Zinc-mediated Reductive Dimerization Cyclization of Ethyl Arylmethylidene-cyanoacetates in Aqueous Media†

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Lei Wang and Yongmin Zhang*

Department of Chemistry, Zhejiang University at Xixi Campus, Hangzhou, 310028, P.R. China

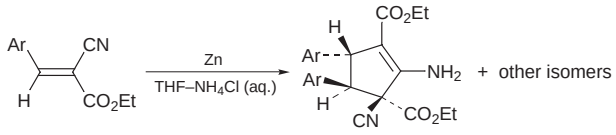
Zinc-mediated reductive dimerization–cyclization of ethyl arylmethylidenecyanoacetates occurs to give diethyl 2-amino-3-cyano-4,5-diaryl-1,3-cyclopentenedicarboxylates in moderate to good yields the *trans, trans*-form isomer being the major product.

Carbon–carbon bond formation is the essence of organic synthesis and the reductive dimerization of carbonyl derivatives by active metal is one of the most valuable methods for establishing carbon–carbon bonds. In general, the carbonyl derivatives are aldehydes, ketones, carboxylic esters, acid chlorides or imines, active metals are alkali or alkaline earth metals and the reactions carried out in anhydrous solvents.[1] Most recently, there are some reports on the reductive dimerization and reductive dimerization cyclization of α,β-unsaturated esters, α,β-unsaturated amides and arylmethylidenecyanoacetates promoted by samarium(III) iodide in THF.[2]

In the last decade, metal-mediated organic reactions in aqueous media have received considerable attention.[3] Such reactions in aqueous media offer a number of advantages over the conventional use of organic solvents, including practicality, environment concerns and avoiding the use of anhydrous organic solvents. Recently, Al(Hg),[4] Cp_2TiCl[5] and Mn[6] have been reported to be effective for the reductive dimerization of aldehydes or ketones under aqueous conditions and metallic zinc, as a cheap and efficient reagent, has been adopted for the preparation of homoallylic alcohols by coupling allylic halides with carbonyl compounds in aqueous media.[7] Here we report that metallic zinc powder mediated reductive dimerization cyclization of electron deficient olefin **1** can occur in aqueous media at room temperature to afford functionalized cyclopentenes (Table 1).

Ethyl arylmethylidenecyanoacetates have enough reactivity to complete the reductive dimerization cyclization in the presence of metallic zinc powder under aqueous conditions due to their carbon–carbon double bonds being activated by attached electron withdrawing cyano and ethoxycarbonyl groups and the stability of five-membered ring product. From Table 1, we found that substrates **1** derived from aromatic aldehydes give the products in 55–87% yields within 10 h at room temp., and the major product is the *trans, trans* isomer. This result was determined by RF-HPLC and confirmed by the X-ray crystal structure of **2b**, which clearly illustrates the *trans, trans*-structure of the major product.[2c] Unfortunately, when substrate **1** derived from aromatic ketones, aliphatic aldehyde or ketones were used, no reductive dimerization cyclization product was isolated.

Table 1 Reductive coupling cyclization of ethyl arylmethylidenecyanoacetates[a]



1 **2**

major minor

Entry	Ar	*T*/°C	*t*/h	Yield(%)[b]	**2**:other isomers[c]
1	Ph	r.t. (50[d], 50[e], 50[f])	8 (12[d], 12[e], 15[f])	71 (0[d], 0[e], 0[f])	84:16(–,–,–)
2	4-ClC_6H_4	r.t.	8	81	87:13
3	4-$MeOC_6H_4$	r.t.	10	55	90:10
4	4-BrC_6H_4	r.t.	8	80	86:14
5	4-MeC_6H_4	r.t.	8	60	88:12
6	4-FC_6H_4	r.t.	8	72	85:15
7	4-$F_3CC_6H_4$	r.t.	6	87	92:8
8	3-BrC_6H_4	r.t.	8	80	84:16
9	2-BrC_6H_4	r.t.	8	78	82:18
10	3,4-$OCH_2OC_6H_3$	r.t.	8	58	91:9

[a]Carried out in THF–NH_4Cl (aq.) (4:1, 5 mL) using substrate (1 mmol) and metallic zinc powder (1.1 mmol). [b]Combined isolated yields. [c]Ratio determined by HPLC. [d]THF–H_2O (4:1, 5 mL) was used as solvent instead of THF–NH_4Cl (aq.) (4:1, 5 mL). [e]THF (anhydrous, 5 mL) was used as solvent instead of THF–NH_4Cl (aq.) (4:1, 5 mL). [f]H_2O (5 mL) was used as solvent instead of THF–NH_4Cl (aq.) (4:1, 5 mL).

