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Advantageous use of ionic liquids for the synthesis of pharmaceutically relevant quinolones

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Abstract

The advantageous use of Ionic Liquids (ILs), as alternatives to common DMF as solvent in the Grohe cycloaracylation, for the synthesis of pharmaceutically relevant quinolones is reported. ILs showed in many cases lower reaction times and higher yields, complete conversions of the reactants, easy workup procedures compared to DMF. Among the ILs, tributylmethylammonium methanesulfonate [TBMA][MsO] was selected as the most suitable for additional studies. Interestingly, a wide substrates scope was observed and a green re-cycling process of the IL was realized. A further step forward in the use of [TBMA][MsO] for quinolone synthesis, was the preparation in a one-pot/three-steps procedure of the representative 3-carboxy-4-quinolone acid **16**, which was obtained in high yields and short time. The greener properties of ILs in comparison to DMF and their non-volatility appoint this method as potentially efficient and an alternative way for the industrial production of quinolones.

Introduction

Ionic Liquids (ILs) are a remarkable class of organic solvents composed by organic and/or inorganic ions.[1] Due to their molecular structures, ILs have peculiar properties such as high thermal stability, high electric conductivity, low vapour pressure.[2–4] One of the most relevant topics where ILs have been finding fruitful application is their use as solvents and/or catalysts for chemical reactions.[5–8] There are many different advantages on the use of ILs in chemical synthesis such as milder reaction conditions, higher yields, easier reaction workups that anyhow represent a non-exhaustive list of them. Moreover, in some cases the synthesis in ILs permitted to obtain products otherwise non-obtainable in other common organic liquids.[9] There is also an ecological advantage that must be considered regarding these salts: the non-volatility of ILs is a key-factor for their use as environmental-friendly alternatives of organic solvents.[10–12]

In the last 15 years, many research groups have reported the use of ILs in different chemical processes related to the production of pharmaceuticals including precursors or intermediates and in most cases ILs are used as reaction media. So far, the synthesis of several non-steroidal anti-inflammatory drugs, antiviral, antimicrobial, anti-malarial, and anti-tumor agents, as well as cholinesterase inhibitors and radiolabelled molecular imaging and therapy agents, have been described.[13]

Although the numerous advantages associated with the use of ILs, in recent years, some critical aspects emerged with regards to toxicity, biodegradability and their potential role as persistent environmental pollutants.[14–18] In particular, ILs have been considered similar to poly chlorinated biphenyls because they produce similar effects on aquatic environment.[19] However, no exhaustive studies have been reported so far and this means that aspects related to toxicity and biodegradability of ILs deserve further investigations. In order to reduce the potential environmental impact of ILs, a recent review reported some recommended guidelines to produce greener ILs and to choose the suitable IL for a desired application.[20]

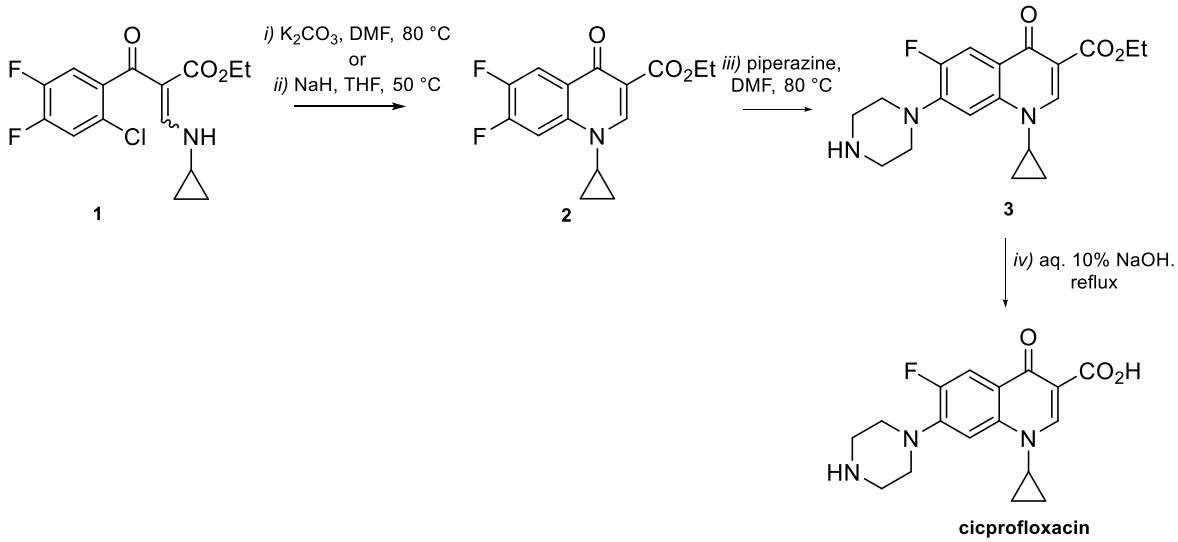
3-Carboxy-4-quinolone nucleus has been extensively developed to obtain anti-bacterial drugs targeting DNA gyrase,[21] prokaryotic counterpart of topoisomerse II, and besides the canonical anti-bacterial activity, several studies have highlighted the versatile nature of this chemical class.

