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Highly stereoselective construction of functionalized cyclopropanes from the reaction between acetylenic esters and C–H acids in the presence of triphenylarsine

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Dedicated to professor Issa Yavari for his constant supervision and guidance during my study at Tarbiat Modares University

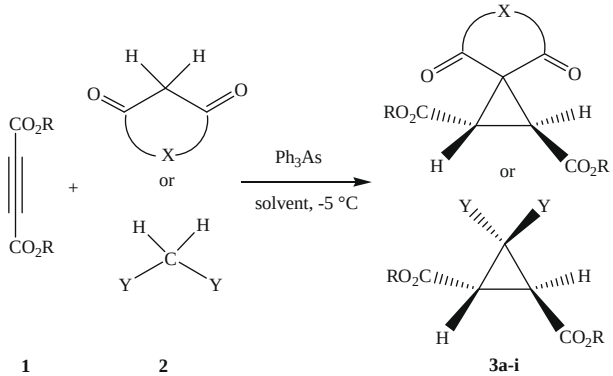
ABSTRACT

A one-pot triphenylarsine-catalyzed synthesis of *trans*-cyclopropane derivatives is achieved by means of the reaction between acetylenic esters and C–H acids in the presence of triphenylarsine. This procedure is simple and proceeds under mild reaction conditions. Its success depends on the choice of solvent, temperature and C–H acid used.

Spirocyclopropane and cyclopropane moieties are present in a number of pharmacologically important natural products some of which belong to the group of alkylating anticancer agents.[1] A number of synthetic approaches to cyclopropanes and spirocyclopropanes have been reported, which include transition metal-catalyzed cyclopropanation of alkenes with diazo compounds,[2] 1,3-dipolar cycloaddition,[3] Diels-Alder,[4] domino aldol/Horner–Wadsworth–Emmons reaction,[5] Simmons–Smith reaction,[6] reaction of alkenes with free carbenes, carbenoids[7] or ylides, for example, phosphorus,[8] sulfur,[9] arsenic[10] and phenyliodonium ylides.[11] In addition, the Michael-initiated ring closure (MIRC) method, which is one of the most important synthetic routes for the preparation of cyclopropanes, has also been employed.[12] Although highly functionalized cyclopropanes can be prepared using these methods, they are non-stereoselective, and a mixture of cis/trans isomers is generally obtained.[13] Huang and co-workers first reported a method for the stereoselective synthesis of cyclopropanes using an arsonium ylide and an alkene.[14] Later, Ding reported a process for the highly stereoselective synthesis of a *cis*-cyclopropane from an arsonium salt and an alkene as starting materials.[15] Ren and Cao reported a procedure for the stereoselective synthesis of spirocyclopropane and 1,2-cyclopropane derivatives using an arsonium salt or ylide and electron-deficient alkenes.[16] More recently, similar reactions of alkenes and arsonium salts yielding *trans*-cyclopropanes have been reported by the same group.[17]

In continuation of our investigations,[18] we report herein a stereoselective synthesis of *trans*-cyclopropanes via the reaction between acetylenic esters and C–H acids in the presence of triphenylarsine (Scheme 1).

The present method benefits from the catalytic role of triphenylarsine, and also allows access to cyclopropane derivatives stereoselectively. The proposed mechanism for the reaction is shown in Scheme 2.



1 2 3a-i

Scheme 1. Synthesis of *trans*-cyclopropane derivatives.

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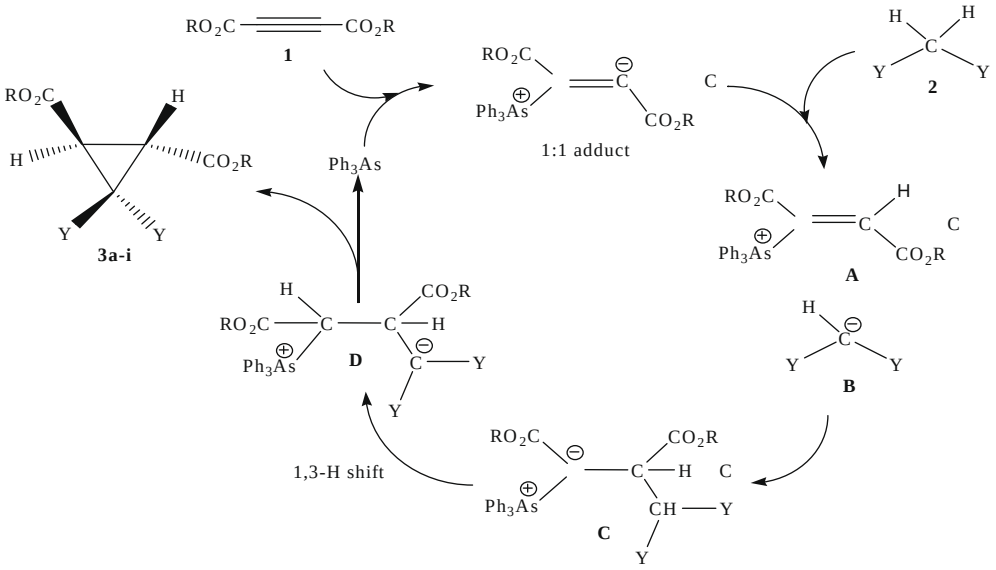