We tested THF (anhydrous), THF–H_2O or H_2O in place of THF–NH_4Cl (aq.). No product was formed under these reaction conditions even after longer reaction times (entry 1). Other metal powders, such as tin or indium were also tested and gave no reaction.

* To receive any correspondence.

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Experimental

Melting points were determined using a microscope melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 560-FTIR spectrophotometer as KBr plates. ^{1}H NMR spectra were obtained on a JEOL PMX 60 SI or a Brucker AC-80 instrument in $CDCl_3$ using TMS as internal standard. Microanalysis were performed on a Carlo Erba 1106 instrument. Mass spectra were obtained on an HP 5989A or a Finnigan MAT mass spectrometer. HPLC determinations were done on a Shimadzu LC-6A chromatographic instrument using tetrahydrofuran–methanol–water (2:6:2) as mobile phase under reversed phase conditions.

Aldehydes, ethyl cyanoacetate and all solvents were purchased from commercial sources and used without purification. Metallic Zinc (AR, 99.8%) was obtained from Shanghai Chemical Reagents Company, P.R. China and used without activation. Ethyl arylmethylidenecyanoacetate was synthesized by the reaction of an aromatic aldehyde with ethyl cyanoacetate using piperidine as catalyst.

General Procedure.—Ethyl arylmethylidenecyanoacetate (1.0 mmol) and powdered zinc (1.1 mmol) were added to satd. aq. NH_4Cl-THF (1–4 mL) and the mixture stirred at room temp. for the time indicated in Table 1. Dilute HCl (0.5 M, 2 mL) was added, the products were extracted with diethyl ether (2×25 mL), the organic layer dried (anhd. Na_2SO_4) and evaporated under reduced pressure. The product was separated from residue through preparative TLC (silica gel) using cyclohexane–ethyl acetate as eluent.

2a: Colorless crystals, mp 173–175 °C; ν_{max} (KBr)/cm^{-1} 3424, 3332, 3253, 3200 (NH_2), 3026 (ArH), 2986, 2934, 2900 (CH), 2250 (CN), 1738 (C=O), 1672 (CC – NH_2). 1637, 1578, 1455 (Ar); δ_H ($CDCl_3$) 0.86 (3H, t, *J* 6.6, CH_3), 1.30 (3H, *J* 6.9, CH_3), 3.73–4.20 (3H, m, CH_2 and CH), 4.26–4.63 (3H, m, CH_2 and CH), 5.98 (2H, br s, NH_2), 7.04–7.82 (3H, m, ArH); *m/z* 404 (M^+, 27%), 403 (100), 402 (34), 374 (35), 332 (24), 331 (85), 312 (23), 311 (46), 286 (33), 285 (82), 258 (37), 257 (57), 181 (18),131 (22),130 (25) (Found: C, 71.31; H, 5.99; N, 6.71. $C_{24}H_{24}N_2O_4$ requires C, 71.27; H, 5.98; N, 6.93%).

2b: Colorless crystals, mp 178–180 °C; ν_{max} (KBr)/cm^{-1} 3425, 3331, 3257, 3202 (NH_2), 3035 (ArH), 2980, 2935, 2910 (CH), 2250 (CN), 1737 (C=O), 1675 (C=C – NH_2). 1638, 1583, 1493 (Ar); δ_H ($CDCl_3$) 0.90 (3H, t, *J* 7.0, CH_3), 1.30 (3H, t, *J* 7.0, CH_3), 3.73–4.25 (3H, m, CH_2 and CH), 4.30–4.75 (3H, m, CH_2 and CH), 6.27 (2H, br s, NH_2), 6.80–7.28 (8H, m, ArH); *m/z* 476, 474, 472 (M^+, 13, 67, 100%), 445 (29), 443 (36), 427 (20), 400 (64), 399 (34), 398 (96), 381 (27), 379, (35), 354 (54), 352 (69), 324 (43), 291 (22), 215 (21), 189 (23), 165 (39) (Found: C, 61.07, H, 4.49, N, 5.71. $C_{24}H_{22}N_2O_4Cl_2$ requires C, 60.90; H, 4.68; N, 5.92%).

