine, (*S*)-2-pyrrolidinemethanol and (*S*)-2-diphenylmethylprolinol gave nearly quantitative conversion of reactants **3** and **4a**, resulting in equal amounts of **6a** and **7a**. Tertiary amines such as triethylamine, quinine and quinidine afforded **6a** in higher amounts than **7a** (ratio 2:1). No enantiomeric excess was obtained when using chiral amines as determined by chiral HPLC. In general, the reaction of **4a** and **3** was faster with secondary amines. It is possible that when tertiary amines were used, slower kinetics allowed a partial facial selection resulting in the increased ratio of **6a**:**7a**.

In conclusion, we have reported an operationally simple one-pot methodology for the synthesis of densely functionalised

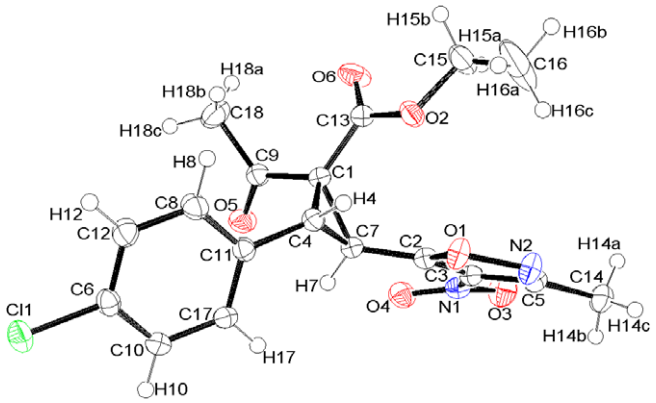
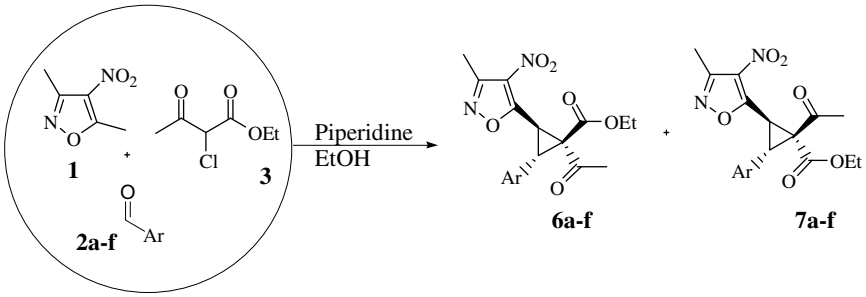


Figure 1. ORTEP diagram of compound **6d**.

Table 1
One-pot synthesis of cyclopropanes **6–7a–f**



Entry	Ar	Yield% of **6**[a]		Yield% of **7**[a]		**6**:**7**[b]	Time (h)
1	C_6H_5	**6a**	42	45	**7a**	1:1	12
2	*p*-Me-C_6H_4	**6b**	36	36	**7b**	1:1	12
3	*p*-MeO-C_6H_4	**6c**	40	19	**7c**	1:2	24
4	*p*-Cl-C_6H_4	**6d**	42	42	**7d**	1:1	6
5	*p*-NO_2-C_6H_4	**6e**	46	46	**7e**	1:1	6
6	*p*-CN-C_6H_4	**6f**	43	43	**7f**	1:1	6

[a] Isolated yields after flash chromatography.
[b] Ratio of the isolated yields.

cyclopropanes. The reaction reported is modular, is run under mild conditions and utilises cheap and commercially available starting materials. Cyclopropanes **6a–f** and **7a–f** contain push–pull elements and could possibly be employed for the generation of chemical diversity.[15]

1. General experimental procedure for the preparation of cyclopropane carboxylic acid ethyl esters 6a–f and 7a–f

A solution of 3,5-dimethyl-4-nitroisoxazole **1** (285 mg, 2.0 mmol), an aromatic aldehyde (1.0 equiv) and piperidine (170 mg, 2.0 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) was refluxed for 2–5 h. After this time, the reaction mixture was cooled to 0 °C and ethyl 2-chloroacetoacetate **4** (330 mg, 2.0 mmol, 1.0 equiv) was added. The resulting reaction mixture was stirred at room temperature for 12 h, then concentrated under reduced pressure and the residue obtained was purified by silica gel column chromatography (eluent 10% ethyl acetate in petroleum spirit) to give pure compounds **6a–f** and **7a–f**.

