Camps reaction for the synthesis of 3-RS-4-arylquinolin-2-ones

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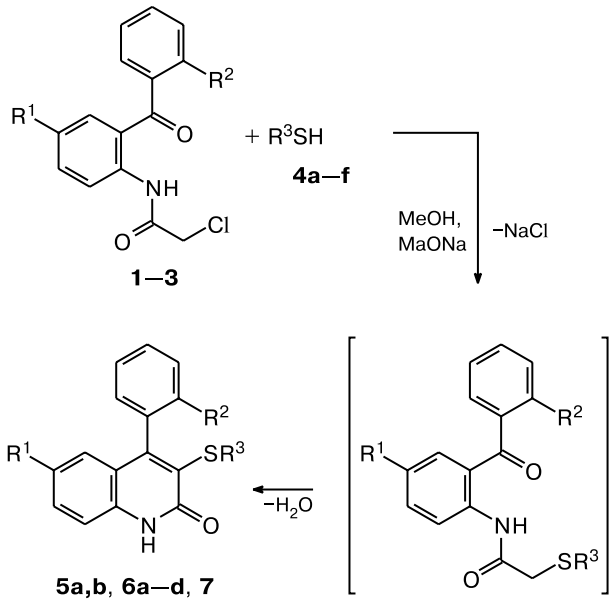
The replacement of the chlorine atom in 2-(chloroacetamido)benzophenones on treatment with RSH (R = Alk, Ar, Hetaryl) in the presence of MeONa is accompanied by intramolecular cyclization following the Camps reaction pattern to give 3-RS-4-arylquinolin-2-ones. Cleavage of 4-aryl-3-(benzoxazol-2-ylthio)quinolin-2-ones by morpholine has resulted in the corresponding 4-aryl-3-mercaptoquinolin-2-ones.

Key words: Camps reaction, 2-(chloroacetamido)benzophenones, thiols, 3-aryl(hetaryl)thioquinolin-2-ones, 4-aryl-3-mercaptoquinolin-2-ones.

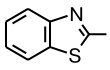
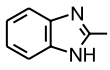
The Camps reaction[1,2] is a convenient method for the synthesis of quinolin-2-ones. An attractive example of this reaction is transformation of *o*-aminoaceto(benzo)phenones to *N*-haloacetyl derivatives followed by replacement of the halogen atom by a functional electron-withdrawing group, which is able to increase the activity of the methylene unit participating in condensation. Using this approach, it is possible to prepare quinolones with a functional group in position 3. For instance, cyclization of the pyridinium salts formed on treatment of 2-chloroacetamidoaceto(benzo)phenones with pyridine resulted in 3-pyridinioquinolin-2-one chlorides, which were treated with aniline to produce 3-aminoquinolin-2-one derivatives.[3] 2-Iodoacetylamino derivatives of aceto(benzo)phenones reacted with morpholine to be converted in two steps into 4-substituted 3-morpholinoquinolin-2-ones.[4] Treatment of 2-iodoacetamidoacetophenone with tetrahydrothiophene, afforded the tetrahydrothiophenium salt, which was transformed at 60 °C to the iodide of the corresponding 3-sulfonium derivative of 4-methylquinolin-2-one.[5]

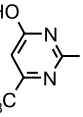
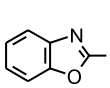
In this study, we report the use of the Camps reaction for the synthesis of 3-alkyl(aryl)- and 3-alkyl(hetaryl)thio-4-arylquinolin-2-ones. It was found that refluxing of 2-(chloroacetamido)benzophenones **1—3** with alkane-, arene-, and hetarenethiols **4a—f** in MeOH in the presence of MeONa gives quinolones **5a,b**, **6a—d**, and **7** in 63—76% yields (Scheme 1). Evidently, the intermediate products formed in the replacement of the Cl atom by the R^3S group easily undergo intramolecular Knoevenagel reaction under the reaction conditions (the initial chlorides **1—3** themselves enter into intermolecular condensation under the action of MeONa to yield pyrazino[1,2-*a*:4,5*a*]diindole-6,13-diones[6]).

Scheme 1



$R^1 = R^2 = H$ (**1**, **5**); R^1 = Cl, R^2 = H (**2**, **6**); $R^1 = R^2$ = Cl (**3**, **7**)

R^3 =  (**4a**, **5a**);  (**4b**, **5b**); Bu (**4c**, **6a**);

4-MeC_6H_4 (**4d**, **6b**);  (**4e**, **6c**);  (**4f**, **6d**, **7**)

Quinolones **5a,b**, **6a—d**, and **7** (Table 1) are white crystalline solids soluble in dioxane, MeOH, DMF, and

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Table 1. Yields, melting points, and elemental analysis data for compounds **5—7**

