Ethyl N-(*o*-Ethynyl)malonanilide as a Useful Building Block for the Preparation of 3,4-Disubstituted-2(1H)-quinolones, 3,4-Disubstituted- and 2,3,4-Trisubstituted Quinolines

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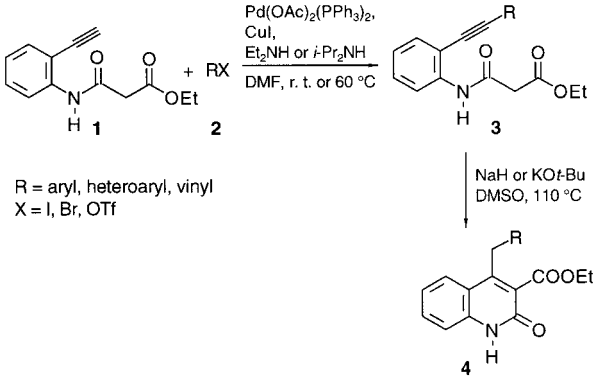
Abstract. 3,4-Disubstituted-2(1H)-quinolones have been prepared through a procedure based on the palladium-catalysed reaction of the readily available ethyl N-(*o*-ethynyl))malonanilide with aryl, heteroaryl and vinyl halides or vinyl triflates followed by the cyclization of the resulting coupling derivatives under basic conditions. It is shown that 3,4-disubstituted-2(1H)-quinolones are useful synthetic intermediates for the preparation of 3,4-disubstituted- and 2,3,4-trisubstituted quinolines.

The construction of heterocyclic derivatives based upon the concept of palladium-catalysed coupling/cyclization of alkyne bearing a proximate (pro)nucleophile has proved to be a versatile and efficient synthetic methodology.[1,2] Our continuing interest in this area, and our involvement in a program designed to identify novel non-nucleoside 2(1H)-quinolone-based anti-AIDS agents, led us to investigate the utilization of this methodology for the preparation of substituted 2(1H)-quinolones.[3] In particular, we decided to evaluate the employment of ethyl N-(*o*-ethynyl)malonanilide **1** as the starting building block. This compound can be readily prepared in 80% overall yield from *o*-iodoaniline through a one-pot three-step procedure.[4]

Now we report that compound **1** reacts with aryl, heteroaryl and vinyl halides or triflates **2** to afford the coupling derivatives **3**[5] and that subsequent treatment of **3** with NaH or KO*t*-Bu in DMSO leads to the formation of the 3,4-disubstituted-2(1H)-quinolones **4** through an intramolecular carbocyclization[6] (Scheme 1).

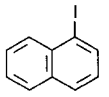
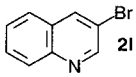
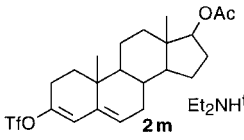


Scheme 1

Most probably the carbocyclization proceeds through a mechanism similar to that proposed for the carbocyclization of propargyl ethylmalonates[2] and involves the intramolecular nucleophilic attack of the carbanion, generated from **3**, on the carbon-carbon triple bond affording, after protonation, a six-membered ring methylidene intermediate that isomerizes to the quinolone derivative **4**. The nature of the substituent linked to the acetylenic moiety, R, is crucial for the success of the cyclization step. Best results were obtained in the presence of aromatic rings bearing electron-withdrawing substituents. No quinolone derivative was obtained, under our standard conditions, in the presence of the electron-donating *p*-methoxyphenyl group or the *n*-butyl group.

Our results are summarized in the Table.