2c: Colorless crystals, mp 160–162 °C: ν_{max} (KBr)/cm^{-1} 408, 3323, 3242, 3190 (NH_2, 3025 (ArH), 2999, 2980, 2935, 2838 (CH), 2251 (CN), 1737 (C=O), 1664 (C=C – NH_2). 1638, 1611, 1567, 1460 (Ar); δ_H ($CDCl_3$) 0.92 (3H, t, *J* 6.7, CH_3), 1.31 (3H, t, *J* 7.0, CH_3). 3.71–4.22 (9H, m, CH_2, CH and $2 \times CH_3O$), 4.28–4.56 (3H, m, CH_2 and CH), 6.08 (2H, br s, NH_2), 6.76–7.84 (8H, m, ArH); *m/z* 464 (M^+, 45%), 418 (11), 390 (30), 372 (11), 371 (34), 344 (28), 317 (18), 237 (10), 233 (13), 232 (56), 186 (10), 161 (24), 160 (100), 159 (15) (Found: C, 67.09; H, 5.82; N, 6.17. $C_{26}H_{28}N_2O_6$ requires C, 67.23; H, 6.08; N, 6.03%).

2d: Colorless crystals, mp 192–194 °C; ν_{max}(KBr)/cm^{-1} 3424, 3328, 3251, 3201 (NH_2), 3045 (ArH), 2995, 2945, 2908 (CH), 2255 (CN), 1737 (C=O), 1674 (C=C – NH_2). 1636, 1582, 1490 (Ar); δ_H ($CDCl_3$) 0.93 (3H, t, *J* 6.7, CH_3), 1.32 (3H, t, *J* 7.0, CH_3), 3.65–4.10 (3H, m, CH_2 and CH), 4.18–4.63 (3H, m, CH_2 and CH), 6.06 (2H, br s, NH_2), 6.73–7.82 (8H, m, ArH); *m/z* 564, 562, 560 (M^+, 52, 100, 50%), 533 (39), 491 (46), 489 (91), 487 (49), 445 (37), 443 (64), 435 (46), 334 (29), 255 (30), 210 (41), 208 (45) (Found: C, 51.37; H, 3.81; N, 4.80. $C_{24}H_{22}N_2O_4Br_2$ requires C, 51.27; H, 3.94; N, 4.98%).

2e: Colorless crystals, mp 189–191 °C; ν_{max}(KBr)/cm^{-1} 3415, 3322, 3238, 3190 (NH_2), 3038 (ArH), 2985, 2931, 2885 (CH), 2250 (CN), 1737 (C=O), 1665 (C=C – NH_2), 1631. 1565, 1460 (Ar); δ_H ($CDCl_3$) 0.90 (3H, t, *J* 7.0, CH_3), 1.30 (3H, t, *J* 6.9, CH_3), 2.22 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.71–4.10 (3H, m, CH_2 and CH), 4.18–4.55 (3H, m, CH_2 and CH), 5.90 (2H, br s, NH_2), 6.90–7.42 (8H, m, ArH); *m/z* 432 (M^+, 100%), 433 (M^++1, 28), 431 (21), 402 (29), 385 (15), 359 (20), 358 (69), 340 (27), 339 (63), 314 (27), 313 (68), 312 (17), 286 (26), 285 (43), 221 (14), 145 (21), 144 (24) (Found: C, 72.05; H, 6.54; N, 6.19. $C_{26}H_{28}N_2O_4$ requires C, 72.20; H, 6.52; N, 6.48%).

2f: Colorless crystals, mp 170–172 °C; ν_{max}(KBr)/cm^{-1} 3423, 3330, 3248, 3201 (NH_2, 3070 (ArH), 2987, 2941, 2905 (CH), 2256 (CN), 1741 (C=O), 1671 (C=C – NH_2), 1637. 1571, 1509 (Ar); dH ($CDCl_3$) 0.91 (3H, t, *J* 7.8, CH_3), 1.30 (3H, t, *J* 6.8, CH_3), 3.53–4.15 (3H, m, CH_2 and CH), 4.25–4.63 (3H, m, CH_2 and CH), 6.09 (2H, br s, NH_2), 6.73–7.91 (8H, m, ArH); *m/z* 440 (M^+, 39%), 410 (15), 366 (40), 347 (26), 320 (40), 294 (21), 293 (32), 220 (25), 199 (10), 173 (10), 149 (31), 148 (100) (Found: C, 65.61; H, 4.97; N, 6.15. $C_{24}H_{22}N_2O_4F_2$ requires C, 65.45; H, 5.03; N, 6.36%).

