AN EFFICIENT SYNTHESIS OF DI- AND TRIMETHOXY-4-QUINOLONES

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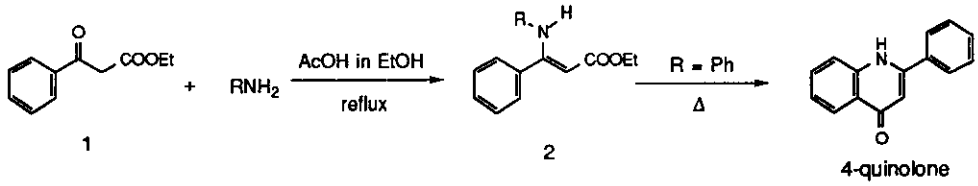
Abstract - An excellent method of preparation of *N*-aryl-enamino esters (**4**) was achieved by developing *N-N* exchange reaction of an *N*-methyl-enamino ester (**6**) with di- and trimethoxyanilines (**3**). Thermolysis of **4** in xylene gave di- and trimethoxy-4-quinolones (**7**) in excellent yields.

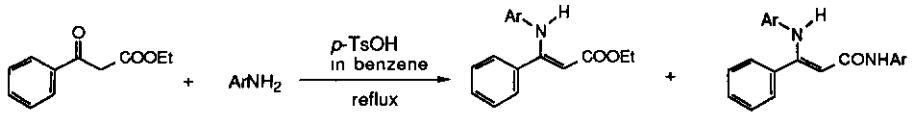
An *N*-aryl-enamino ester (3-arylaminopropenoate) is known to serve as a key intermediate for synthesizing 4-quinolones.[1] Recently, the compound has received attention from biological point of view since some 2-phenyl-4-quinolones were reported to possess potent anti-tumor activity.[2] In this paper we describe an efficient 4-quinolone synthesis which was achieved by developing a new method of preparation of *N*-aryl-enamino esters by *N-N* exchange reaction.



Scheme 1

The reaction of ethyl benzoylacetate (**1**) with aliphatic and aromatic primary amines, when the mixture in ethanol was heated in the presence of acetic acid, readily caused dehydration to give the corresponding enamino esters (**2**) in high yield.[3] However, the enamination of **1** with some arylamines such as dimethoxyanilines did not occur under these mild conditions because of their low basicity, requiring somewhat stronger conditions for dehydration. When a mixture of **1** and 3,4-dimethoxyaniline (**3a**) in benzene was heated under reflux for 25 h in the presence of *p*-toluenesulfonic acid (*p*-TsOH), the enamination proceeded to give an *N*-

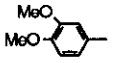
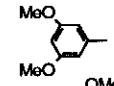
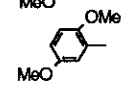
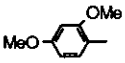
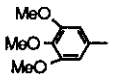
aryl-enamino ester (**4a**) in 87% yield. 3,5-Dimethoxyaniline (**3b**) under similar conditions also afforded the enamino ester (**4b**) in 68% yield although an *N*-aryl-enaminoamide (**5b**) was obtained as a by-product in 4% yield. This by-product was formed by amidation of the ester followed by enamination of the ketone. 2,5-Dimethoxyaniline (**3c**), 2,4-dimethoxyaniline (**3d**), and 3,4,5-trimethoxyaniline (**3e**) under similar conditions yielded the undesired amide (**5c-e**) in considerable yield (**5c**: 25%, **5d**:11% and **5e**: 36% yield), although the desired *N*-aryl-enamino esters (**4c-e**) were obtained as a major product (**4c**: 57%, **4d**: 31% and **4e**: 51% yield). In addition to a disappointed result producing the by-product in considerable amounts, this method had a disadvantage that arylamines were used in a large excess (3-5 molar eq.) because of the extremely slow reaction (25-70 h). The results are summarized in Table I.