Indeed, suitable functionalization of the quinolone scaffold has allowed the shifting from bacterial uses towards other therapeutic areas such as viral infections and cancer.[22,23] Eviltegravir is a quinolone able to inhibit the HIV integrase approved in 2012 by the FDA as antiretroviral drug;[24] furthermore, we and other groups reported anti-HIV[25] and anti HCV quinolones.[26–28] Vosaroxin (also called voreloxin) is a mammalian topoisomerase II inhibitor currently in phase III of clinical development for cancer therapy.[29] More recently, the old antibacterial drug enoxacin has been described as new antitumor agent endowed with a novel epigenetic mode of cell differentiation regulation.[30]

Due to the wide therapeutic employment of quinolones and the great value in pharmaceutical and biological chemistry, the development of general and more efficient methods for the construction of 4-quinolone nucleus and its functionalization has attracted considerable interest. One of the typical synthetic routes to these heterocycles is the Grohe method, known also as cycloaracylation procedure,[31] applied for the preparation of ciprofloxacin, one of the most employed antibacterial agents. The Grohe's procedure is based on the intramolecular nucleophilic aromatic substitution of an ethyl *N*-monosubstituted 3-amino-2-benzoyl acrylate intermediate (e.g. **1**[31]) that cyclizes to afford the quinolone nucleus (intermediate **2**[31]) (Scheme 1 – synthesis of ciprofloxacin as representative example). Classic reaction conditions are *i)* the use of a base such as K_2CO_3 in high-boiling dipolar aprotic solvents (e.g. DMF, DMSO) at 80-100 °C or *ii)* NaH in apolar solvents (THF or toluene) at 40-60 °C. The subsequent functionalization at C-7 position usually employs a cyclic amine (e.g. piperazine) which provides intermediate **3** through intermolecular nucleophilic displacement in dipolar aprotic solvents (e.g. DMF, DMSO, NMP) at 80-100 °C. The intermediate **3** is then hydrolized by basic or acid conditions into the corresponding carboxylic acid ciprofloxacin (Scheme 1).[32]

To the best of our knowledge no publications has been reported on the use of ILs for the synthesis of pharmaceutically relevant quinolones although ILs have been used in previous works for the synthesis of similar compounds,[33] or as extracting agents of quinolone molecules from biological matrixes.[34]. In this work we aimed to explore the synthesis 3-carboxy-4-quinolones using ILs as

reaction media in place of DMF usually employed during the synthetic procedures. More precsisely,



Scheme 1. Classic example of synthesis of the antibacterial ciprofloxacin based on the Grohe method.

At first we explored the use of ILs as reaction media in place of DMF for the cyclization step of the Grohe's procedure. A set of differently structured ILs have been analysed and studied as reaction media: 1-butyl-3-methylimidazolium methanesulfonate ([BMIM][MsO]), 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]), tributylmethylammonium methanesulfonate ([TBMA][MsO]), and tributylmethylammonium bromide ([TBEA][Br]).[35][36] They were selected because they are all water-soluble quaternary ammonium/imidazolium salts having inert anions thus permitting to evaluate the effects of different cations and anions.

Furthermore, we proposed the synthesis of a representative 3-carboxy-4-quinolone acid carrying out the entire process in a selected IL medium.

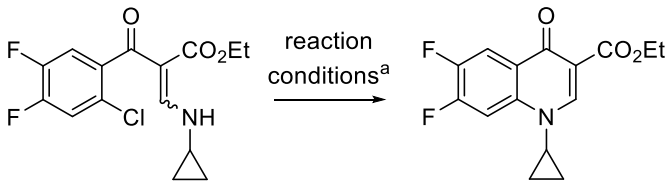
Results and Discussion

The first step of the work was to explore the cyclization of acrylate intermediate **1**[31] into the corresponding quinolone **2**[31] using the aforementioned ILs in absence/presence of K_2CO_3 at 80 °C (Table 1 – entries 1-4 and 6-9). The screening of the ILs was carried out in parallel and in

comparison to the same reaction performed in DMF (Table 1 – entries 5 and 10). In absence of the base, no reaction was detected both using ILs and DMF, as reaction media (entries 1-5). Adding K_2CO_3, regardless of the reaction medium, total conversion of acrylate **1** into the desired quinolone **2** was observed (entries 6-10). Aqueous work-up afforded pure powders of compound **2** from all the reaction mixtures with the different ILs. The use of [BMIM][MsO] (entry 6) or [TBMA][MsO] (entry 8) gave similar results, affording derivative **2** in high yields (78 and 80%, respectively) and shorter reaction time (2 h) in comparison to DMF (65%, 6 h - entry 10), the classic solvent for this reaction. Lower yields were observed carrying out the reaction in [BMIM][BF_4] (50% - entry 7) or in [TBEA][Br] (50% - entry 9), in the last case coupled with longer reaction time (6h – entry 9).

The higher yields and the shorter reaction times obtained using the ILs with mesylate anion could be explained with a better solubility of the base in such media with respect to tetrafluoroborate or bromide ILs, as already observed in a previous study.[37]

Table 1. Screening of ILs as reaction media for cycloaracylation.