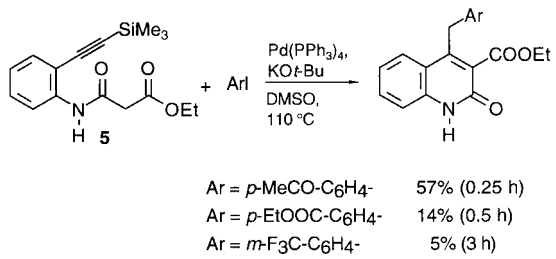
Table. Synthesis of 3,4-Disubstituted-2(1H)-quinolones **4**

entry	RX **2**	base (coupling)[a]	yield % [b] of **3** (reaction time, h)	base (cyclization)[c]	yield %[b] of **4** (reaction time, h)
1	*p*-MeCO-C_6H_4-I **2a**	Et_2NH	**3a** 63 (0.25)	NaH	**4a** 75 (0.25)
2	*p*-F-C_6H_4-I **2b**	Et_2NH	**3b** 88 (1.0)	NaH	**4b** 56 (6.0)
3	*m*-O_2N-C_6H_4-I **2c**	Et_2NH	**3c** 66 (1.5)	NaH	**4c** 70 (0.5)
4	**2c**	"	"	KO*t*-Bu	**4c** 62 (0.5)
5	*m*-F_3C-C_6H_4-I **2d**	Et_2NH	**3d** 65 (1.0)	NaH	**4d** 63 (2.5)
6	*m*-EtOOC-C_6H_4-I **2e**	Et_2NH	**3e** 63 (1.0)	NaH	**4e** 62 (7.0)
7	*o*-MeOOC-C_6H_4-I **2f**	Et_2NH	**3f** 62 (1.5)	NaH	**4f** 63 (0.75)
8	*p*-EtOOC-C_6H_4-I **2g**	Et_2NH	**3g** 76 (1.0)	NaH	**4g** 67 (0.75)
9	*p*-MeOOC-C_6H_4-I **2h**	Et_2NH	**3h** 83 (0.25)	NaH	**4h** 60 (0.75)
10	PhI **2i**	Et_2NH	**3i** 70 (0.5)	NaH	**4i** 60 (4.0)
11	 **2j**	Et_2NH	**3j** 72 (0.75)	NaH	**4j** 67 (0.5)
12	PhCH=CHBr **2k**[d]	*i*-Pr_2NH[e]	**3k** 65 (1.5)	NaH	**4k** 50 (0.75)
13	 **2l**	*i*-Pr_2NH[e]	**3l** 77 (0.75)	NaH	**4l** 30 (1.0)
14	**2l**	"	"	KO*t*-Bu	**4l** 33 (1.0)
15	 **2m**	Et_2NH[f]	**3m** 48 (3.0)	NaH	**4m** 38 (5.0)

[a] Unless otherwise stated, coupling reactions were carried out at room temperature in DMF in the presence of an excess of Et_2NH (10 equiv.) under argon using the following molar ratios: **1**:**2**:$Pd(OAc)_2(PPh_3)_2$:CuI = 1:1.2:0.04:0.01. [b] Yields refer to single runs and are given for pure isolated products. All compounds had satisfactory elemental analysis and spectral data were consistent with the postulated structures. [c] Reactions were carried out at 80 °C in DMSO under argon using the following molar ratio: **3**:base = 1: 1.5. [d] As an *E*/*Z* mixture. However, only the styryl derivative from the *E* isomer was isolated. [e] At 60 °C. [f] **1**:**2m** = 1:1

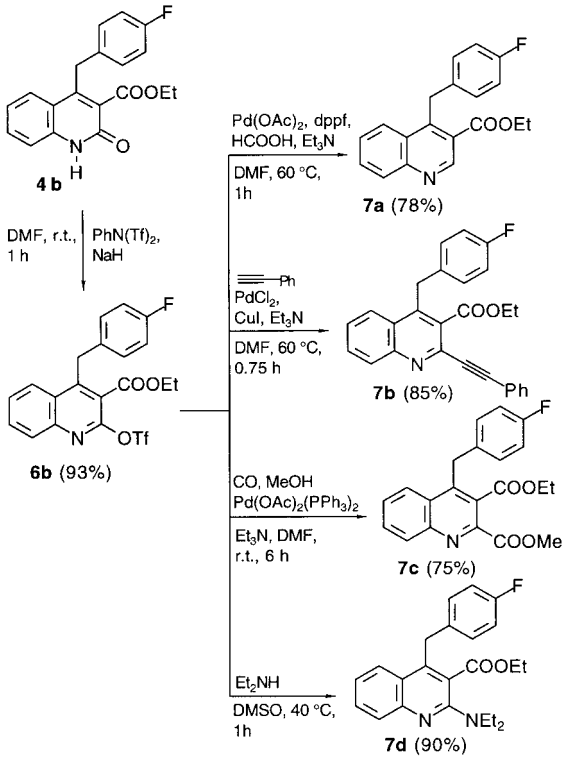
To keep the methodology as simple as possible, we briefly investigated the development of an *in situ* coupling/cyclization procedure starting from the silyl derivative **5**. We used reaction conditions similar to those employed by us in the palladium-catalysed coupling/cyclization of *o*-[(trimethylsilyl)ethynyl]phenyl acetates with aryl halides or vinyl triflates.[7] This protocol, however, provided satisfactory results only with *p*-iodoacetophenone (Scheme 2).