1 3 4 5

Scheme 2

Table I. Enamination of Ethyl Benzoylacetate (1) with Arylamines (3) in Benzene Catalyzed by *p*-TsOH

	Arylamines 3 Ar		Time (hr)	Yield (%) 4	Yield (%) 5
a		(3,4-diOMe)	25	87	—
b		(3,5-diOMe)	45	68	4
c		(2,5-diOMe)	70	57	25
d		(2,4-diOMe)	70	31	11
e		(3,4,5-triOMe)	40	51	36

The problems observed in the enamination of the β-keto ester were solved by applying *N-N* exchange reaction for the *N*-methyl-enamino ester (**6**) and arylamines (**3**). Hojo *et al.* reported that in enamines activated by trifluoroacetyl group an *N-N* exchange reaction proceeded readily under non-catalytic conditions.[4] In our cases, however, the *N-N* exchange reaction did not occur in the absence of catalyst, and pyridinium *p*-toluenesulfonate (PPTS) was found to be superior to other catalysts (*p*-TsOH and boron trifluoride etherate).

Thus, the mixture of **3**, **6**, and PPTS in acetonitrile on heating under reflux for 2.5 h gave **4c** and **5c** in 53% and 31% yield, respectively (Table II: Runs 1, 2). The results showed that this treatment caused not only the expected *N-N* exchange but also the undesired amidation of the ester. The side reaction even under the conditions of a decreased amount of PPTS was still observed (Runs 3, 4).

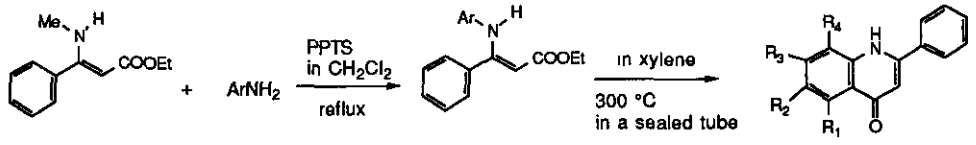
Table II. *N-N* Exchange Reaction of *N*-Methyl-enaminoester (**6**) with Arylamines (**3**) Catalyzed by PPTS

Run (No)	**3** (mol eq)	**6** (mol eq)	PPTS (mol eq)	Solvent	Time (hr)	Yield (%) **4**	Yield (%) **5**
1	1.0 (**3c**)	1.2	non	MeCN	2	0	0
2	1.0 (**3c**)	1.2	1.2	MeCN	2.5	53	31
3	1.0 (**3c**)	1.2	0.1	MeCN	44	19	3
4	1.0 (**3c**)	1.2	0.5	MeCN	8	38	7
5	1.0 (**3a**)	1.1	1.1	CH_2Cl_2	30	95	—
6	1.0 (**3b**)	1.1	1.1	CH_2Cl_2	30	99	—
7	1.0 (**3c**)	1.1	1.1	CH_2Cl_2	30	94	—
8	1.0 (**3d**)	1.1	1.1	CH_2Cl_2	30	88	—
9	1.0 (**3e**)	1.1	1.1	CH_2Cl_2	30	79	—

Finally, we found that the undesired amidation reaction was avoidable by using dichloromethane as a solvent, instead of acetonitrile; that is, when a mixture of **6** (1.1 molar eq.) and **3** (1.0 molar eq.) in dichloromethane was heated under reflux for 30 h in the presence of PPTS (1.1 molar eq.), the desired *N*-aryl-enamino esters (**4**) were obtained as a sole product in excellent yields, regardless of the properties of the arylamines used (Runs 5-9).

The synthesis of 4-quinolones was achieved by simply heating **4a-e** in xylene at 300 °C in a sealed tube, giving rise to di- and trimethoxy-4-quinolones (**7a-e**) in excellent yields (Scheme 3). This method of thermal cyclization reaction in xylene seems to be superior to the method in diphenyl ether which is widely applied for 4-quinolone syntheses[1,2] because of its easy isolation of the product from the reaction mixture.

In summary, di- and trimethoxy-4-quinolones (**7**) were synthesized *via* the *N-N* exchange reaction of the *N*-methyl-enamino ester (**6**) with di- and trimethoxyanilines (**3**) followed by thermolysis of the resulting *N*-aryl-enamino esters (**4**), providing an efficient and probably generally applicable method of synthesis of 4-quinolones.