1 **2**

Entry	Reaction medium	Base	Time (h)	Yield (%)
1	[BMIM][MsO]	No base	ND[b]	ND[b]
2	[BMIM][BF_4]	No base	ND[b]	ND[b]
3	[TBMA][MsO]	No base	ND[b]	ND[b]
4	[TBEA][Br]	No base	ND[b]	ND[b]
5	DMF	No base	ND[b]	ND[b]
6	[BMIM][MsO]	K_2CO_3 (2 eq.)	2	78
7	[BMIM][BF_4]	K_2CO_3 (2 eq.)	2	50
8	[TBMA][MsO]	K_2CO_3 (2 eq.)	2	80
9	[TBEA][Br]	K_2CO_3 (2 eq.)	6	50
10	DMF	K_2CO_3 (2 eq.)	6	65

[a] solvent (0.5 mL), 80 °C. [b] ND = not determined because no reaction was observed

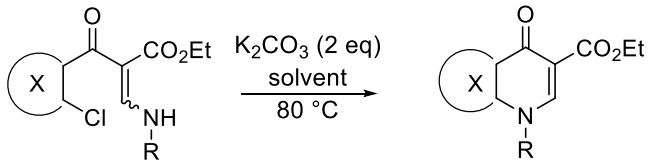
This first survey indicated [BMIM][MsO] and [TBMA][MsO] as suitable replacer of DMF for the cyclization of acrylate into quinolone for the high yields and the short reaction times observed. However, [TBMA][MsO] was chosen between these two ILs to proceed in the next steps of our studies for different reasons: (*i*) the cost of the reagents for the preparation of [TBMA][MsO] is lower than the one of [BMIM][MsO] and the former was prepared by nucleophilic substitution between tributylamine and methylmethanesulfonate in acetonitrile considered as a usable solvent concerning the environmental impact;[36] (*ii*) the stability of [TBMA][MsO] is higher than [BMIM][MsO] under the employed conditions since the C-2 hydrogen in imidazolium cation could lead to unwanted side-reactions with K_2CO_3 at high temperatures in longer reaction times as observed in precedent work;[37] (*iii*) [TBMA][MsO] partially fits the general guidelines proposed by Bubalo et al.[20] In fact, the core differs from an imidazolium which is not recommended for both toxicity and biodegradability, while the mesylate anion is tolerated and in addition the medium size of alkyl chain appears more advantageous in terms of biodegradability although not suitable for toxicity.

Then, in order to explore the scope of the reaction, a set of acrylate intermediates differently functionalized at the arene ring (**3**,[38] **4**,[39] **5**,[40] and **6**[41] – entries 1-4 – [TBMA][MsO] – Table 2) or at the acrylic nitrogen (**7**[42] and **8**[43] – entries 5 and 6 – [TBMA][MsO] – Table 2) were cyclized in [TBMA][MsO] as reaction medium, in presence of K_2CO_3 at 80 °C (Table 2). Also in this case, the results were compared to those derived from parallel reactions conducted in DMF (entry 1-6 – DMF – Table 2). Overall, [TBMA][MsO] resulted a good choice for the cyclization of all the acrylates **3-8** into the corresponding quinolones **9**,[38] **10**,[39] **11**,[40] **12**,[41] **13**,[42] and **14**[43] (entries 1-6 – [TBMA][MsO]), obtained in good yields (68-80%) and in short reaction times (2-5 h). In comparison to the cyclization reactions in DMF (entries 1-6 – DMF), in general the use of the IL gave slightly higher yields. Regarding intermediates **3-6** differently substituted at the arene ring, the activated substrates **4** and **5** (entries 2 and 3 – [TBMA][MsO] vs. DMF), as expected, afforded the corresponding quinolones **10** and **11** in the shorter reaction times and with the highest yields. Worthy of note, the use of [TBMA][MsO] as medium afforded compound **9** from the unsubstituted and less activated acrylate **3** after 5 h in 68% yields (entry 1 – [TBMA][MsO]). On the contrary,

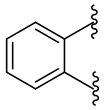
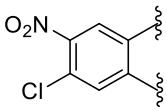
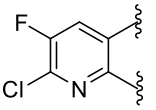
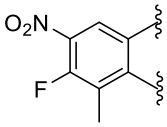
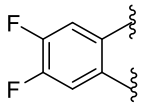
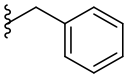
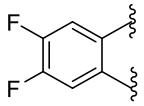
using DMF, only partial conversion of starting material **3** into the desired quinolone **9** was observed after 4 days (entry 1 – [TBMA][MsO]), as checked by TLC (eluent: $CHCl_3$/MeOH 98:2; Rf of compounds **3** and **9** of 0.7 and 0.4, respectively). Regarding intermediate **6**, no significant differences were observed between the IL and DMF. The cyclization of *N*-phenyl **7** and *N*-benzyl **8** acrylates in [TBMA][MsO] (entries 5 and 6 – [TBMA][MsO]) provided comparable results to the reaction carried out in DMF (entries 5 and 6 – DMF) in terms of time and yield.

The results obtained in this second reactions set strongly indicated [TBMA][MsO] as suitable replacer of the classic DMF as medium for the construction of a variety of different functionalized quinolone scaffolds exploiting the cycloaracylation method.

Table 2. Cyclization step of acrylate intermediates **3-8** into quinolones **9-14** using [TBMA][MsO].



