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Novel Quinoline-Imidazolium Adducts via the Reaction of 2-Oxoquinoline-3-Carbaldehyde and Quinoline-3-Carbaldehydes with 1-Butyl-3-Methylimidazolium Chloride [BMIM][Cl]

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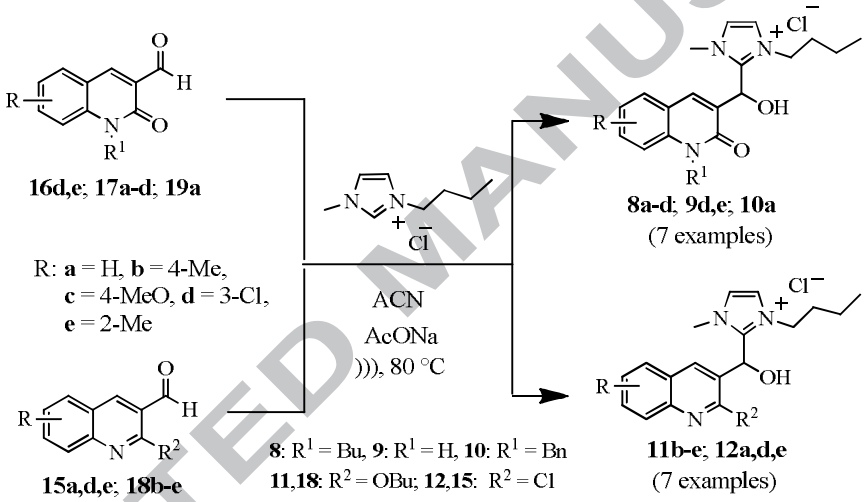

Abstract: A library of hydroxyquinolin-3-ylmethylimidazolium adducts were prepared in high yields from the reaction of [BMIM][Cl] with various substituted quinoline-3-carbaldehydes and 2-oxoquinoline-3-carbaldehydes under mild conditions by using sodium acetate in MeCN under ultrasound irradiation. The use of sodium acetate and imidazolium chloride was crucial for the success of these C-C bond forming reactions. Attempted coupling with thiazolium bromide led instead to quinoline-3-carboxylic acid.

Keywords: quinolone-3-carbaldehyde; ionic liquids (IL´s); 3-butyl-1-methylimidazolium acetate; N-heterocyclic carbenes (NHCs), hydroxyquinolin-3-ylmethylimidazolium adducts; thiazolium salts; quinoline-3-carboxylic acids.

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Quinolines and their oxo-derivatives have attracted considerable interest for many years due to their presence in the skeleton of a large number of bioactive compounds and natural products.[1] Among them, 2-chloro- and 2-oxoquinoline-based compounds have recently emerged as promising antibiotic, CNS stimulant and effective lead structures for the tyrosine kinase receptors (KDR) inhibition mechanism, a key class of enzymes for the tumor cell proliferation.[2] Thus, the 2-chloro derivatives **1** and **2** have displayed antimicrobial activity,[2a,2b] compounds **3** and **4** have been evaluated as potent and selective cannabinoid-2 receptor ligands through a bioisosteric approach,[2c] while structures **5** represent some examples of the 2-oxoquinoline based anti-tumor agents[2d] as well as a series of benzimidazoloquinolin-2-ones **6** recently reported by one us[2e,2f] (Figure 1).