Compound	Starting benzophenone	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)					Molecular formula
				C	H	N	S	Cl	
5a	**1**	68	276—277 (dioxane)	68.46 / 68.39	3.31 / 3.62	7.01 / 7.25	16.19 / 16.67	—	$C_{22}H_{14}N_2OS_2$
5b	**1**	65	354—356 (dioxane)	71.21 / 71.54	3.92 / 4.07	11.73 / 11.38	8.26 / 8.67	—	$C_{22}H_{15}N_3OS$
6a	**2**	76	245—246 (ethanol)	66.21 / 66.47	5.57 / 5.25	4.09 / 4.08	8.97 / 9.33	9.92 / 10.30	$C_{19}H_{18}ClNOS$
6b	**2**	72	298—299 (dioxane)	69.47 / 69.84	3.98 / 4.23	3.45 / 3.70	8.11 / 8.46	9.68 / 9.25	$C_{22}H_{16}ClNOS$
6c	**2**	64	261—263 (ethanol)	52.97 / 53.33	2.14 / 2.44	8.96 / 9.33	6.69 / 7.11	8.23 / 7.78	$C_{21}H_{12}ClF_3N_2O_2S$
6d	**2**	69	286—288 (dioxane)	65.01 / 65.19	2.92 / 3.21	6.57 / 6.91	7.56 / 7.90	9.06 / 8.64	$C_{22}H_{13}ClN_2O_2S$
7	**3**	63	274—276 (dioxane)	60.49 / 60.14	2.51 / 2.73	5.97 / 6.38	6.96 / 7.29	16.37 / 15.95	$C_{22}H_{12}C_{12}N_2O_2S$

Table 2. Data of ^{1}H NMR, IR, and mass spectra for compounds **5—7**

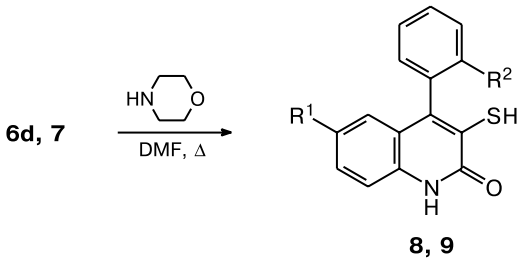
Compound	^{1}H NMR, δ, *J*/Hz (DMSO-d_6)	IR, ν/cm^{-1}	Mass spectrum, *m*/*z*, $[M]^+$
5a	7.10 (m, 2 H, benzothiazolyl); 7.25—7.60 (m, 9 H, C_6H_4, Ph); 7.75, 7.85 (both d, 2 H, benzothiazolyl, *J* = 7.0); 12.30 (s, 1 H, NH)	3420 (NH), 1640 (CO), 1580, 1545	386
5b	7.10, 7.10 (both t, 4 H, 2 H benzimidazolyl and 2 H C_6H_4); 7.40 (m, 4 H, 2 H benzimidazolyl and 2 H C_6H_4); 7.50 (s, 5 H, Ph); 12.10 (s, 1 H, NH)	3410, 3380 (NH), 1645 (CO), 1585	369
6a	0.80 (t, 3 H, Me, *J* = 5); 1.10—1.40 (m, 4 H, 2 CH_2); 2.90 (t, 2 H, SCH_2, *J* = 5); 5.00 (d, 2 H, *o*-H, Ph, *J* = 7.5); 6.75 (s, 1 H, C(5)H); 7.40 (d, 1 H, C(8)H, *J* = 7.0); 7.55 (m, 4 H, C(7)H and Ph); 12.20 (s, 1 H, NH)	3400 (NH), 1645 (CO), 1585	343
6b	2.25 (s, 3 H, Me); 6.85 (s, 1 H, C(5)H); 7.00 (t, 4 H, *p*-H, C_6H_4, *J* = 6.5); 7.30 (d, 2 H, C(7)H, C(8)H, *J* = 7); 7.50 (m, 5 H, Ph); 12.25 (s, 1 H, NH)	3410 (NH), 1640 (CO), 1580, 1550	377
6c	6.60 (s, 1 H, CH pyrimid.); 6.85 (s, 1 H, C(5)H); 7.30 (s, 2 H, C(7)H, C(8)H); 7.55 (t, 3 H, Ph, *J* = 7.5); 7.65 (d, 2 H, Ph, *J* = 7.5); 12.50 (s, 1 H, NH); 12.70—13.70 (br.s, 1 H, OH)	3490, 3430 (NH, OH), 1635 (CO), 1600, 1590	449
6d	6.95 (s, 1 H, C(5)H); 7.30 (m, 2 H, benzoxazolyl); 7.38 (d, 2 H, C(7)H, C(8)H, *J* = 7.0); 7.60 (s, 5 H, Ph); 7.80 (m, 2 H, benzoxazolyl); 12.10 (s, 1 H, NH)	3420 (NH), 1645 (CO), 1570, 1550	404
7	6.92 (s, 1 H, C(5)H); 7.30 (m, 2 H, benzoxazolyl); 7.38 (d, 2 H, C(7)H, C(8)H, *J* = 7.0); 7.55—7.70 (m, 4 H, C_6H_4); 7.75 and 7.77 (both d, 2 H, benzoxazolyl, *J* = 7.0); 12.30 (s, 1 H, NH)	3410 (NH), 1640 (CO), 1585, 1560	438

DMSO. Their mass spectra exhibit molecular-ion peaks; the data of IR and ^{1}H NMR spectra also confirm the structures of the compounds. Indeed, the ^{1}H NMR spectra of quinolones do not contain signals for the $COCH_2$ group of the initial benzophenones **1—3**; however, signals for the R^3S-group protons are observed together with signals for the 4-arylquinolone fragment (Table 2).

