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[C_8dabco]Br: a mild and convenient catalyst for intramolecular cyclization of 2-aminochalcones to the corresponding 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

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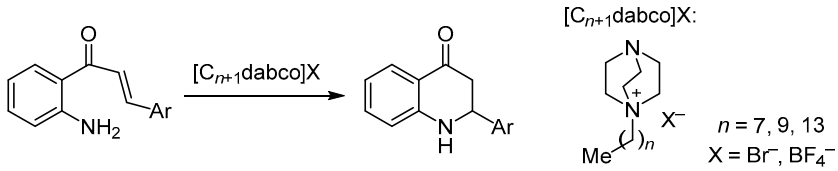


A new and convenient synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones has been described using the intramolecular cyclization of 2-aminochalcones catalyzed by 1-octyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide ([C_8dabco]Br). Recyclability of the catalyst, high yields, simple isolation of the products, and high atom economy are the noteworthy aspects of the protocol.

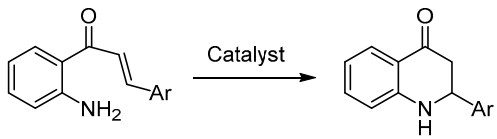
Keywords: 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones, [C_8dabco]Br, ionic liquids, aza-Michael reaction, cyclization.

2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones are valuable precursors[1] for the synthesis of medicinally important substances;[2] these compounds also are common structural intermediates in the biogenesis of naturally occurring flavonoid-type derivatives.[3] Derivatives of 2-arylquinolin-4-ones have displayed interesting biological properties.[4] Over the last years, the interest in 2-arylquinolin-4(1*H*)-ones and their analogs has prompted extensive studies of their properties, such as cytotoxicity against human tumor cell lines and tubulin polymerization inhibition,[5] anticancer activity in the xenograft ovarian OVCAR-3 model, 13% increase in lifespan of mice,[6] hepatoprotective activity,[7] and potential use as scintillator dyes in photooxidative stability as well as antiplatelet agents.[8]

The methodology most widely used to prepare 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones involves the cyclization of the corresponding 2-aminochalcones, bearing substituents in the aromatic rings, by an intramolecular aza-Michael reaction (Scheme 1). This cyclization has been carried out under a variety of conditions: using acids,[9] such as orthophosphoric[10] or sulfuric,[11] zeolites,[12] silica gel,[13] PEG-400,[14] microwave irradiation,[15] chiral Brønsted acids and bases,[16] and others.[17]

Very recently, $InCl_3$,[18] $CeCl_3 \cdot 7H_2O$,[19] and $TaBr_5$[20] immobilized on inorganic solid support have also been

Scheme 1



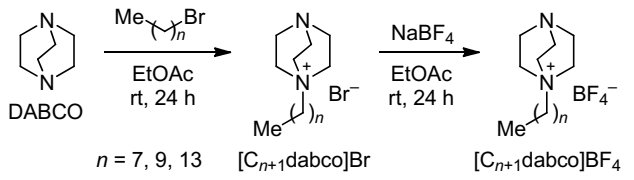
successfully used for such cyclization. Intramolecular cyclization in the presence of basic catalyst such as NaOH[21] is well documented in literature. Other methods like thermolysis,[22] electrolysis,[23] photolysis,[24] as well as use of Ni/Zn/K halides[25] or ZnO-supported metal oxides,[26] were also employed for the cyclization.

However, most of these procedures have limited synthetic utility because of the use of corrosive acids, strong alkalis, hazardous and expensive reagents. Moreover, many of them are of limited synthetic scope because of poor yields, long reaction times, need for large amount of catalyst, high temperature, specialized solvents,[27] some others employ microwave irradiation with solid support.[28] Therefore, the development of new methods that lead to a more convenient procedure and better yield is still desirable.

In the last decade, ionic liquids (ILs) have increasingly found use in various organic transformations due to their tunable chemical and physical properties and catalytic

behavior.[29] In particular, Lewis basic ILs [C_{n+1}dabco]X derived from 1,4-diazabicyclo[2.2.2]octane (DABCO) have proved their catalytic activity[30] and attracted the attention of scientific community due to their easy preparation from commercially available and relatively inexpensive starting materials. Besides, Carlo Pretti et al. have reported that acute toxicity and biodegradability of DABCO-based ILs are comparable with those of biodegradable functionalized imidazolium-based ILs.[31] The synthesis and general structure of DABCO-based ILs used in this work are shown in Scheme 2.