3-8 **9-14**

Entry	Cmpd	R	X	Solvent	Time (h)	Yield (%)
1	**3**, **9**			[TBMA][MsO]	5	68
				DMF	-[a]	-[a]
2	**4**, **10**			[TBMA][MsO]	2	77
				DMF	3	77
3	**5**, **11**			[TBMA][MsO]	2	80
				DMF	2	53
4	**6**, **12**			[TBMA][MsO]	4	71
				DMF	2	66
5	**7**, **13**			[TBMA][MsO]	4.5	75
				DMF	5	73
6	**8**, **14**			[TBMA][MsO]	5.0	80
				DMF	5	80

[a] After 4 days only partial conversion of starting acrylate **3** was observed by TLC

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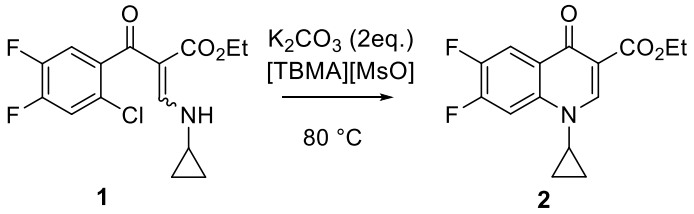
In order to investigate the re-usability of [TBMA][MsO] as solvent, three cycles of cycloaracylation were realized using intermediate **1** as representative starting compound. At first, a method as greener as possible was designed to recover the IL after the first reaction cycle entailing the use of EtOH as washing solvent of the evaporated aqueous mixture of [TBMA][MsO] and inorganic salts which was obtained after the aqueous work-up, before mentioned. In particular, after precipitation of quinolone intermediate **2** in aqueous medium, water was evaporated to dryness to give a slurry containing the IL, the excess of K_2CO_3, and the formed KCl. EtOH was then used to separate the soluble [TBMA][MsO] from the large part of inorganics and the IL was recovered by EtOH evaporation. Through this procedure, [TBMA][MsO] was used for additional two cycles and for a total of three cyclizations. Interestingly, quinolone **2** was obtained with a total conversion, comparable reaction times and yields, and no side products were observed by TLC employing re-cycled IL in comparison to the first reaction using fresh IL (Table 3, see also Table 1, entry 8 for comparison). This result showed that the re-usability of [TBMA][MsO] for cycloaracylation can be realized with low costs and reduced environmental impact.

Table 3. Re-cycling of [TBMA][MsO] in the cyclization of acrylate **1** into quinolone intermediate **2**



1 **2**

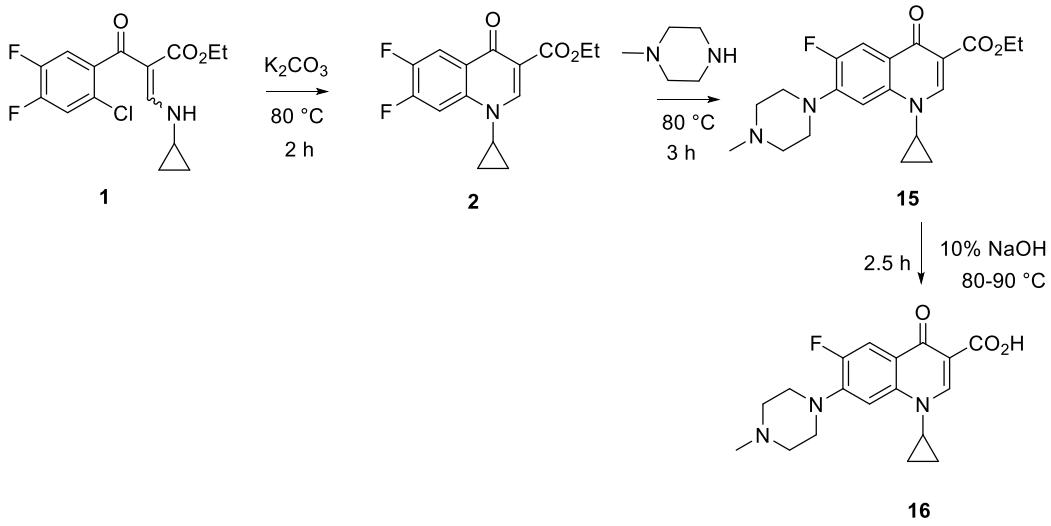
Entry	Cycle	Time (h)	Yield (%)[a]
1	1st	2	80
2	2nd	2	81
3	3rd	2	77

[a] Total conversion no side products were observed by TLC

Finally, the entire process (i.e., ring closure, aromatic nucleophilic substitution, and saponification of the 4-carboxylic ester), performed in [TBMA][MsO] as solvent, was applied to synthesize compound **16**.[31] This latter is also known as UB-8902 and is an old fluoroquinolone recently explored against multiresistant bacteria such as *Acinetobacter baumannii.*[44,45] First, starting

acrylate **1** was cyclized into the corresponding quinolone intermediate **2**, in presence of K_2CO_3 at 80°C for 2 h. After total conversion of starting material, methylpiperazine was added to give, after 3 h, the C-7 functionalized derivative **15**, which was obtained after aqueous work-up and filtration in good yield (overall yield = 72%). For comparison, these first two steps were carried out also in DMF and resulted in longer reaction time (24 h) and lower yield (40%). Therefore, the use of [TBMA][MsO] resulted advantageous in comparison to DMF.