The scope of this facile synthesis of 2(1H)-quinolones is tremendously broadened by the ease of their conversion into a variety of 3,4-disubstituted- and 2,3,4-trisubstituted quinolines through the corresponding triflates **6**.[8,9] For example, quinoline derivatives



Scheme 2

7a-d[10-17] were obtained in good to high yields from **6b**[18] according to the conditions reported in Scheme 3.



Scheme 3

Acknowledgments. The authors are greatly indebted to the Fondazione Cenci Bolognetti for financial support of this research. The authors are also indebted to Dr. Luciana Turchetto of the Istituto Superiore di Sanità for obtaining the mass spectra of new products.

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3. For other approaches to substituted 2(1H)-quinolones, see: Fourquez, J.M.; Godard, A.; Marsais, F.; Quéguiner, G. *J. Heterocyclic Chem.* **1995**, *32*, 1165; Kuroda, T.; Suzuki, F. *Tetrahedron Lett.* **1991**, *32*, 6915; Bell, A.S.; Greenhill, J.V. In *The Chemistry of Heterocycles*; Taylor, E.C. Ed.; J. Wiley & Sons: Chichester, 1990; Vol. 32, part III; Roberts, D.A.; Ruddock, K.S. *Synthesis* **1987**, 843; Gaston, J.L.; Greer, R.J.; Grundon, M. F. *J. Chem. Research (S)* **1985**, 135; Terpko, M.O.; Heck, R.F. *J. Am; Chem. Soc.* **1979**, *101*, 5281; Walser, A.; Szente, A.; Hellerbach, J. *J. Org. Chem.* **1973**, *38*, 449; Fryer, R.L.; Brust, B.; Sternbach, L.H. *J. Chem. Soc.* **1964**, 3097.
4. Preparation of ethyl N-(*o*-ethynyl))malonanilide **1**: to a solution of *o*-iodoaniline (3.0 g, 13.7 mmol) in DMF (6.0 mL) were added Et_2NH (10 mL), trimethylsilylacetylene (2.28 mL, 16.4 mmol), $Pd(OAc)_2(PPh_3)_2$ (0.205 g, 0.27 mmol) and CuI (0.104 g, 0.54 mmol). The reaction mixture was stirred at room temperature under argon for 2 h. After this time, it was diluted with ethyl acetate, washed with a saturated NH_4Cl solution and a saturated NaCl solution. The organic layer was separated, dried (Na_2SO_4) and concentrated at reduced pressure.
To the residue were added MeOH (10 mL) and K_2CO_3 (0.189 g, 1.37 mmol) and the mixture was stirred at room temperature for 1 h. Then, MeOH was evaporated under vacuum and the residue was dissolved in ethyl acetate. The solution was washed with a saturated NaCl solution, the organic layer was separated, dried (Na_2SO_4) and concentrated at reduced pressure.
The residue was dissolved in anhydrous THF and the solution was cooled at 0 °C. Then, ethyl malonylchloride (4.1 g, 27.4 mmol) was added at 0 °C and the resulting reaction mixture was stirred at room temperature for 15 min. After this time, the mixture was diluted with ethyl acetate, washed with a saturated NaCl solution, the organic layer was separated, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by chromatography on silica gel eluting with a *n*-hexane/ethyl acetate 80/20 (v/v) mixture to give **1** (2.5 g, 80% yield; mp = 75-7 °C; IR (KBr) 3279, 2150, 1728, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t , J = 7.1 Hz, 3 H), 3.55 (s, 1 H), 3.52 (s, 2 H), 4.26 (q, J = 7.1 Hz, 2 H), 7.07-8.44 (m, 4 H), 9.41 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.4, 42.1, 52.7, 79.0, 84.6, 111.5, 119.9, 123.8, 130.1, 132.3, 139.8, 163.0, 169.5; MS *m/e*: 231 (M^+, 24), 186 (3), 117 (100).