The sulfides with structures **5—7** have not been described in the literature. In order to elucidate the strength of the C—S bond, we studied the behavior of these compounds toward nucleophiles, in particular, amines. It was found that butylthioquinolone **6a** and tolylthioquinolone **6b** do not react with primary or secondary amines or with hydrazine on refluxing in DMF. However, treatment of sulfides **6d** and **7**, which contain a benzoxazolyl fragment, with morpholine under the same conditions allowed the synthesis of 4-aryl-3-mercapto-2-quinolones **8** and **9**, difficult to prepare by other methods (Scheme 2).

This process is accompanied by partial resinification and the yields of thiols **8** and **9** do not exceed 30—35%; however, sulfides **6d**, **7** are cleaved regioselectively; GC/MS analysis of the reaction products did not show

Scheme 2



R^1 = Cl, R^2 = H (**8**); R^1 = R^2 = Cl (**9**)

the presence of the corresponding 4-aryl-3-morpholino-2-quinolones, which were expected to form upon the alternative version of the attack by the amine.

Mercaptoquinolones **8** and **9** cannot be prepared by a similar route from other (hetarylthio)quinolones. However, 2-mercaptobenzoxazole is known to be easily converted into 2-aminobenzoxazoles on refluxing with secondary amines in xylene.[7] Presumably, the replacement of the mercapto group is due to the tendency of the oxazole ring, typical of benzoxazoles, to be cleaved upon an attack by an electrophilic reagent.

The structures of thiols **8** and **9** were confirmed by the data of mass and ^{1}H NMR spectra.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument, IR spectra were measured on a Specord M-80 instrument (KBr pellets), and mass spectra were run on a Kratos MS-30 mass spectrometer (EI, 70 eV, temperature of the ionization chamber 250 °C) using direct sample injection.

The starting *N*-chloroacetamido-2-benzophenones **1—3** were prepared by a known procedure.[8]

Synthesis of 3-R^3S-4-aryl-6-R^1-quinolin-2-ones 5a,b, 6a—d, 7 (general procedure). Benzophenone **1—3** (9 mmol) was added to a boiling solution containing MeONa (11 mmol) and a thiol **4** (10 mmol) in 40 mL of MeOH, and the mixture was refluxed for 10 h. The precipitate was filtered off, washed with water, and recrystallized from EtOH or dioxane to give quinolones **5a,b**, **6a—d**, **7**. The yields, melting points, and elemental analysis data are given in Table 1 and the spectral data are in Table 2.

Synthesis of 4-aryl-6-chloro-3-mercaptoquinolin-2-ones (8, 9) (general procedure). A solution of sulfide **6d** or **7** (6.3 mmol) and morpholine (7 mmol) in 5 mL of DMF was refluxed for 2 h and cooled to 15 °C. The precipitate was filtered off, washed with water and acetone, and dried to give 3-mercaptoquinolones **8** and **9**.

6-Chloro-3-mercapto-4-phenylquinolin-2-one (8). Yield 35%. M.p. 352—354 °C. Found (%): C, 62.77; H, 3.36; N, 4.95; S, 10.78; Cl, 11.99. $C_{15}H_{10}ClNSO$. Calculated (%): C, 62.60; H, 3.48; N, 4.86; S, 11.13; Cl. 12.35. MS, *m/z*: 287 $[M]^+$. IR (KBr), ν/cm^{-1}: 3200—2600 (NH, CH), 1670 (CO), 1595. ^{1}H NMR (DMSO-d_6), δ: 6.70 (s, 1 H, C(5)H); 6.85 (d, 2 H, C(7)H, C(8)H, J = 7.0 Hz); 7.22 (t, 2 H, Ph, J = 7.5 Hz); 7.40 and 7.50 (two d, 2 H, *o*-H, Ph, J = 7.6 Hz); 7.60 (t, 1 H, *p*-H, Ph, J = 7.4 Hz); 12.10 (s, 1 H, NH).

6-Chloro-4-(2-chlorophenyl)-3-mercaptoquinolin-2-one (9). Yield 31%. M.p. 335—337 °C. Found (%): C, 55.24; H, 2.60; N, 4.51; S, 9.54; Cl, 21.61. $C_{15}H_9Cl_2NSO$. Calculated (%): C, 55.90; H, 2.79; N, 4.35; S, 9.94; Cl. 22.05. MS, *m/z*: 321 $[M]^+$. IR (KBr), ν/cm^{-1}: 3200—2800 (NH, CH), 1670 (CO), 1590. ^{1}H NMR (DMSO-d_6), δ: 6.65 (d, 1 H, C(8)H, J = 7.0 Hz); 6.90 (d, 1 H, C(7)H, J = 7.0 Hz); 7.20 (s, 1 H, C(5)H); 7.40—7.70 (m, 4 H, C_6H_4); 12.00—12.40 (br.s, 1 H, NH).

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