The hydrolysis of the ethyl ester was explored in the same reaction medium without isolation of derivative **15**. Obviously, this attempt was performed only in the IL while it is not possible using DMF. Therefore, the first two steps of this procedure in [TBMA][MsO] were replicated and when ethyl ester intermediate **15** was obtained, aq. 10% NaOH was added to the mixture to provide target acid **16**, after 2.5 h. Worthy of note the desired acid **16** was obtained, after simply aqueous work-up and filtration, in 65% overall yield (over 3 steps) and short time (7.5 h for the entire process).



Scheme 2. Synthesis of target quinolone **16** performed in the same medium, using [TBMA][MsO], in a one-pot/three steps procedure.

Worth noting, all the procedure described have been realized avoiding the use of highly toxic organic solvents and work-up of reactions as well as IL recycling have been carried out by green procedures thus allowing the synthesis of desired quinolones outside the fume hood.

Conclusions

In this work we explored the use of ILs instead of the classic DMF as reaction medium in the Grohe cycloaracylation procedure for the synthesis of representative compounds based on the pharmaceutically relevant 4-quinolone scaffold. In particular, ILs demonstrated to be suitable replacers of DMF in the cyclization step to build the quinolone nucleus, demonstrating in most cases higher yields and shorter reaction times; among the ILs screened, [TBMA][MsO] was selected for further applications because of its favourable balance between results (times and yields) and environmental impact. Importantly, we demonstrated that [TBMA][MsO] can be recycled several times during the cyclization step increasing the "greenness" of the procedure. Furthermore, we advantageously carried out the entire synthetic process using [TBMA][MsO] as medium to obtain a 3-carboxy quinolone in the same reaction mixture in a one-pot/three steps procedure.

The greener properties of ILs compared to DMF and their non-volatility, promote this method as an efficient and green way to synthesise quinolones from benzoylacrylate intermediate via Grohe reaction. The developed procedure can be used as an alternative way for the industrial production of quinolones and it also meets several principles of green chemistry, such as: a) atom economy; b) less hazardous chemical synthesis; c) safer solvents and auxiliaries; d) reduction of derivatives; e) inherently safer chemistry for accident prevention; f) use of renewable feedstocks, g) prevention of waste.[46]

Materials and Methods

General chemistry. ILs were synthesized and purified following a previous procedure.[35,36]The other reagents and solvents were purchased from common commercial suppliers and were used as such. All reactions were routinely checked by TLC on silica gel 60F254 (Merck) and visualized by using UV or iodine. Melting points were determined in capillary tubes (Büchi Electrotermal model 9100) and are uncorrected. Yields were of pure products and were not optimized. ^{1}H NMR spectra were recorded at 400 MHz (BrukerAvance DRX 400) while ^{13}C NMR spectra were recorded at 100 MHz (BrukerAvance DRX-400). Chemical shifts are given in ppm (δ) relative to

TMS. Spectra were acquired at 298 K. Data processing was performed with standard Bruker software XwinNMR and the spectral data are consistent with the assigned structures. The purity of the compounds was assesed by UHPLC using an Agilent 1290 series machine equipped with DAD detector from 190 to 640 nm and the purity was estimated by peaks integration at 254 nm. A Phenomenex Luna C18 polar (2.1 mm × 100 mm, 1.7 µm particle size) column was used with gradient of 0-100% acetonitrile with 0.1% formic acid (channel B) in water with 0.1% formic acid (channel A) for 15 min (time 0 min A = 99.5%, time 6 min A=80%, time 12 min A=0%, time 15 min stop run) at 0.3 mL/min. Injection volume was of 1.0 µL and column temperature of 40 °C. Peaks retention time are given in minutes.

General procedure of cyclization of compound 1 employing ILs. A mixture of the starting acrylate intermediate **1** (100 mg, 0.3 mmol) and K_2CO_3 (83.5 mg, 0.6 mmol) in the opportune hot IL (0.5 mL) was heated at 80 °C until the disappearance of the starting material. After cooling, the reaction mixture was poured into ice/water to give a precipitate that was filtered under vacuum and crystallized by EtOH to afford the desired quinolone as white solid. In particular, by using: i) [BMIM][MsO], the reaction time was of 2h and the yield was of 78% (entry 6, Table 1); ii) [BMIM][BF_4], the reaction time was of 2h and the yield was of 50% (entry 7, Table 1); iii) [TBMA][MsO], the reaction time was of 2h and the yield was of 80%; and iv) [TBEA][Br], the reaction time was of 6h and the yield was of 50%.