5. A typical procedure for the palladium-catalysed coupling is as follows: to a solution of **1** (0.200 g, 0.87 mmol) in DMF (2 mL), Et_2NH (2 mL), *m*-nitrophenyl iodide **2c** (0.259 g, 1.04 mmol), $Pd(OAc)_2(PPh_3)_2$ (0.032 g), and CuI (0.017 g, 0.087 mmol) were added. The reaction mixture is gently purged with argon and stirred at room temperature for 1.5 h under argon. Then, ethyl acetate and HCl 0.2 N were added, the organic layer was separated, washed with a saturated $NaHCO_3$ solution, a saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by chromatography eluting with a 95/5 (v/v) *n*-hexane/EtOAc mixture to give **3c** (0.202 g, 66% yield); mp = 112-113 °C; IR (KBr) 2984, 2130, 1720, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3 H), 3.57 (s, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.34-7.57 (m, 3 H), 7.95 (d, J = 7.7 Hz, 1 H), 8.16 (d, J = 8.3 Hz, 1 H), 8.48 (d, J = 8.3 Hz, 1 H), 8.76 (s, 1 H), 10.44 (sb, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 41.3, 62.4, 87.3, 94.0, 111.9, 120.1, 123.2, 123.9, 125.0, 126.8, 129.4, 130.5, 132.5, 137.5, 139.6, 148.4, 163.4, 170.5; MS *m/e*: 352 (M^+, 1), 293 (15), 277 (13), 262 (31), 208 (11), 149 (100), 144 (28).
6. A typical procedure for the carbocyclization is as follows: to a solution of **3c** (0.200 g, 0.57 mmol) in DMSO (5 mL) was added KO*t*-Bu (0.159 g, 1.42 mmol). The reaction mixture was stirred at 110 °C for 0.5 h, then poured into a separatory funnel containing ethyl acetate and a saturated NaCl solution. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by chromatography eluting with a 60/40 (v/v) *n*-hexane/EtOAc mixture to give **4c**

(0.124 g, 62% yield): mp = 223-5 °C; IR (KBr) 1720, 1663 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 6.4 Hz, 3 H), 4.30 (m, 4 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.35 (d, J = 7.6 Hz, 1 H), 7.48-7.79 (m, 4 H), 8.07 (d, J = 8.1 Hz, 1 H), 8.23 (s, 1 H), 12.2 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 34.5, 61.4, 116.0, 117.3, 1221.7, 122.5, 123.0, 126.0, 128.2, 130.1, 131.5, 135.1, 138.8, 140.1, 144.8, 147.9, 158.7, 166.0; MS *m/e* 352 (M^+, 32), 306 (100), 276 (15), 260 (40), 232 (48), 204 (50), 176 (13).

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10. **7a** (prepared according to the conditions described in ref. 11): mp = 85-7 °C; IR (KBr) 2992, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3 H), 4.41 (q, J = 7.1 Hz), 4.85 (s, 2 H), 6.91 (t, J = 8.7 Hz, 2 H), 7.05 (t, J = 3.2 Hz, 2 H), 7.54 (m, 1 H), 7.77 (m, 1 H), 8.11 (m, 1 H), 9.34 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (*C*H_3-CH_2-O), 35.6 (-*C*H_2-C_6H_4-*p*-F), 61.9 (CH_3-*C*H_2-O), 161.5 (F-*C*$_{aromatic}$, J = 241.0 Hz), 166.7 (-*C*OOEt); MS *m/e*: 309 (M^+, 5), 263 (100), 235 (21), 207 (8), 184 (7).