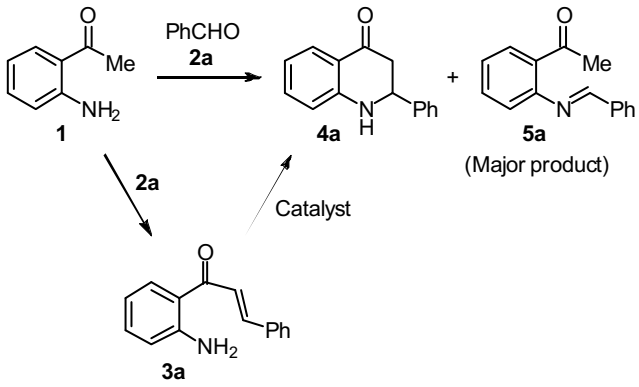
Scheme 2



In this paper we would like to report an efficient process for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-one derivatives by employing Lewis basic DABCO-based ILs as efficient and recyclable catalysts.

We first investigated the possibility of synthesizing 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (**4a**) directly from 2-aminoacetophenone (**1**) and benzaldehyde (**2a**) in one step, using different reaction conditions including the use of acids or bases ($Bi(OTf)_3$, $SbCl_3$, and Et_3N) as catalysts. However, the desired product **4a** was formed in very poor yield (<10%); the efforts made so far to improve the yields of compound **4a** have failed and furnished the corresponding imine **5a** as the major product with yields up to 90% (Scheme 3).

Scheme 3



This prompted us to explore an alternative strategy based on the intramolecular cyclization of 2-aminochalcone **3a** which was initially carried out under catalyst-free conditions using MeCN as the solvent. However, also in this case the reaction was very slow, and the yields of dihydroquinolinone **4a** were also very poor (Table 1, entry 1). In order to improve the yield, the same reaction was initially examined in the presence of a series of acidic or basic catalysts traditionally used for such cyclization. In all cases, the desired product **4a** was obtained in moderate to fair yields and the reactions gave complex mixtures including starting material **3a** (entries 2–8).

Table 1. Conditions of aza-Michael cyclization of 2-aminochalcone **3a** and yields of dihydroquinolinone **4a***

Entry	Catalyst	Amount of catalyst, mol %	Solvent	Time, h	Yield, %
1	–	–	MeCN	24	Traces
2	$ArB(OH)_2$	10	MeCN	24	10
3	$(NH_4)_2Ce(NO_3)_6$	10	DMF	24	15
4	$Bi(OTf)_3$	10	MeCN	24	0
5	$POCl_3$	10	DMF	24	10
6	Et_3N	10	MeCN	24	Traces
7	Piperidine	10	10% aq KOH	24	Traces
8	PPh_3	10	PhMe	24	0
9	[C_{14}dabco]Br	100	–	4	65
10	[C_{14}dabco]BF_4	100	–	4	61
11	[C_{10}dabco]Br	100	–	3	80
12	[C_{10}dabco]BF_4	100	–	3	67
13	[C_8dabco]Br	100	–	2	90 88 (85)**
14	[C_8dabco]BF_4	100	–	2	83

* Load of 2-aminochalcone **3a** – 1 mmol; reaction temperature: reflux (for entries 1–8) or 150°C (for entries 9–14).
** Yields with recovered (twice recovered) catalyst.

We have observed that there are few reports in the literature on the use of ionic liquids in the synthesis of dihydroquinolinones.[32] Hence, we decided to investigate catalytic performance of a series of DABCO-based ILs in the preparation of the target compounds (Scheme 3).

For this purpose, IL [C_{14}dabco]Br was used as the catalyst, and we were pleased to see that the reaction under solvent-free conditions proceeded efficiently, resulting after 4 h in good yield of the desired product **4a** (entry 9). The effect of using other ILs on the reaction was also investigated. The [C_{14}dabco]BF_4, too, showed a good activity, but lower yield (entry 10). [C_{10}dabco]BF_4 gave similar results (entry 12), whereas [C_{10}dabco]Br was found to be more active, affording the corresponding dihydroquinolinone **4a** in very good yield (entry 11).