Scheme 2. Proposed mechanism for the Ph_3As-catalyzed cyclopropanation.

Table 1
Reactions of acetylenic esters with C–H acids containing an X group in the presence of Ph_3As (50 mol %)

Entry	R	X	Solvent	Product **3**	Time (min)	Yield[a] (%)
1	Me	$-OC(Me)_2O-$	EtOH	**3a**	120	85
2	Me	$-CH_2C(Me)_2CH_2-$	CH_3CN	**3b**	120	82
3	Me		EtOH	**3c**	100	90
4	Et		EtOH	**3d**	90	88
5	*t*-Bu		EtOH	**3e**	120	96
6	Me	–N(Me)CON(Me)–	EtOH	**3f**	90	90

[a] Isolated yield.

Table 2
Reactions of acetylenic esters with C–H acids involving a Y group in the presence of Ph_3As (50 mol %)

Entry	R	Y	Solvent	Product **3**	Time (min)	Yield[a] (%)
1	Me	PhCO	EtOH	**3g**	90	95
2	Et	PhCO	EtOH	**3h**	90	90
3	Me	CN	Acetone	**3i**	120	80

[a] Isolated yield.

Compounds **3a–i** (Tables 1 and 2) result from the initial addition of triphenylarsine to the acetylenic ester **1** and subsequent protonation of the 1:1 adduct by the C–H acid **2**. Next, the positively charged arsonium ion (**A**) is attacked by the anion of the C–H acid (**B**) to produce intermediate arsonium ylide (**C**). This intermediate undergoes a 1,3-H shift to give 1,4-diionic zwitterionic compound (**D**). Finally, intramolecular attack and ring closure form the cyclopropane ring with elimination of triphenylarsine.

To determine the effect of solvent on the reaction, various experiments were run with solvents of different polarities. The results show that the reaction only proceeded in a high dielectric constant medium (i.e., CH_3CN, ethanol or acetone) (Tables 1 and 2). In addition, the effect of the pK_a of the C–H acids was also investigated. In the pK_a range studied, it was ascertained that the reactions were favoured with lower pK_a and proceeded successfully with Meldrum's

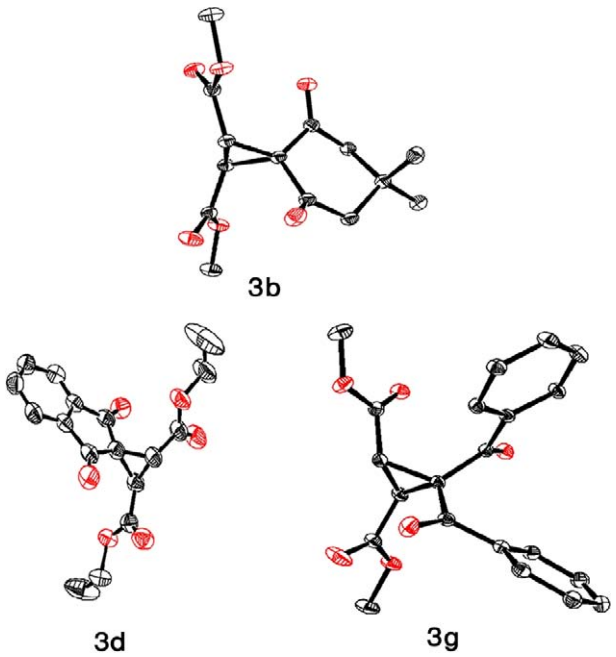

Figure 1. ORTEP representations of the X-ray structures of cyclopropanes **3b**, **3d** and **3g**.

acid, dimedone, 1,3-indandione, 1,3-dimethylbarbituric acid, dibenzoylmethane and malononitrile. The reactions did not occur in the presence of C–H acids with high pK_as (such as dimethyl and diethyl malonate, and methyl and ethyl acetoacetate).