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12. **7b** (prepared according to the conditions described in ref. 13): mp = 128-130 °C; IR (KBr) 2927, 2212, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3 H), 4.43 (m, 4 H), 6.94 (t, J = 8.4 Hz, 1 H), 7.14 (t, J = 8.4 Hz, 2 H), 7.26-7.64 (m, 8 H), 7.72 (t, J = 8.2 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 1 H), 8.14 (d, J = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (*C*H_3-CH_2-O), 35.0 (-*C*H_2-C_6H_4-*p*-F), 62.4 (CH_3-*C*H_2-O), 87.4 (C_{sp}–*C*$_{sp}$-Ph), 92.9 (*C*$_{sp}$–C_{sp}-Ph), 161.7 (F-*C*$_{aromatic}$, J = 246.0 Hz), 167.0 (-*C*OOEt); MS *m/e*: 409 (M^+, 57), 380 (100), 364 (27), 352 (19), 335 (24), 322 (21), 234 (13), 207 (17).

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14. **7c** (prepared according to the conditions described in ref. 15): oil; IR (neat) 2951, 1728, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J + 7.2 Hz, 3 H), 4.09 (s, 3 H), 4.41 (q, J = 7.2 Hz, 2 H), 4.50 (s, 2 H), 6.92 (t, J = 8.6 Hz, 2 H), 7.13 (t, J = 5.5 Hz, 2 H), 7.60 (m, 1 H), 7.78 (m, 1 H), 7.98 (d, J = 8.5 Hz, 1 H), 8.28 (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (*C*H_3-CH_2-O), 34.4 (-*C*H_2-C_6H_4-*p*-F), 60.3 (*C*H_3-O), 62.1 (CH_3-*C*H_2-O), 161.5 (F-*C*$_{aromatic}$, J = 244.0 Hz), 165.6, 167.7 (-*C*OOMe and -*C*OOEt); MS *m/e*: 367 (M^+, 100), 322 (25), 307 (27), 279 (64), 263 (80), 234 (79), 207 (36), 156 (31).

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16. **7d** (prepared according to the conditions described in ref. 17): oil; IR (neat) 3419, 2976, 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86-1.55 (m, 9 H), 3.52 (q, J = 7.0 Hz, 4 H), 4.27 (m, 4 H), 6.91 (t, J = 8.7 Hz, 2 H), 7.05-7.35 (m, 4 H), 7.52 (t, J = 7.1 Hz, 1 H), 7.72 (t, J = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.3 (*C*H_3-CH_2-O), 14.1 (*C*H_3-CH_2-N), 34.8 (–*C*H_2-C_6H_4-*p*-F), 44.3 (CH_3-*C*H_2-N), 157.3 (F-*C*$_{aromatic}$, J = 182.3 Hz), 169.6 (–*C*OOEt); MS *m/e*: 380 4M^+, 15), 351 (97), 337 (15), 305 (100), 264 (18), 235 (28), 207 (14).

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18. The triflate **6b** was prepared in 93% yield by treating **4b** (0.140 g, 0.431 mmol) with $PhN(Tf)_2$ (0.184 g, 0.517 mmol) in the presence of NaH (0.021 g, 0.517 mmol) in DMF (3 mL) at room temperature for 1 h: oil; IR (neat) 3082, 2992, 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3 H), 4.41 (q, J = 7.1 Hz, 2 H), 4.51 (s, 2 H), 6.94 (t, J = 8.6 Hz, 2 H), 7.12 (t, J = 5.4 Hz, 2 H), 7.57 (t, J = 7.1 Hz, 1 H), 7.77 (t, 8.3 Hz, 1 H), 8.00 (t, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0 (*C*H_3-CH_2O), 34.9 (-*C*H_2-C_6H_4-*p*-F), 63.1 (CH_3-*C*H_2-O), 118.6 (*C*F_3, J = 320.0 Hz) 161.1 (F-*C*$_{aromatic}$, J = 181.1 Hz), 164.5 (-*C*OOEt).