2. 1-Acetyl-2-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylcyclopropane carboxylic acid ethyl ester 6a

Colourless oil, 299 mg (42% yield), $R_f = 0.41$ (10%, EtOAc in Petroleum spirit); ν_{max} (KBr)/cm^{-1}: 1739 (CO_2), 1701 (CO), 1521 (NO_2); δ_H (400 MHz, $CDCl_3$) 7.32–7.29 (5H, m), 4.09 (1H, d, J = 8.0), 3.97 (1H, d, J = 8.0), 3.92 (2H, q, J = 4.0), 2.49 (3H, s), 2.35 (3H, s), 0.88 (3H, t, J = 7.0); δ_c (100.6 MHz) 198.2, 168.4, 165.3, 155.3, 132.0, 131.1, 128.6, 128.4, 127.9, 61.6, 49.7, 36.1, 29.2, 27.7, 13.1, 11.0; *m/z* (EI) 357 (100%, M-H$^+$); HRMS found: [M-H$^+$] 357.1097, $C_{18}H_{17}N_2O_6$ requires 357.1087.

3. 1-Acetyl-2-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylcyclopropane carboxylic acid ethyl ester 7a

Colourless oil, 322 mg (45% yield), $R_f = 0.43$ (10%, EtOAc in petroleum spirit); ν_{max} (KBr)/cm^{-1}: 1735 (CO_2), 1702 (CO), 1517 (NO_2); δ_H (400 MHz, $CDCl_3$) 7.31–7.29 (3H, m), 7.24 (2H, d, J = 7.0), 4.30(1H, d, J = 9.0), 4.19 (2H, q, J = 6.0), 4.00 (1H, d, J = 8.0), 2.54 (3H, s), 2.06 (3H, s), 1.19 (3H, t, J = 7.0); δ_c (100.6 MHz) 195.7, 168.7, 166.3, 155.4, 130.8, 130.1, 128.4, 128.2, 127.9, 62.1, 50.9, 37.1, 29.0, 24.7, 13.3, 11.1; *m/z* (EI) 357 (100%, M-H$^+$); HRMS found: [M-H$^+$] 357.1088, $C_{18}H_{17}N_2O_6$ requires 357.1087.

4. 1-Acetyl-2-(4-chloro-phenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)cyclopropane carboxylic acid ethyl ester 6d

Colourless oil, 332 mg (42% yield), $R_f = 0.41$ (10%, EtOAc in petroleum spirit); ν_{max} (KBr)/cm^{-1}: 1740 (CO_2), 1719 (CO), 1516 (NO_2); δ_H (400 MHz, $CDCl_3$) 7.32 (2H, d, J = 8.5), 7.24 (2H, d, J = 8.5), 4.08 (1H, d, J = 8.0), 4.03 (2H, q, J = 7.0), 3.98 (1H, d, J = 8.0), 2.57 (3H, s), 2.40 (3H, s), 1.01 (3H, t, J = 7.0); δ_c (100.6 MHz) 197.9, 168.0, 165.2, 155.4, 133.7, 131.1, 130.5, 129.6, 128.2, 61.9, 49.6, 35.4, 29.2, 27.8, 13.3, 11.2; *m/z* (EI) 391 (100%, M-H$^+$); HRMS found: [M-H$^+$] 391.0688, $C_{18}H_{16}N_2O_6{}^{35}Cl$ requires 391.0694.

5. 1-Acetyl-2-(4-chloro-phenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)cyclopropane carboxylic acid ethyl ester 7d

Colourless oil, 328 mg (42% yield), $R_f = 0.44$ (10%, EtOAc in petroleum spirit); ν_{max} (KBr)/cm^{-1}: 1749 (CO_2), 1713 (CO), 1520 (NO_2); δ_H (400 MHz, $CDCl_3$) 7.31 (2H, d, J = 8.0), 7.20 (2H, d, J = 8.0), 4.29 (1H, d, J = 8.0), 4.22 (2H, q, J = 7.0), 3.96 (1H, d, J = 8.0), 2.57 (3H, s), 2.11 (3H, s), 1.21 (3H, t, J = 7.0); δ_c (100.6 MHz) 195.4, 168.2, 166.1, 155.5, 133.8, 131.5, 130.1, 129.3, 128.4, 62.2, 50.9, 36.5, 29.1, 24.8, 13.3, 11.1; *m/z* (EI) 391 (100%, M-H$^+$); HRMS found: [M-H$^+$] 391.0678, $C_{18}H_{16}N_2O_6{}^{35}Cl$ requires 391.0697.

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