6 3 4 7

	R_1	R_2	R_3	R_4	Yield (%)
a	H	OMe	OMe	H	93
b	OMe	H	OMe	H	83
c	OMe	H	H	OMe	97
d	H	OMe	H	OMe	99
e	OMe	OMe	OMe	H	98

Scheme 3

EXPERIMENTAL

Unless otherwise stated, the following procedures were adopted. All melting points were taken on a Yanagimoto micro hot-stage melting point apparatus and are uncorrected. Infrared (Ir) spectra were measured with a JASCO FT/IR-5000 and are given in ν_{max} cm^{-1}. Ultraviolet (Uv) spectra were measured with a Hitachi U-3200 spectrophotometer in dioxane and given in λ_{max} nm (ε). Nuclear magnetic resonance (Nmr) spectra were taken on a JEOL EX-90 NMR spectrometer (^1H; 90 MHz, ^{13}C; 22.5 MHz) in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts are given in δ values. Low and high resolution mass spectra (LR- and HRms) were determined with a JEOL JMS-D 300 spectrometer at 30 eV.

Enamination of Ethyl Benzoylacetate (1) with Arylamines 3 Catalyzed by *p*-TsOH (General Procedure)

A mixture of **1** (10 g, 52 mmol), **3** (3-5 mol eq.), and *p*-TsOH (20 mol%) in anhydrous benzene (300 ml) was heated under reflux with Dean-Stark water separator *until* **1** *was not detected by thin layer chromatography*. After the reaction mixture was diluted with CH_2Cl_2, the organic layer was washed with water, then 5%HCl, dried over Na_2SO_4, and concentrated to dryness *in vacuo*. The residue was purified by SiO_2 column chromatography (eluting with benzene) followed by recrystallizations from an appropriate solvent to give **4** and **5**. The yields were given in Table I.

4a: A pale yellow oil. Ir (film): 1740,1653, 1593. Uv: 253 (13600), 330 (14900). ^1H-Nmr: 1.32 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.53, 3.77 (each 3H, s, $OC\underline{H}_3$), 4.21 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.95 (1H, br s, olefinic H), 6.21 (1H, dd, *J*=3, 8 Hz, ArH), 6.33 (1H, d, *J*=3 Hz, ArH), 6.61 (1H, d, *J*=8 Hz, ArH), 7.31 (5H, s, PhH), 10.27 (1H, br s, NH). LRms (*m/z*): 327 (M^+), 207 (base peak).

4b: Pale yellow prisms from ether-hexane, mp 51-53°C. Ir: 1642, 1601. Uv: 252 (17000), 327 (15400). ^1H-Nmr: 1.31 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.52 (6H, s, 2 x $OC\underline{H}_3$), 4.21 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.99

(1H, s, olefinic H), 5.80 (2H, d, *J*=2 Hz, ArH), 6.03 (1H, d, *J*=2 Hz, ArH), 7.34 (5H, s, PhH), 10.28 (1H, s, NH). LRms (*m/z*): 327 (M^+), 55 (base peak).

5b: Yellow prisms from ether-CH_2Cl_2, mp 158-160°C. Ir: 3350, 1600. Uv: 249 (18000), 346 (29000). ^{1}H-Nmr: 3.74, 3.76, 3.78, 3.79 (each 3H, s, $OC\underline{H}_3$), 4.90 (1H, s, olefinic H), 6.25 (2H, t, *J*=2 Hz, ArH), 6.77 (2H, d, *J*=2 Hz, ArH), 6.83 (2H, d, *J*=2 Hz, ArH), 7.36 (5H, s, PhH). LRms (*m/z*): 434 (M^+), 282 (base peak).

4c: Pale yellow prisms from ether, mp 72-73.5°C. Ir: 1657, 1595, 1576. Uv: 213 (25000), 263 (15600), 343 (19500). ^{1}H-Nmr: 1.22 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.22, 3.79 (each 3H, s, $OC\underline{H}_3$), 4.13 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.91 (1H, br s, olefinic H), 5.68 (1H, d, *J*=3 Hz, ArH), 6.28 (1H, dd, *J*=3, 9 Hz, ArH), 6.65 (1H, d, *J*=9 Hz, ArH), 7.26 (5H, s, PhH), 10.21 (1H, br s, NH). LRms (*m/z*): 327 (M^+), 207 (base peak).

5c: Yellow prisms from ether, mp 147-149°C. Ir: 1742, 1634, 1599. Uv: 252 (15500), 360 (25500). ^{1}H-Nmr: 3.33, 3.81, 3.83, 3.88 (each 3H, s, $OC\underline{H}_3$), 5.01 (1H, s, olefinic H), 5.81 (1H, d, *J*=3 Hz, ArH), 6.36, 6.51 (each 1H, dd, *J*=3, 9 Hz, ArH), 6.73, 6.78 (each 1H, d, *J*=9 Hz, ArH), 7.36 (5H, s, PhH), 8.21 (1H, d, *J*=3 Hz, ArH). LRms (*m/z*): 434 (M^+), 282 (base peak).