However, when [C_8dabco]Br and [C_8dabco]BF_4 were used, excellent yields of 90 and 83% respectively has been achieved (entries 13, 14). Therefore, [C_8dabco]Br was identified as the most effective IL catalyst, and was thus chosen as the model catalyst for further investigation. This shows that all the DABCO-based ILs can very efficiently catalyze the cyclization of 2-aminochalcones, when 100 mol % of the catalyst was used. Reduction of the concentration of the catalyst from 100 to 50 or 20 mol % resulted in decreasing yield of cyclized product.

It is well known that the stability and reusability of the catalyst system are the two key factors that determine its potential of practical application in industry. To test the catalyst recyclability, the reaction was carried out under identical conditions in the presence of a catalytic amount of [C_8dabco]Br. The catalyst was recovered after the product was separated out from the reaction mixture by distillation

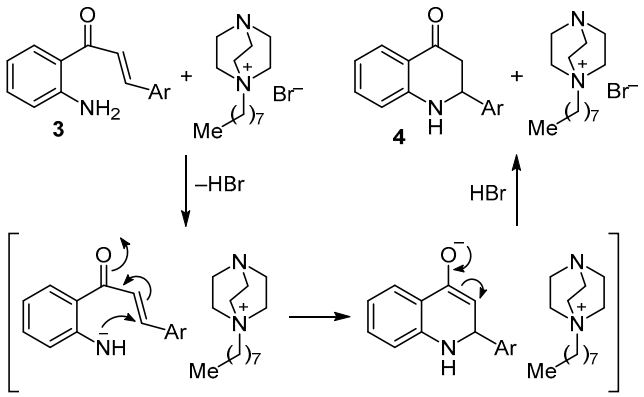
under reduced pressure and then used for the next run without further purification under the same conditions. The results as listed in Table 1 indicate that no significant drop in the yield of compound **4a** was detected after three successive cycles (entry 13).

Having successfully optimized the reaction conditions by using [C_8dabco]Br as catalyst, we investigated the scope of this intramolecular cyclization by utilizing various chalcones **3a**–**m** as substrates. As shown in Table 2, electron-rich and electron-poor 2-aminochalcones **3a**–**m**, including *ortho*-substituted ones, were converted into the corresponding dihydroquinolinones **4a**–**m** in good to excellent yields. In general, electron-donating amino-chalcones reacted better and gave the desired products **4a**–**f** in excellent yields. Functionalized chalcones bearing electron-withdrawing substituents, such as chloro, bromo, fluoro, or nitro, were readily transformed into the corresponding condensation products **4g**–**m** albeit in moderate to good yields.

The structures of the products were established from their spectral properties (IR, ^{1}H and ^{13}C NMR) and also by comparison with available literature data.[32,33] In the case of compounds **4f**,**i**, suitable single crystals could be obtained, and their structures were additionally confirmed by the single crystal X-ray diffraction data (Figs. 1, 2).

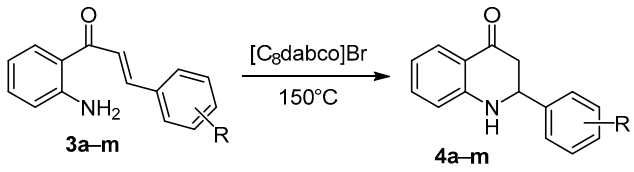
A plausible reaction mechanism can be envisioned for the ring closure of aminochalcones. Being quite strong bases,[34] the ionic liquid would deprotonate the amine group in compounds **3** to give the intermediate species. It is expected that enhanced nucleophilicity of amino group and ability of ionic liquid to stabilize the formation of charged species are probable reasons for the increased reaction rate. It is expected also that this activates the nucleophilic attack at β-carbon inducing the cyclization. Products **4** were obtained by tautomerization of the corresponding intermediates (Scheme 4).