Ethyl 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (2). m.p.: 225-226 °C (litt.:[31] 227 °C). ^{1}H NMR (400 MHz, [D_6]DMSO): δ=8.43 (s, 1H, H-2), 8.08 (dd, J = 12.1, 6.8 Hz, 1H, H-5), 8.00 (dd, J = 10.7, 8.9 Hz, 1H, H-8), 4.19 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 3.62-3.53 (m, 1H, cyclopropyl-CH), 1.26-1. (m, 5H, cyclopropyl-CH_2, and OCH_2CH$_3$), 1.10-1.04 ppm (m, 2H, cyclopropyl-CH_2). ^{13}C NMR (100 MHz, [D_6]DMSO): δ=171.74, 164.52, 152.62 (dd, $J_{C\text{-}F}$ = 250.0, 15.0 Hz, C-7), 149.17, 148.03 (dd, $J_{C\text{-}F}$ = 247.0, 14.0 Hz, C-6), 138.20 (d, $J_{C\text{-}F}$ = 8 Hz, C4a), 125.41 (d, $J_{C\text{-}F}$ = 4 Hz, C8a), 113.99 (d, $J_{C\text{-}F}$ = 17 Hz, C-5), 110.38, 107.40 (d, $J_{C\text{-}F}$ = 22 Hz, C-8), 60.32, 35.54, 14.62, 7.98 ppm. HPLC ret. time: 8.95; purity: 97.3%.

Melting point values and the spectral data for the compound obtained from all the reactions are identical and in agreement with those reported in literature.[31]

General procedure of cyclization of acrylate intermediates employing [TBMA][MsO] as suitable IL. A mixture of the starting acrylate intermediate (**3**,**4**,**5**,**6**,**7**, and **8**) (0.3 mmol) and K_2CO_3 (0.6 mmol) in hot [TBMA][MsO] (0.5 mL) was heated at 80 °C until the disappearance of the starting material. After cooling, the reaction mixture was poured into ice/water to give a precipitate that was filtered under vacuum and crystallized by EtOH to afford the desired quinolone as solid.

Ethyl 1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (9). White solid, reaction time: 5h; yield: 68%; m.p.: 165-167 °C (litt.:[38] 167-168 °C). ^{1}H NMR (400 MHz, [D_6]DMSO): *δ*=8.46, (s, 1H, H-2), 8.18 (dd, *J* = 8.0, 1.4 Hz, 1H, H-5), 8.04 (d, *J* = 8.2, 1H, H-8), 7.80 (dt, *J* = 8.2, 1.5 Hz, 1H, H-7), 7.24 (dt, *J* = 8.0, 0.7 Hz, 1H, H-6), 4.18 (q, *J* = 7.2 Hz, 2H, O*CH*$_2$CH$_3$), 3.64-3.59 (m, 1H, cyclopropyl-CH), 1.28-1.19 (m, 5H, cyclopropyl-CH_2, and O*CH*$_2$CH$_3$), 1.07-1.03 ppm (m, 2H, cyclopropyl-CH_2). ^{13}C NMR (100 MHz, [D_6]DMSO): *δ*=173.26, 164.88, 148.80, 140.83, 132.96, 128.09, 126.50, 125.37, 117.90, 110.22, 61.15, 35.05, 14.69, 7.95 ppm. HPLC ret. time: 8.45; purity: 95.9%.

The spectral data are in agreement with those reported in literature.[38]

Ethyl 7-chloro-1-cyclopropyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (10). Yellow solid, reaction time: 2h; yield: 77%; m.p.: >280 °C (litt.:[39] >280 °C). ^{1}H NMR (400 MHz, [D_6]DMSO): *δ*=8.67 (s, 1H, H-5), 8.48 (s, 1H, H-2), 8.25 (s, 1H, H-8), 4.19 (q, J = 4.03 Hz, 2H, O*CH*$_2$CH$_3$), 3.69-3.65 (m, 1H, cyclopropyl-CH), 1.26-1.18 (m, 5H, cyclopropyl-CH_2, and O*CH*$_2$CH$_3$), 1.12-1.08 ppm (m, 2H, cyclopropyl-CH_2). ^{13}C NMR (100 MHz, [D_6]DMSO): *δ*=171.99, 164.14, 150.61, 143.97, 143.60, 129.54, 126.55, 125.03, 121.51, 112.05, 60.72, 35.68, 14.67, 8.17 ppm. HPLC ret. time: 9.38; purity: 96.8%.

The spectral data are in agreement with those reported in literature.[39]

Ethyl 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (11). Whitish solid, reaction time: 2h; yield: 80%; m.p.: 216-217 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=8.54 (s, 1H, H-2), 8.41 (d, J = 7.8 Hz, 1H, H-5), 4.20 (q, J = 7.2 Hz, 2H, O*CH$_2$*CH$_3$), 3.64-3.58 (m, cyclopropyl-CH), 1.17 (t, J = 7.2 Hz, 3H, OCH$_2$*CH$_3$*), 1.13-1.00 ppm (m, 4H, cyclopropyl-CH$_2$). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=172.66, 164.14, 152.08 (d, $J_{C\text{-}F}$ = 256.0 Hz, C-6), 149.71, 146.43, 140.86 (d, $J_{C\text{-}F}$ = 22.0 Hz, C-7), 123.75, 123.37 (d, $J_{C\text{-}F}$ = 20.3 Hz, C-5), 111.56, 60.58, 34.78, 14.60, 7.45 ppm. HPLC ret. time: 9.40; purity: 94.7%.