4d: Pale yellow prisms from ether-CH_2Cl_2, mp 84-86°C. Ir: 1657, 1591. Uv: 257 (14300), 337 (13500). ^{1}H-Nmr: 1.31 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.69, 3.82 (each 3H, s, $OC\underline{H}_3$), 4.20 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.92 (1H, s, olefinic H), 6.07 (1H, dd, *J*=2, 9 Hz, ArH), 6.26 (1H, d, *J*=9 Hz, ArH), 6.40 (1H, d, *J*=2 Hz, ArH), 7.29 (5H, s, PhH), 10.06 (1H, s, NH). LRms (*m/z*): 327 (M^+, base peak).

5d: Yellow prisms from ether-CH_2Cl_2, mp 168-170°C. Ir: 3400, 1610. Uv: 252 (18300), 263 (15900), 357 (23700). ^{1}H-Nmr: 3.69, 3.80, 3.81, 3.84 (each 3H, s, $OC\underline{H}_3$), 4.90 (1H, s, olefinic H), 6.07 (1H, dd, *J*=3, 9 Hz, ArH), 6.27 (1H, dd, *J*=6, 9 Hz, ArH), 6.3-6.6 (4H, m, ArH), 7.30 (5H, s, PhH), 10.66 (1H, s, NH). LRms (*m/z*): 434 (M^+), 282 (base peak).

4e: Colorless prisms from ether, mp 116-117°C. Ir: 2988, 1659. Uv: 255 (15100), 330 (16200). ^{1}H-Nmr: 1.32 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.53 (6H, s, 2x$OC\underline{H}_3$), 3.73 (3H, s, $OC\underline{H}_3$), 4.21 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.97 (1H, s, olefinic H), 5.86 (2H, s, ArH), 7.34 (5H, s, PhH), 10.31 (1H, br s, NH). LRms (*m/z*): 357 (M^+), 69 (base peak).

5e: Colorless prisms from benzene-MeOH, mp 99-101°C. Ir: 3546, 3408, 1601. Uv: 251 (18100), 353 (29000). ^{1}H-Nmr: 3.53 (6H, s, 2 x $OC\underline{H}_3$), 3.73, 3.82 (each 3H, s, $OC\underline{H}_3$), 3.86 (6H, s, 2 x $OC\underline{H}_3$), 4.90 (1H, s, olefinic H), 5.87, 6.83 (each 2H, s, ArH), 7.00 (1H, br s, NH), 7.35 (5H, s, PhH), 10.98 (1H, br s, NH). LRms (*m/z*): 494 (M^+), 183 (base peak).

***N-N* Exchange of the *N*-Methyl-enamino ester (6) with Arylamine (3) (General Procedure)** A mixture of **3** (5 g, 27 or 33 mmol), **6**[3] (1.1 mol eq.), and PPTS (1.1 mol eq.) in CH_2Cl_2 (100 ml) was heated under reflux for 30 h. After cooling, insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* to dryness and the residue was purified by SiO_2 or Al_2O_3 column chromatography (CH_2Cl_2 as an eluent) followed by recrystallizations from an appropriate solvent to give **4** in yields given in Table II.

Synthesis of 4-Quinolone 7 (General Procedure) A mixture of **4** (1 g) and anhydrous xylene (25 ml) was heated at 300°C in a sealed tube for an appropriate time (21 hr for **4a-d**, 8 hr for **4e**). Evaporation of the solvent *in vacuo* and recrystallizations from an appropriate solvent gave **7** in yields given in Scheme 3.

7a: Colorless prisms from CH_2Cl_2-ether, mp 279-280°C. Ir: 3156, 1609, 1599, 1578. Uv: 256 (29500), 311 (8500), 336 (9000). ^{1}H-Nmr: 3.82, 3.94 (each 3H, s, $OC\underline{H}_3$), 6.37, 7.06 (each 1H, s, ArH), 7.3-7.6 (6H, m, ArH). ^{13}C-Nmr: 55.9 (q), 56.1 (q), 99.3 (d), 103.9 (d), 107.0 (d), 119.0 (s), 127.2 (dx2), 129.1 (dx2), 130.4 (d), 134.3 (s), 136.7 (s), 147.7 (s), 149.9 (s), 153.9 (s), 177.9 (s). LRms (*m/z*): 281 (M^+, base peak). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.41; H, 5.49; N, 4.97.

