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A mild and efficient synthesis of 4-aryl-quinolin-2(1*H*)-ones via a tandem amidation/Knoevenagel condensation of 2-amino-benzophenones with esters or lactones

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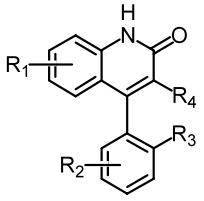
Abstract—Using LiHMDS as the base, a tandem amidation/Knoevenagel condensation of 2-aminobenzophenones with α-methylene esters or lactones gives 4-aryl-quinolin-2(1*H*)-ones in 65–96% yield. This method is mild, highly efficient, and amenable to scaleup.

4-Aryl-quinolin-2(1*H*)-ones **1** are inhibitors of acyl coenzyme A and cholesterol acyltransferase[1] and are potent openers of the high conductance, calcium-activated K^+-channels.[2] These compounds are useful as hypolipidemic, antiatherosclerosis agents and in afflictions arising from dysfunction of cellular membrane polarization and conductance. As part of our research program, we required an efficient synthesis of 4-aryl-quinolin-2(1*H*)-ones. In particular, we were interested in a practical synthesis of compound **7**, which we needed in large quantities.



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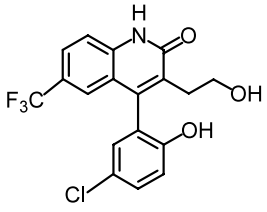

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The most common method for synthesis of quinolines is the Friedlander quinoline synthesis, condensation of 2-amino aryl aldehydes or ketones with α-methylene aldehydes or ketones.[3–5] This methodology has been expanded to synthesize 4-aryl-quinolin-2(1*H*)-ones by condensation of 2-amino aryl aldehydes or ketones with α-methylene esters or carboxylic acids. However, an additional activating group, such as -COR, -COOR, $-CONR_1R_2$, -CN, $-NO_2$, or -COOH, is required at the α-position of the ester or carboxylic acid in order to obtain a good yield of 4-aryl-quinolin-2(1*H*)-ones.[6–8]

It has been reported that with unactivated α-methylene esters or carboxylic acids, such as $PhCH_2COOEt$, the reaction using piperidine as the base at elevated temperature (100–180°C) gave an impure product in poor yield (17%).[8] With *t*-BuOK as the base, the reaction afforded the cyclic hydroxyl intermediate, and $POCl_3$ was required to finish conversion to the expected product.[9] In this communication we describe our efforts toward the mild and efficient synthesis of 4-aryl-quinolin-2(1*H*)-ones via a tandem amidation/Knoevenagel condensation of 2-aminobenzophenones with unactivated α-methylene esters or lactones using LiHMDS.

Under the reaction conditions described in Scheme 1, the tandem amidation/Knoevengel condensation of commercially available or readily prepared 2-amino-benzophenones with α-methylene esters or lactones gave 4-aryl-quinolin-2(1*H*)-ones in good to excellent yields (Table 1).[10] As the proposed reaction path shown in Scheme 2 indicates, 3 equiv. of LiHMDS are required for reaction completion. The first equivalent of LiHMDS deprotonates the aniline NH_2 to activate the nitrogen for amidation with γ-valerolactone. In our