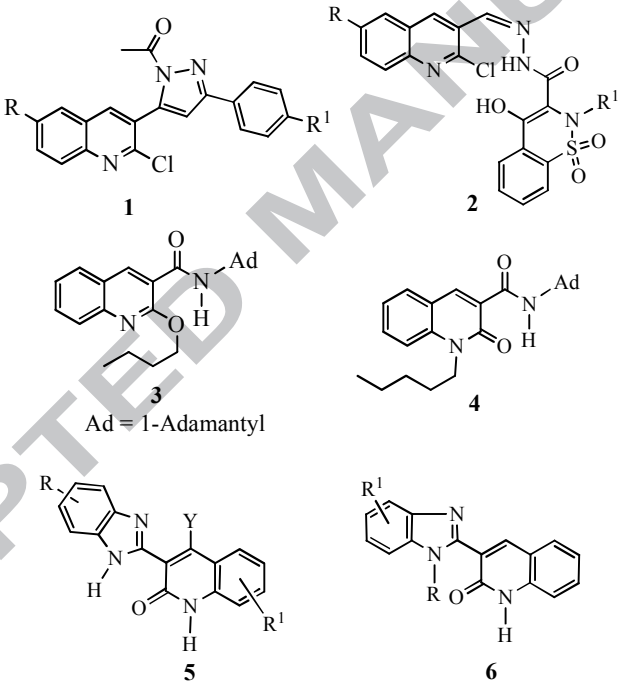


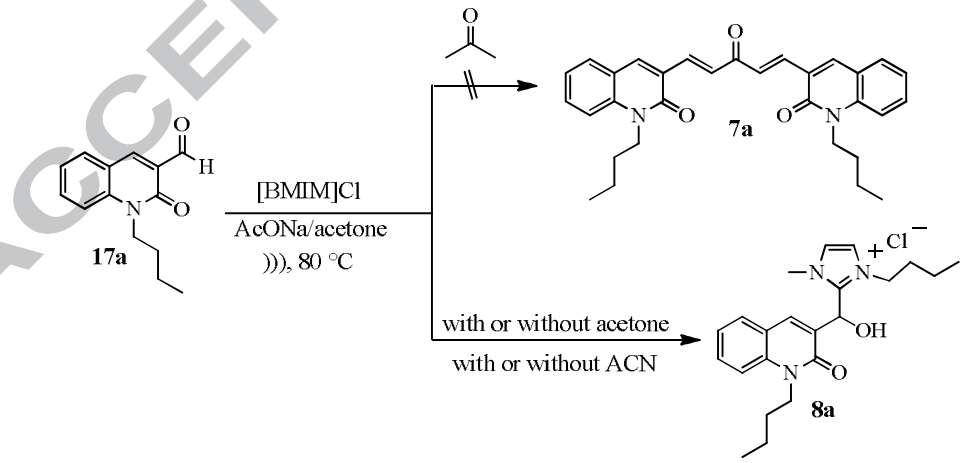
Figure 1. The 2-chloro- and 2-oxoquinoline based compounds of biological interest

Imidazolium salts, especially those that are room temperature ionic liquids (RTILs) are among the most widely investigated classes of onium salts with wide application as alternative solvents and catalysts.[3] Due to surprisingly high acidity at the C2 position imidazolium and

thiazolium salts are easily deprotonated,[4a,4b] and their conjugate base acts as source of N-heterocyclic carbenes (NHCs) that are increasing employed as organocatalyst in synthesis.[4c-g]

In connection to an ongoing program on the development of quinoline-based structures of biological interest,[2e,f-5] and our continuing interest in synthesis and catalysis in ILs,[6] herein we report a facile one-pot synthetic method for the preparation of novel hydroxyquinolin-3-ylmethylimidazolium adducts by reacting substituted quinoline-3-carbaldehydes and the 3-butyl-1-methylimidazolium chloride.