The spectral data are in agreement with those reported in literature.[40]

Ethyl 1-cyclopropyl-7-fluoro-8-methyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (12). Yellow solid, reaction time: 4h; yield: 71%; m.p.: 197-199 °C (litt.:[41] 198-200 °C). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=8.63-8.57 (m, 2H, H-2, and H-5), 4.23-4.17 (m, 3H, O*CH$_2$*CH$_3$, and cyclopropyl-CH), 2.72 (d, J = 3.2 Hz, 3H, CH$_3$), 1.24 (t, J = 7.1 Hz, 3H, O*CH$_2$*CH$_3$), 1.20-1.10 (m, 2H, cyclopropyl-CH$_2$), 1.00-0.92 ppm (m, 2H, cyclopropyl-CH$_2$). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=171.97, 163.79, 155.40 (d, $J_{C\text{-}F}$ = 257.1 Hz, C-7), 153.81, 146.18 (d, $J_{C\text{-}F}$ = 7.0 Hz, C-8a), 134.48 (d, $J_{C\text{-}F}$ = 12.0Hz, C-6), 125.05 (brs, C4a), 122.84 (brs, C5), 119.96 (d, $J_{C\text{-}F}$ = 19.0 Hz, C8), 111.71, 60.62, 40.56, 14.58, 13.88, 13.56, 6.53 ppm. HPLC ret. time: 9.35; purity: 90.0%.

The ^{1}H NMR spectral data are in agreement with those reported in literature.[41]

Ethyl 6,7-difluoro-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylate (13). White solid, reaction time: 4.5h; yield: 75%; m.p.: 252-254 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=8.43 (s, 1H, H-3), 8.12-8.07 (m, 1H, H-5), 7.70-7.60 (m, 5H, phenyl-H), 6.9 (dd, J = 11.6, 6.6 Hz, 1H, H-8), 4.17 (q, J = 7.1 Hz, 2H, O*CH$_2$*CH$_3$), 1.21 ppm (t, J = 7.1 Hz, 3H, OCH$_2$*CH$_3$*). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=171.92, 164.23, 152.50 (dd, $J_{C\text{-}F}$ = 251.0, 14.0 Hz, C-7), 149.45, 148.00 (dd, $J_{C\text{-}F}$ = 246.4, 13.7 Hz, C-6), 140.40, 138.10 (d, $J_{C\text{-}F}$ = 9.0 Hz, C-8a), 130.91, 130.66, 127.86, 125.09 (brs, C-4a), 114.20 (d, $J_{C\text{-}F}$ = 19.0 Hz, C-5), 110.80, 107.56 (d, $J_{C\text{-}F}$ = 23.3 Hz, C-5), 60.49, 14.57 ppm. HPLC ret. time: 9.34; purity: 93.7%.

The spectral data are in agreement with those reported in literature.[38]

Ethyl 1-benzyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (14). White solid, reaction time: 5h; yield: 80%; m.p.: 208-210 °C (litt.:[43] 208-209 °C). ^{1}H NMR (400 MHz, [D_6]DMSO): δ=8.89 (s, 1H, H-2), 8.08-8.03 (m, 1H, H-5), 7.80 (dd, J = 12.09, 6.51 Hz, 1H, H-8), 7.35-7.21 (m, 5H, benzyl-H), 5.63 (s, 2H, benzyl-CH_2), 4.19 (q, J = 6.9 Hz, 2H, O$CH_2$$CH_3$), 1.24 ppm (t, J = 6.9 Hz, 2H, O$CH_2$$CH_3$). ^{13}C NMR (100 MHz, [D_6]DMSO): δ=171.78, 164.65, 152.66 (dd, $J_{C\text{-}F}$ = 250.0, 15.0 Hz, C-7), 150.83, 147.86 (dd, $J_{C\text{-}F}$ = 246.6, 13.8 Hz, C-6), 136.86 (d, $J_{C\text{-}F}$ = 10.4 Hz, C-8a), 135.76, 129.36, 128.41, 126.98, 126.22 (brs, C-4a), 114.35 (d, $J_{C\text{-}F}$ = 19.0 Hz, C-5), 110.62, 107.62 ($J_{C\text{-}F}$ = 246.6, 22.0 Hz, C-8), 60.40, 56.09, 14.64 ppm. HPLC ret. time: 9.33; purity: 90.0%.

The spectral data are in agreement with those reported in literature.[43]

Procedure for [TBMA][MsO] recycling. A mixture of the starting acrylate **1** (100 mg, 0.3 mmol) and K_2CO_3 (83.5 mg, 0.6 mmol) in hot [TBMA][MsO] (0.5 mL) was heated at 80 °C for 2h. After cooling, aqueous work-up and filtration afforded quinolone **2** as above described. The water was evaporated to dryness to give a slurry constituted by the [TBMA][MsO], the excess of K_2CO_3 and the formed KCl. EtOH (5 mL) was added to the slurry to dissolve [TBMA][MsO] and to precipitate the inorganics that were removed by filtration. Then, EtOH was evaporated to give the [TBMA][MsO] which was used for additional two reaction cycles. Yields, reaction time, conversion and quality of reaction checked by TLC were perfectly comparable to the same reaction conducted with fresh [TBMA][MsO].