2g: Colorless crystals, mp 184–186 °C; ν_{max}(KBr)/cm^{-1} 3425, 3332, 3254, 3200 (NH_2), 3042 (ArH), 2985, 2932, 2905 (CH), 2245 (CN), 1739 (C=O), 1674 (C=C – NH_2), 1638, 1577, 1467 (Ar); δ_H ($CDCl_3$) 0.85 (3H, t, *J* 7.0, CH_3), 1.31 (3H, t, *J* 7.0, CH_3), 3.70–4.20 (3H, m, CH_2 and CH), 4.25–4.68 (3H, m, CH_2 and CH), 6.07 (2H, br s, NH_2), 7.00–7.83 (8H, m, ArH); *m/z* 540 (M^+, 74%), 539 (26), 511 (28), 495 (27), 468 (31), 467 (100), 448 (29), 422 (36), 421 (82), 393 (51), 392 (49), 324 (14), 249 (16), 203 (24),199 (27) (Found: C, 57.58; H, 4.07; N, 4.97. $C_{26}H_{22}N_2O_4F_6$ requires C, 57.78; H, 4.10; N, 5.18%).

2h: Colorless crystals, mp 150–152 °C; ν_{max}(KBr)/cm^{-1} 3420, 3331, 3255, 3204 (NH_2), 3065 (ArH), 2988, 2939, 2904 (CH), 2246 (CN), 1739 (C=O), 1673 (C=C – NH_2), 1639, 1580, 1477 (Ar); δ_H ($CDCl_3$) 0.91 (3H, t, *J* 7.0, CH_3),1.32 (3H, t, *J* 7.2, CH_3), 3.72–4.13 (3H, m, CH_2 and CH), 4.25–4.70 (3H, m, CH_2 and CH), 6.23 (2H, br s, NH_2), 6.85–7.75 (8H, m, ArH); *m/z* 564, 562, 560 (M^+, 44, 86, 45%), 533 (40), 516 (28), 491 (51), 489 (100), 487 (54), 445 (55), 443 (85), 415 (44), 362 (23), 255 (39), 209 (29), 154 (22), 102 (20) (Found: C, 51.06; H, 3.89; N, 4.78. $C_{24}H_{22}N_2O_4Br_2$ requires C, 51.27; H, 3.94; N, 4.98%).

2i: Colorless crystals, mp 192–194 °C; ν_{max}(KBr)/cm^{-1} 3420, 3320, 3251, 3192 (NH_2), 3055 (ArH), 2984, 2943, 2908 (CH), 2244 (CN), 1753 (C=O), 1671 (C=C – NH_2), 1640, 1571, 1469 (Ar); δ_H ($CDCl_3$) 0.92 (3H, t, *J* 7.0, CH_3), 120 (3H, t, *J* 6.0, CH_3), 3.98–4.60 (3H, m, CH_2 and CH), 4.74–5.15 (3H, m, CH_2 and CH), 6.30 (2H, br s, NH_2), 7.10–8.22 (8H, m, ArH); *m/z* 564, 562, 560 (M^+, 10, 19, 10%), 489 (30), 483 (100), 481 (99), 443 (17), 408 (13), 362 (26), 334 (12), 283 (20), 255 (41), 240 (15), 181 (10), 102 (12) (Found: C, 51.08; H, 3.85; N, 5.09. $C_{24}H_{22}N_2O_4Br_2$ requires C, 51.27; H, 3.94; N, 4.98%).

2j: Colorless crystals, mp 186–188 °C; ν_{max}(KBr)/cm^{-1} 3422, 3321, 3247, 3185 (NH_2), 3070 (ArH), 2987, 2918, 2882 (CH), 2248 (CN), 1739 (C=O), 1660 (C=C – NH_2), 1632. 1562, 1489 (Ar); δ_H($CDCl_3$) 0.94 (3H, t, *J* 7.0, CH_3), 1.30 (3H, t, *J* 7.2, CH_3), 3.90–4.40 (3H, m, CH_2 and CH), 4.52–4.98 (3H, m, CH_2 and CH), 6.25 (2H, s, OCH_2O), 6.33 (2H, s, OCH_20), 6.38 (2H, br s, NH_2), 6.93–7.72 (6H, m, ArH); *m/z* 492 (M^+, 86%), 463 (10), 419 (35), 399 (42), 372 (41), 344 (23), 297 (11), 268 (14), 246 (53), 202 (13), 174 (100), 144 (27) (Found: C, 63.62; H, 4.76; N, 5.56. $C_{26}H_{24}N_2O_8$ requires C, 63.41; H, 4.91; N, 5.69%).

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