7b: Colorless prisms from MeOH-acetone, mp 220-222°C. Ir: 3072, 1615, 1580. Uv: 265 (50700), 333 (3000). ^{1}H-Nmr: 3.86, 3.88 (each 3H, s, $OC\underline{H}_3$), 6.27, 6.68 (each 1H, d, *J*=2 Hz, ArH), 6.45 (1H, s, olefinic H), 7.4-7.7 (5H, m, PhH). ^{13}C-Nmr: 55.6 (q), 55.7 (q), 92.2 (d), 95.7 (d), 109.5 (d), 110.7 (s), 127.4 (dx2), 129.2 (dx2), 130.6 (d), 134.3 (s), 145.5 (s), 150.1 (s), 161.0 (s), 163.5 (s), 179.2 (s). LRms (*m/z*): 281 (M^+, base peak). HRms (*m/z*): Calcd for $C_{17}H_{15}NO_3$ (M^+): 281.1050. Found: 281.1045.

7c (4-Hydroxyquinoline form): Pale yellow prisms from ether-MeOH, mp 138-139°C [lit.[5] mp 142-143°C]. Ir: 3386, 1628, 1580. Uv: 269 (33500), 334 (6000). ^{1}H-Nmr (CD_3OD): 3.87, 3.99 (each 3H, s, $OC\underline{H}_3$), 6.47 (1H, s, olefinic H), 6.76, 7.17 (each 1H, d, J=9 Hz, ArH), 7.5-7.8 (5H, m, PhH). ^{13}C-Nmr: 56.0 (q), 56.5 (q), 104.4 (d), 110.5 (d), 112.4 (d), 116.3 (s), 127.9 (dx2), 129.9 (dx2), 131.4 (d), 134.2 (s), 134.7 (s), 143.2 (s), 150.5 (s), 153.6 (s), 180.4 (s). (CD_3OD): 56.3 (q), 56.8 (q), 104.7 (d), 112.7 (d), 116.6 (s), 128.2 (dx2), 130.2 (dx2), 131.8 (d), 134.5 (s), 134.9 (s), 143.5 (s), 150.6 (s), 153.9 (s), 180.9 (s). LRms (*m/z*): 281 (M^+), 266 (base peak). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.36; H, 5.51; N, 4.95.

7d: Colorless prisms from MeOH-hexane, mp 148-151°C. Ir: 3364, 1593, 1547, 1512. Uv: 263 (28600), 346 (8600). ^{1}H-Nmr: 3.92, 4.00 (each 3H, s, $OC\underline{H}_3$), 6.58 (1H, d, J=2 Hz, olefinic H), 6.73, 7.30 (each 1H, d, *J*=2 Hz, ArH), 7.5-7.8 (5H, m, PhH). ^{13}C-Nmr: 55.9 (q), 56.2 (q), 95.9 (d), 102.9 (d), 108.1 (d), 126.1 (s), 126.5 (S), 126.5 (dx2), 129.5 (dx2), 130.6 (s), 134.7 (s), 147.5 (s), 148.9 (s), 156.5 (s), 178.2 (s). LRms (*m/z*): 281 (M^+, base peak). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.43; H, 5.47; N, 4.98.

7e: Colorless prisms from AcOEt-acetone, mp 227-229°C. Ir: 3158, 1630, 1611, 1580. Uv: 264 (50300), 303 (9700). ^{1}H-Nmr: 3.96, 4.00, 4.18 (each 3H, s, $OC\underline{H}_3$), 7.4-8.1 (7H, m, PhH). ^{13}C-Nmr: 56.5 (q), 61.9 (q), 62.5 (q), 96.6 (d), 109.2 (d), 114.8 (s), 127.9 (dx2), 129.9 (dx2), 131.3 (d), 135.0 (s), 140.7 (s), 141.1 (s), 151.0 (s), 153.1 (s), 158.4 (s), 179.4 (s). LRms (*m/z*): 311 (M^+, base peak). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.27; H, 5.62; N, 4.40.

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