Procedure for the preparation of ethyl 1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (15) using [TBMA][MsO] trough subsequent cyclization and nucleophilic substitution. A mixture of the starting acrylate **1** (100.0 mg, 0.3 mmol) and K_2CO_3 (83.5 mg, 0.6 mmol) in hot [TBMA][MsO] (0.5 mL) was heated at 80 °C for 2h until total conversion into quinolone **2**. Then, methylpiperazine (0.05 mL, 0.46 mmol) dissolved in hot [TBMA][MsO] (0.2 mL) was added and the resulting mixture was heated for additional 3h. After cooling, the reaction mixture was poured into ice/water to give a precipitate that was filtered under

vacuum to afford the title compound **15** as a white solid (81 mg, 72%); m.p. 202-204 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ=8.37 (s, 1H, H-2), 7.69 (d, J = 13.6 Hz, 1H, H-5), 7.38 (d, J = 7.4 Hz, 1H, H-8), 4.16 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.63-3.58 (m, 1H, cyclopropyl-CH), 3.20-3.15 and 2.53-2.49 (m, each 4H, piperazine-CH_2), (s, 3H, piperazine-CH_3), 1.24-1.18 (m, 5H, OCH_2CH_3, and cyclopropyl-CH_2), 1.07-1.00 ppm (m, 2H, cyclopropyl-CH_2). ^{13}C NMR (100 MHz, [D_6]DMSO): δ=171.95, 164.85, 152.95 (d, $J_{C\text{-}F}$ = 245.0 Hz, C-6), 148.40, 144.24 (d, $J_{C\text{-}F}$ = 10.2 Hz, C-8a), 138.45, 121.12 (d, $J_{C\text{-}F}$ = 6.4 Hz, C-4a), 111.85 (d, $J_{C\text{-}F}$ = 23 Hz, C-5), 109.62, 106.56, 60.12, 54.74, 49.81, 46.11, 35.07, 14.68, 7.90 ppm. HPLC ret. time: 9.33; purity: 90.0%.

The spectral data are in agreement with those reported in literature.[31]

One-pot/three steps procedure conducted in [TBMA][MSO] for the synthesis of 1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16). Starting acrylate **1** (200.0 mg, 0.6 mmol) and K_2CO_3 (167.0 mg, 1.2 mmol) were added while stirring at 80 °C to the preheated [TBMA][MsO] (1.0 mL) and the resulting reaction mixture was kept under stirring at 80 °C for 2h until total conversion into quinolone **2**, as observed by TLC ($CHCl_3$/MeOH 99:1, R_f = 0.3). Then, a preheated solution of methylpiperazine (0.1 mL, 0.9 mmol) in [TBMA][MsO] (0.4 mL) was added and the reaction mixture was maintained at 80 °C for additional 3h. After conversion of intermediate **2** into **15**, as observed by TLC ($CHCl_3$/MeOH 90:10, R_f = 0.5), aq. 10% NaOH (2 mL) was added and the resulting mixture was heated at 80-90 °C for 3h. After cooling, the reaction mixture was poured into ice/water and neutralized with HCl 2N to give a precipitate that was filtered under vacuum to afford the title compound **16** as white solid (134 mg, 65%); m.p. 246-248 °C (litt,[31] 248-250 °C). ^{1}H NMR (400 MHz, [D_6]DMSO): δ=15.08 (brs, 1H, CO_2H), 8.61 (s, 1H, H-2), 7.84 (d, J = 13.3 Hz, 1H, H-5), 7.51 (d, J = 7.4 Hz, 1H, H-8), 3.80-3.75 (m, 1H, cyclopropyl-CH), 3.30-3.25 and 2.53-2.49 (m, each 4H, piperazine-CH_2), 2.21 (s, 3H, piperazine-CH_3), 1.30-1.25 and 1.13-1.10 ppm (m, each 2H, cyclopropyl-CH_2). ^{13}C NMR (100 MHz, [D_6]DMSO): δ=176.71, 166.27, 153.38 (d, $J_{C\text{-}F}$ = 250.0 Hz, C-6), 148.29, 145.50 (d, $J_{C\text{-}F}$ = 10 Hz, C-8a), 139.59, 118.96 (d, $J_{C\text{-}F}$ = 10 Hz, C-4a), 111.32 (d, $J_{C\text{-}F}$ = 23 Hz, C-5), 106.65 (d, $J_{C\text{-}F}$ = 4 Hz, C-8), 54.66, 49.66, 46.06, 36.19, 7.93 ppm. HPLC ret. time: 6.11; purity: 92.8%.

The spectral data are in agreement with those reported in literature.[31]

Keywords

Quinolones; heterocycles; ionic liquids; green chemistry

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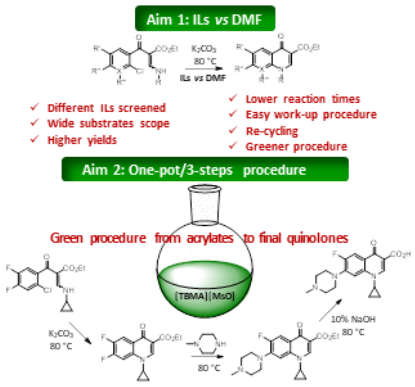

Several advantages were observed using ILs instead of common DMF in the Grohe cycloaracylation for synthesis of pharmaceutically relevant quinolones. [TBMA][MsO] resulted the most favourable IL due to good balance between performance/green properties and was used in a one-pot/3-steps procedure for the preparation of quinolone acid **16** by using a totally green procedure. Our procedures can represent an alternative way for the industrial production of quinolones.