The products **3a–i** were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectroscopy and by X-ray crystallography. Unambiguous structural elucidation was accomplished by single crystal X-ray diffraction (Fig. 1). The assignment of the 1,2-cyclopropanes as the trans isomers was confirmed by the X-ray crystallography analysis.[19,21]

In conclusion, we have developed a method for the highly stereoselective cyclopropanation reaction of acetylenic esters and C–H acids with triphenylarsine as catalyst. The reaction conditions are mild and the products were obtained in good yields favouring formation of the trans isomer.

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19. *General procedure for the synthesis of cyclopropanes (**3a–i**)*: To a magnetically stirred solution of triphenylarsine (0.153 g, 0.5 mmol) and C–H acid **2** (1 mmol) in 10 mL of solvent was added dropwise, 1 mmol of acetylenic ester **1** at −5 °C over 10 min. The extent of reaction was monitored by TLC. The reaction mixture was then allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 1:3) to give the products **3a–i**. The triphenylarsine could be recovered. Crystallographic information (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 716766, 716767 and 716768 for compounds **3b**, **3d** and **3g**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). The X-ray diffracted intensities from single crystals of compounds **3b**, **3d** and **3g** were measured on an Oxford Diffraction Gemini-R Ultra CCD diffractometer. Data have been corrected for Lorentz and polarization effects and absorption corrections applied using multiple symmetry equivalent reflections. The structures were solved by direct methods and refined on F^2 using the SHELX-97 crystallographic package.[20] A full matrix least-squares refinement procedure was used. Non-hydrogen atoms were refined anisotropically using all reflections. The positions of hydrogen atoms were localized from difference Fourier synthesis and their atomic parameters were constrained to the bonded atoms during refinement.
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21. *trans-1,2-Di(methoxycarbonyl)-6,6-dimethyl-5,7-dioxaspiro[2,5]octane-4,8-dione (**3a**)*. Yellow solid; mp: 195–197 °C; IR (KBr): 1777, 1750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.89 (s, 6H, 2 × CH_3), 3.54 (s, 2H, 2CCH), 3.79 (s, 6H, 2OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.65 (CH_3), 33.17 (C_{spiro}), 37.46 (C–H), 53.18 (OCH_3), 106.31 (OCO), 163.59 (CO_2), 164.64 (CO_2CH_3); MS *m/z* (%) (EI): 286 (M^+, 1), 271 (6), 255 (3), 229 (19), 197 (63), 185 (49), 168 (19), 156 (100), 141 (48), 125 (43), 98 (10), 82 (8), 69 (31), 59 (41), 43 (74); Anal. Calcd for $C_{12}H_{14}O_8$: C, 50.35; H, 4.93. Found: C, 50.41; H, 5.01.
*trans-1,2-Di(methoxycarbonyl)-6,6-dimethylspiro[2,5]oct-ane-4,8-dione (**3b**)*. White solid; mp: 107–109 °C; IR (KBr): 1743, 1725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (s, 6H, 2 × CH_3), 2.61 (d, 2H, $^2J_{HH}$ = 16.8, CH_2), 2.66 (d, 2H, $^2J_{HH}$ = 16.8, CH_2), 3.32 (s, 2H, 2CCH), 3.72 (s, 6H, 2OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.42 (CH_3), 30.32 ($C(CH_3)_2$), 38.60 (C–H), 47.48 (C_{spiro}), 52.68 (CH_2), 53.40 (OCH_3), 166.17 (CO_2CH_3), 201.93 (C=O); MS *m/z* (%) (EI): 282 (M^+, 15), 251 (18), 224 (8), 223 (28), 208 (38), 191 (25), 179 (19), 156 (33), 139 (23), 125 (20), 108 (12), 91 (19), 83 (78), 59 (100), 55 (75), 41 (56); Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.63; H, 6.38. Crystal/refinement details for compound **3b**: $C_{14}H_{18}O_6$, M = 282.28, crystal size, 0.28 × 0.24 × 0.23 mm^3, crystal system, triclinic, space group $P\bar{1}$ (No. 2), a = 5.8850(3), b = 9.5512(4), c = 12.4207(6) Å, α = 81.424(4)°, β = 80.983(4)°, γ = 83.167(4)°, V = 678.54(6) Å^3, Z = 2, D_c =

1.382 g/cm^3, μ = 0.108 mm^{-1}, F_{000} = 300, Mo Kα radiation, λ = 0.71073 Å, T = 100(2) K, $2\theta_{max}$ = 75.4°, R_1 = 0.0504, wR_2 = 0.1057, GOF = 1.000, $|\Delta\rho_{max}|$ = 0.42(6) e Å^{-3}. CCDC 716766.