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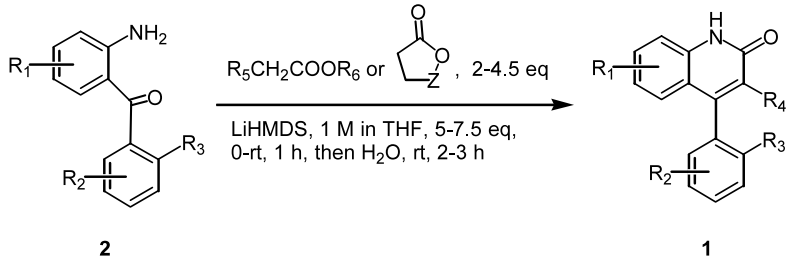
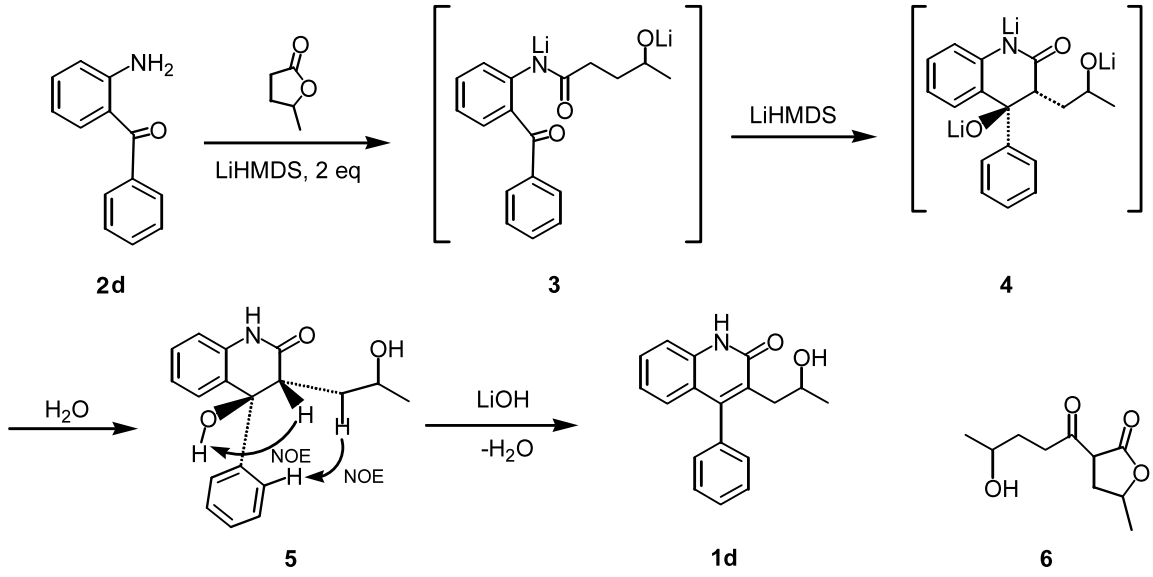


Scheme 1.

Table 1. Synthesis of 4-aryl-quinolin-2(1*H*)-ones **1a–j** from 2-aminobenzophenones **2a–j**

Entry	R_1	R_2	R_3	Ester (R_5, R_6) or lactone (Z) (equiv.)	LiHMDS (equiv.)	R_4	Product	Isolated yield (%)
1	5-Cl	H	H	R_5=H; R_6=Et (2 equiv.)	5	H	**1a**	96
2	5-CF_3	5′-Cl	OMe	R_5=Et; R_6=Et (2 equiv.)	5	Et	**1b**	80
3	5-CF_3	5′-Cl	OMe	R_5=H; R_6=*n*-Bu (2 equiv.)	5	H	**1c**	92
4	H	H	H	Z=CHMe (4.5 equiv.)	7.5	$CH_2CHOHMe$	**1d**	82
5	H	H	H	Z=$(CH_2)_2$ (4.5 equiv.)	7.5	$(CH_2)_3OH$	**1e**	65
6	4-Me	H	H	Z=CHMe (4.5 equiv.)	7.5	$CH_2CHOHMe$	**1f**	76
7	5-Cl	H	H	Z=CHMe (4.5 equiv.)	7.5	$CH_2CHOHMe$	**1g**	93
8	5-CF_3	5′-Cl	OBn	Z=CH_2 (4.5 equiv.)	7.5	CH_2CH_2OH	**1h**	66
9	5-CF_3	5′-Cl	OMe	Z=CH_2 (4.5 equiv.)	7.5	CH_2CH_2OH	**1i**	75
10	5-CF_3	5′-Cl	MOM	Z=CH_2 (4.5 equiv.)	7.5	CH_2CH_2OH	**1j**	90



Scheme 2. Proposed reaction path for the tandem amidation/Knoevenagel condensation.

previous report,[11] we demonstrated that quenching the reaction at this stage by addition of water afforded the amidation products in high yield. The second equivalent of LiHMDS effects deprotonation of the amide NH to form dianion **3**. The third equivalent of LiHMDS is necessary to deprotonate the α-H of the amide, the resulting anion subsequently attacking the carbonyl group to form trianion **4**. Quenching the reaction at this stage by addition of water and rapid extraction afforded the cyclic tertiary alcohol **5**. In another experiment, intermediate **5** was isolated in 72% yield and its structure demonstrated by NOE experiments (Scheme 2). Finally, the *syn* dehydration of **5** by LiOH (during prolonged workup) generated the expected product **1d**. It is noteworthy that in the series of the α-methylene lactones, 7.5 equiv. of LiHMDS and 4.5 equiv. of lactone were necessary, while in the series of α-methylene esters only 5 equiv. of LiHMDS and 2 equiv. of ester were required for reaction completion. This difference could be attributable to the relative propensity for self-condensation of α-methylene lactones and α-methylene esters in the presence of LiHMDS with the former being more reactive. Indeed, the self-condensation product **6** of γ-valerolactone was identified during the

isolation of **5**. The results and equivalents of LiHMDS and the α-methylene esters or lactones are listed in Table 1.