Scheme 4



In conclusion, a very efficient method has been developed for the synthesis of substituted dihydroquinolinones catalyzed by [C_8dabco]Br under conventional heating. This method has several advantages, such as high conversion level, simplicity in operation, cost efficiency, and use of an ionic liquid as catalyst and solvent, which significantly contribute to the practice of green chemistry. The use of

Table 2. Conditions of aza-Michael cyclization of 2-aminochalcones **3a**–**m** catalyzed by [C_8dabco]Br, yields and mp of obtained dihydroquinolinones **4a**–**m**



Compound	R	Reaction time, h	Yield, %	Mp, °C
4a	H	2	90	148–150 (148–149)[33a]
4b	4-Me	2	92	150–152 (148–149)[32a]
4c	2-OMe	2	76	128–130 (126–128)[33e]
4d	4-OMe	2	83	142–144 (144–146)[33a]
4e	4-NMe_2	3	80	179–181 (183–184)[33b]
4f	4-Ph	2	86	186–188
4g	2-Cl	2	75	143–145 (146–147)[33b]
4h	4-Cl	3	73	170–172 (170–172)[33a]
4i	3,4-Cl_2	2	72	204–206 (205–208)[33b]
4j	4-Br	3	76	160–162 (160)[33d]
4k	4-F	3	81	134–136 (134)[33c]
4l	3-NO_2	3	70	160–162 (159–160)[32b]
4m	2-Cl-5-NO_2	2	82	168–170

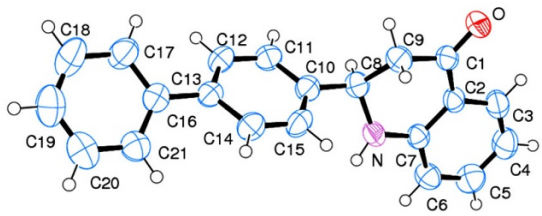


Figure 1. Molecular structure of compound **4f**. Thermal ellipsoids are shown at the 50% probability level.

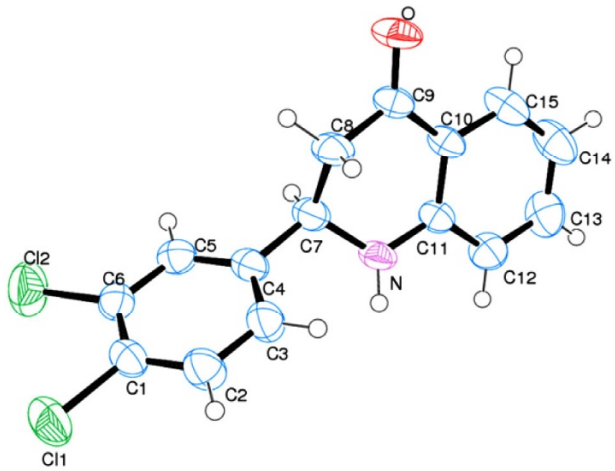


Figure 2. Molecular structure of compound **4i**. Termal ellipsoids are shown at the 50% probability level.

ionic liquid as a non-volatile medium, simple work-up, neutral reaction conditions, and high yields of the products make our methodology a valid contribution to the existing processes in the field of dihydroquinolinone synthesis.

Experimental

IR spectra were obtained on a Shimadzu FT IR 8201 PC spectrophotometer in KBr, only significant absorption band frequencies are listed. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-250 Avance spectrometer (250 and 63 MHz, respectively, compound **4f**) and on a Bruker Avance 400 instrument (400 and 100 MHz, respectively, compound **4m**), solvent – $CDCl_3$, internal standard – TMS. High-resolution mass spectra were recorded with a MicroTof-Q 98 mass spectrometer using electrospray ionization method. Elemental analyzes were performed on a CHN ThermoScientific Flash 2000 apparatus. Melting points were determined on an Electrothermal capillary fine control apparatus and are uncorrected. Column chromatography was carried out using silica gel 60 (Merck, 230–400 mesh ASTM). TLC was performed on Merck aluminum plates coated with silica gel 60, layer thickness 0.2 mm, eluent hexane–EtOAc, 4:1. The chemicals were used as obtained commercially.

Synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones 4a–m (General method). 2-Aminochalcone **3a**–**m** (0.5 mmol) was added to a stirred solution of ionic liquid [C_8dabco]Br (153 mg, 0.5 mmol). The reaction mixture was heated at 150°C for 2–3 h, and the reaction progress was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, then poured into water. The product was recovered by extracting several times with Et_2O and evaporation of the ether extracts. The residue was percolated through a band of silica gel (60–120 mesh) using hexane–EtOAc, 9:1, as an eluent to afford the respective product **4a**–**m**. The catalyst was recovered by evaporation of the aqueous layer under reduced pressure and then used for the next run without further purification under the same conditions. Alternatively, the reaction mixture was directly applied on a silica gel column and eluted with hexane–EtOAc, 9:1, to afford the pure products. Selected spectroscopic data and analytical data are presented below.

2-(Biphenyl-4-yl)-2,3-dihydroquinolin-4(1*H*)-one (4f). Yellow solid, mp 186–188°C. IR spectrum, ν, cm^{-1}: 3302 (NH), 1656 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.93 (1H, d, *J* = 7.9, H Ar); 7.67–7.35 (10H, m, H Ar); 6.84 (1H, td, *J* = 7.2, *J* = 0.8, H Ar); 6.77 (1H, d, *J* = 8.2, H Ar); 4.83 (1H, dd, *J* = 13.1, *J* = 4.3, 2-CH); 4.60 (1H, s, NH); 3.02–2.80 (2H, m, 3-CH_2). ^{13}C NMR spectrum, δ, ppm: 193.4; 151.7; 141.6; 140.1; 135.6; 129.0; 127.8; 127.7; 127.6; 127.2; 119.2; 118.6; 116.1; 58.3; 46.5. Found, *m*/*z*: 322.1233 $[M+Na]^+$. $C_{21}H_{17}NNaO$. Calculated, *m*/*z*: 322.1208. Found, %: C 84.49; H 5.93; N 4.89. $C_{21}H_{17}NO$. Calculated, %: C 84.25; H 5.72; N 4.68.

2-(2-Chloro-5-nitrophenyl)-2,3-dihydroquinolin-4(1*H*)-one (4m). Yellow solid, mp 168–170°C. IR spectrum, ν, cm^{-1}: 3315 (NH), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.54 (1H, d, *J* = 2.4, H Ar); 8.04 (1H, dd, *J* = 8.8, *J* = 2.8, H Ar); 7.76 (1H, dd, *J* = 8.0, *J* = 1.6, H Ar); 7.51 (1H, d, *J* = 8.8, H Ar); 7.31 (1H, td, *J* = 8.0, *J* = 1.6, H Ar); 6.78–6.74 (2H, m, H Ar); 5.21 (1H, dd, *J* = 12.0, *J* = 3.6, 2-CH); 4.64 (1H, s, NH); 2.90–2.60 (2H, m, 3-CH_2). ^{13}C NMR spectrum, δ, ppm: 190.7; 150.1; 149.8; 146.1; 139.7; 138.3; 134.8; 130.0; 126.5; 123.0; 121.8; 118.3; 115.4; 53.4; 42.8. Found, *m*/*z*: 325.0378 $[M+Na]^+$. $C_{15}H_{11}ClN_2NaO_3$. Calculated, *m*/*z*: 325.0356. Found, %: C 59.65; H 3.66; N 9.05. $C_{15}H_{11}ClN_2O_3$. Calculated, %: C 59.52; H 3.66; N 9.25.

X-ray structural study of compounds 4f,i. The crystals of compounds **4f**,**i** for X-ray study were obtained by slow crystallization from EtOH. The data collection for crystallographic analysis were performed on a Bruker APEXII diffractometer with mirror MoKα radiation (λ 0.71073 Å) at room temperature. The structure was solved by direct methods and refined by full-matrix least-squares methods with SHELXL-97 programs.[35] Crystallographic data (excluding structure factors) for compounds **4f**,**i** have been deposited at the Cambridge Crystallographic Data Center (deposits CCDC 997180 and CCDC 997181, respectively).

Supplementary information file to this article containing selected spectral and analytical data of the synthesized compounds is available online at http://link.springer.com/journal/10593.

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