trans-1,2-Di(methoxycarbonyl)-benzo[e]spiro[2,4]octane-4,7-dione (**3c**). Pale pink solid; mp: 151–153 °C; IR (KBr): 1732, 1710, 1592 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.47 (s, 2H, 2CCH), 3.77 (s, 6H, 2OCH_3), 7.88 (dd, $^3J_{HH}$ = 5.6, $^4J_{HH}$ = 3.1, 2H, 2H$_{meta}$), 8.01 (dd, $^3J_{HH}$ = 5.6, $^4J_{HH}$ = 3.1, 2H, 2H$_{ortho}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.04 (C–H), 42.24 (C$_{spiro}$), 52.76 (OCH_3), 123.28 (C$_{ortho}$), 135.65 (C$_{meta}$), 141.98 (C$_{ipso}$), 165.53 (CO_2), 193 (C=O); MS m/z (%) (EI): 288 (M$^+$, 56), 256 (91), 229 (100), 213 (5), 197 (51), 185 (20), 170 (57), 163 (40), 141 (11), 128 (18), 114 (42), 104 (32), 88 (16), 76 (54), 59 (43), 50 (18), 41 (3); Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20. Found: C, 62.57; H, 4.25.

trans-1,2-Di(ethoxycarbonyl)-benzo[e]spiro[2,4]octane-4,7-dione (**3d**). White solid; mp: 91-93 °C; IR (KBr): 3039, 2992, 1753, 1715, 1597 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (t, $^3J_{HH}$ = 7.1, 6H, 2CH_3), 3.46 (s, 2H, 2CCH), 4.21 (q, $^3J_{HH}$ = 7.1, 4H, 2OCH_2), 7.87 (dd, $^3J_{HH}$ = 5.6, $^4J_{HH}$ = 3.1, 2H, 2H$_{meta}$), 8.01 (dd, $^3J_{HH}$ = 5.6, $^4J_{HH}$ = 3.1, 2H, 2H$_{ortho}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.05 (CH_3), 35.37 (C–H), 42.43 (C$_{spiro}$), 61.97 (OCH_2), 123.23 (C$_{ortho}$), 135.65 (C$_{meta}$), 141.98 (C$_{ipso}$), 165.53 (CO_2), 193.00 (C=O); MS m/z (%) (EI): 316 (M$^+$, 32), 271 (100), 243 (44), 215 (32), 198 (48), 170 (97), 128 (8), 115 (37), 103 (11), 88 (10), 76 (27), 63 (8), 51 (21); Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.61; H, 5.16; Crystal/refinement details for compound **3d**: $C_{17}H_{16}O_6$, M = 316.30, crystal size, 0.30 × 0.17 × 0.15 mm^3, crystal system, triclinic, space group $P\bar{1}$ (No. 2), a = 8.1326(3), b = 10.6218(3), c = 10.8956(5) Å, α = 101.359(3)°, β = 105.720(3)°, γ = 112.272(3)°, V = 789.54(5) Å^3, Z = 2, D_c = 1.330 g/cm^3, μ = 0.101 mm^{-1}, F_{000} = 332, Mo Kα radiation, λ = 0.71073 Å, T = 250(2) K, $2\theta_{max}$ = 65.2°, R_1 = 0.0528, wR_2 = 0.1434, GOF = 1.002, $|\Delta\rho_{max}|$ = 0.28(4) e Å^{-3}. CCDC 716767.

trans-1,2-Di(t-butoxycarbonyl)-benzo[e]spiro[2,4]octane-4,7-dione (**3e**): Orange solid; mp: 150–153 °C; IR (KBr): 3050, 2974, 1728, 1719, 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 18H, 2 × t-Bu), 3.32 (s, 2H, 2CCH), 7.85 (dd, $^3J_{HH}$ = 5.6, $^4J_{HH}$ = 3.1, 2H, 2H$_{meta}$), 7.99 (dd, $^3J_{HH}$ = 5.6, $^4J_{HH}$ = 3.1, 2H, 2H$_{ortho}$); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 27.89 (3CH_3), 36.75 (C–H), 42.82 (C$_{spiro}$), 82.69 (C–O), 123.08 (C$_{ortho}$), 135.43 (C$_{meta}$), 142.03 (C$_{ipso}$), 164.30 (CO_2), 193.43 (C=O); Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.54; H, 6. 67.