Utilizing the methodology disclosed here, compounds **1h**, **1i** and **1j** were prepared efficiently and readily converted to the quinolin-2(1*H*)-one **7** in good to excellent yield by removal of the protecting groups using the standard methods. Based on this work, we have developed a scalable and highly efficient, five-step synthesis of the target molecule **7** from 4-trifluoromethyl aniline. We will disclose the experimental details in the near future.

In conclusion, a tandem amidation/Knoevenagel condensation of 2-aminobenzophenones with unactivated α-methylene esters or lactones promoted by LiHMDS has been described as a general and practical approach for a mild and efficient synthesis of 4-aryl-quinolin-2(1*H*)-ones.

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10. Representative procedure: A 250 ml, 2-necked flask was charged with **2j** (4.0 g, 11.1 mmol) and THF (10 ml). The resulting solution was cooled to 0°C and LiHMDS (1 M in THF, 83.3 ml) was added over 10 min. The internal temperature was controlled <5°C. The resulting brown solution was stirred at 0°C for 10 min, then γ-butyrolactone (4.3 g, 50.0 mmol) was added over 2 min. The reaction solution was allowed to warm to rt and stirring was continued for 1 h. Water (10 ml) was added over 5 min, and the resulting two-phase solution was stirred at 25°C for 2 h. Ethyl acetate (100 ml) was added. The organic solution was washed with water (30 ml) and brine (50 ml) and dried over anhydrous sodium sulfate. Removal of the solvents gave a residue which was purified by column chromatography on silica gel. The fraction eluted by ethyl acetate/*n*-hexane (1:5) was collected. Removal of the solvents gave 4.3 g (90%, HPLC AP 96) of **1j** as a white solid. HRMS FAB (*m*-NAB) calcd for $C_{20}H_{17}ClF_3NO_4$: $(M+1)^+$ 428.0901; found 428.0876. IR ($CHCl_3$): 3431, 2985, 1654, 1490, 1385, 1326, 1285, 1225, 1127, 1035, 955 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H, NH), 7.78 (d, $J=8.7$, 1H), 7.56 (d, $J=8.2$, 1H), 7.39 (d, $J=8.2$, 1H), 7.39 (s, 1H), 7.35 (d, $J=8.7$, 1H), 7.02 (s, 1H), 5.17 (d, $J=6.8$, 1H), 5.05 (d, $J=6.8$, 1H), 4.55 (b, 1H, OH), 3.43–3.35 (m, 2H), 3.07 (s, 3H); 2.61–2.53 (m, 1H), 2.42–2.38 (m, 1H) ppm; ^{13}C NMR (400 MHz, DMSO-d_6): 161.9, 152.5, 143.8, 140.1, 131.3, 130.3, 130.2, 126.6, 126.1, 125.9, 124.5 (q, $J=271$, CF_3), 122.5, 122.3 (q, $J=32$), 119.6, 116.7, 116.6, 94.3, 59.8, 56.3, 31.8 ppm.
Compound **5**: MS: $(M+H)^+$ 298; ^1H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H, N-H), 7.46–6.929 (m, 9H), 6.15 (s, 1H, OH), 4.57 (s, 1H, OH), 3.85–3.81 (m, 1H), 3.20–3.16 (m, 1H), 1.65–1.53 (m, 2H), 1.05 (d, $J=6.8$, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 143.9, 136.4, 133.2, 128.5, 128.2, 127.2, 126.3, 125.9, 122.8, 115.6, 75.3, 65.4, 49.3, 34.0, 24.7 ppm.
Compound **1c**: MS: $(M+H)^+$ 354; ^1H NMR (400 MHz, DMSO-d_6): δ 12.30 (s, 1H, N-H), 7.92–7.35 (m, 7H), 3.75 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 161.8, 155.3, 147.7, 141.6, 130.7, 126.9, 126.3, 125.0, 124.1, 123.6, 122.7, 122.5, 122.1, 118.3, 117.2, 113.9, 56.2 ppm.
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