trans-1,2-Di(methoxycarbonyl)-5,7-dimethyl-5,7-diazaspiro[2,5]octane-4,6,8-trione (**3f**): White solid; mp: 125–127 °C; IR (KBr): 2947, 1734, 1671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.34 (s, 6H, 2NCH_3), 3.50 (s, 2H, 2CCH), 3.78 (s, 6H, 2OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.08 (N–CH_3), 36.42 (C$_{spiro}$), 39.04 (C–H), 52.97 (OCH_3), 150.85 (NCON), 164.62 (NCO), 165.10 (CO_2); MS m/z (%) (EI): 298 (M$^+$, 25), 239 (100), 195 (36), 180 (32), 93 (21), 59 (51), 51 (54); Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.30; H, 4.76; N, 9.61.

trans-1,2-Di(methoxycarbonyl)-3,3-dibenzoylcyclopropane (**3g**): White solid; mp: 174–176 °C; IR (KBr): 2956, 1737, 1672, 1579; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.53 (s, 6H, 2OCH_3), 3.61 (s, 2H, 2CCH), 7.41 (t, 4H, $^3J_{HH}$ = 7.8, 4H$_{meta}$), 7.52 (t, 2H, $^3J_{HH}$ = 7.4, 2H$_{para}$), 8.05 (d, 4H, $^3J_{HH}$ = 7.3, 4H$_{ortho}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.54 (C–H), 52.48 (OCH_3), 53.60 (C(COPh)$_2$), 128.67 (C$_{meta}$), 129.57 (C$_{ortho}$), 134.01 (C$_{para}$), 135.24 (C$_{ipso}$), 168.10 (CO_2), 189.70 (C=O); MS m/z (%) (EI): 366 (M$^+$, 6), 335 (3), 275 (2), 261 (1), 247 (1), 115 (2), 105 (100), 89 (2), 77 (47), 59 (2), 51 (7); Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 68.93; H, 4.87. Crystal/refinement details for compound **3g**: $C_{21}H_{18}O_6$, M = 366.35, crystal size, 0.45 × 0.34 × 0.20 mm^3, crystal system, monoclinic, space group $P2_1/c$ (No. 14), a = 9.1230(1), b = 9.2436(1), c = 21.3842(3) Å, β = 93.129(1)°, V = 1800.63(4) Å^3, Z = 4, D_c = 1.351 g/cm^3, μ = 0.099 mm^{-1}, F_{000} = 768, Mo Kα radiation, λ = 0.71073 Å, T = 100(2) K, $2\theta_{max}$ = 75.2°, R_1 = 0.0443, wR_2 = 0.1179, GOF = 1.005, $|\Delta\rho_{max}|$ = 0.51(5) e Å^{-3}. CCDC 716768.

trans-1,2-Di(ethoxycarbonyl)-3,3-dibenzoylcyclopropane (**3h**): White solid; mp: 202–204 °C; IR (KBr): 1740, 1680, 1605; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (t, 6H, $^3J_{HH}$ = 7.1, 2CH_3), 3.60 (s, 2H, 2CCH), 3.96 (q, 4H, $^3J_{HH}$ = 7.1, 2OCH_2), 7.40 (t, 4H, $^3J_{HH}$ = 7.8, 4H$_{meta}$), 7.52 (t, 2H, $^3J_{HH}$ = 7.4, 2H$_{para}$), 8.08 (d, 4H, $^3J_{HH}$ = 7.3, 4H$_{ortho}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.77 (CH_3), 31.55 (C–H), 53.62 (C(COPh)$_2$), 61.63 (OCH_2), 128.61 (C$_{meta}$), 129.64 (C$_{ortho}$), 133.96 (C$_{para}$), 135.32 (C$_{ipso}$), 167.61 (CO_2), 189.67 (C=O); MS m/z (%) (EI): 394 (M$^+$, 2), 349 (3), 341 (27), 321 (35), 279 (7), 257 (9), 176 (3), 167 (18), 137 (17), 123 (25), 111 (23), 105 (7), 97 (38), 81 (52), 69 (100), 57 (62), 51 (34), 43 (53); Anal. Calcd for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 70.11; H, 5.67.

trans-1,2-Di(methoxycarbonyl)-3,3-dicyanocyclopropane (**3i**): Light yellow solid; mp: 81–83 °C; IR (KBr): 2254, 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.19 (s, 2H, 2CCH), 3.91 (s, 6H, 2OCH_3); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 11.82 (C(CN)$_2$), 33.05 (C–H), 54.04 (OCH_3), 110.15 (CN), 163.99 (CO_2); MS m/z (%) (EI): 208 (M$^+$, 23), 176 (10), 149 (13), 133 (6), 121 (15), 105 (12), 89 (9), 75 (10), 64 (32), 59 (100), 43 (22); Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.03; H, 3.95; N, 13.50.