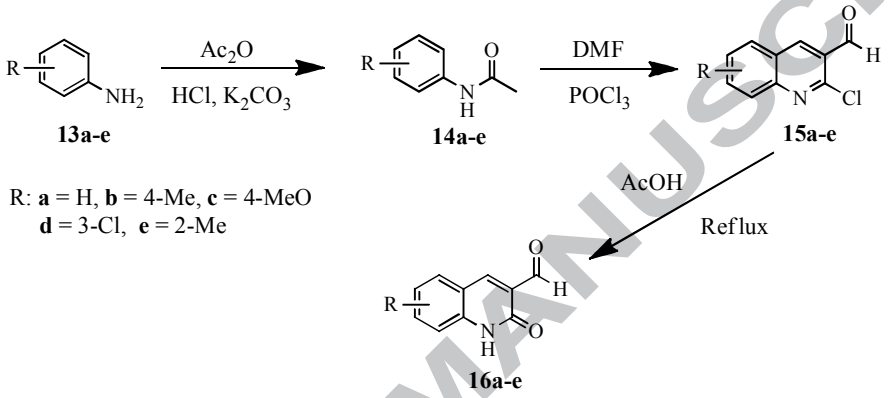
In an attempt to develop an alternative procedure to obtain the biologically active *bis*-quinolone based chalcone **7a**[5] by using a basic ionic liquid (IL) acting both as solvent and as catalyst, a mixture of the *N*-butylformylquinolone 1**7a** (2 equiv), acetone (1 equiv) and the IL [BMIM][OAc] (3 mL) was subjected to reaction under ultrasound irradiation at 80 °C. Upon consumption of 1**7a** (TLC control) a white solid was formed, isolated and purified. A complete spectroscopic analysis indicated that the structure of this solid corresponded to the hydroxyquinolin-3-ylmethylimidazolium adduct **8a** and not to the expected *bis*-chalcone **7a** (Scheme 1). In order to improve the synthesis of the unexpected adduct **8a** the reaction was repeated between the formylquinolone 1**7a** (1 equiv), 3-butyl-1-methylimidazolium chloride [BMIM][Cl] (1.3 equiv) and AcONa (1.0 equiv) in acetonitrile (3 mL) as solvent, under microwave irradiation at 80 °C, ([BMIM][OAc] is formed *in situ* by reacting [BMIM][Cl] with AcONa). After purification of the crude reaction mixture compound **8a** was isolated in 89% yield.[7]



Scheme 1. Synthesis of the quinoline-imidazolium adduct **8a** by addition of the [BMIM]Cl to the formylquinolone 1**7a**

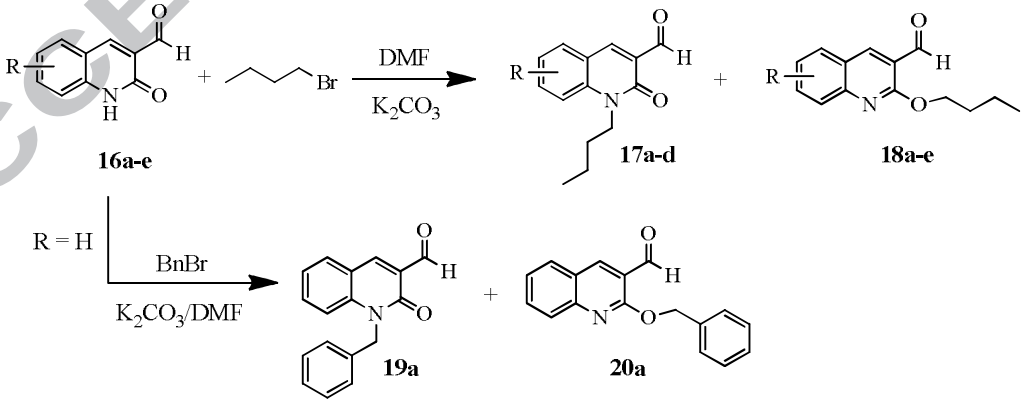
In order to expand the scope and to evaluate the generality of our above optimized protocol we performed the synthesis of diversely substituted *N*-butyl- and *N*-benzyl-quinolones **17** and **19**, respectively, as well as the *O*-butyl- and *O*-benzyl-quinolines **18** and **20** (see supplementary information), with the aim to obtain a new series of quinolone-based imidazolium adducts type **8a** and analogues.

At the onset, a series of 2-chloroquinoline-carbaldehydes **15** and formyl-quinolones **16** were prepared according to Scheme 2.



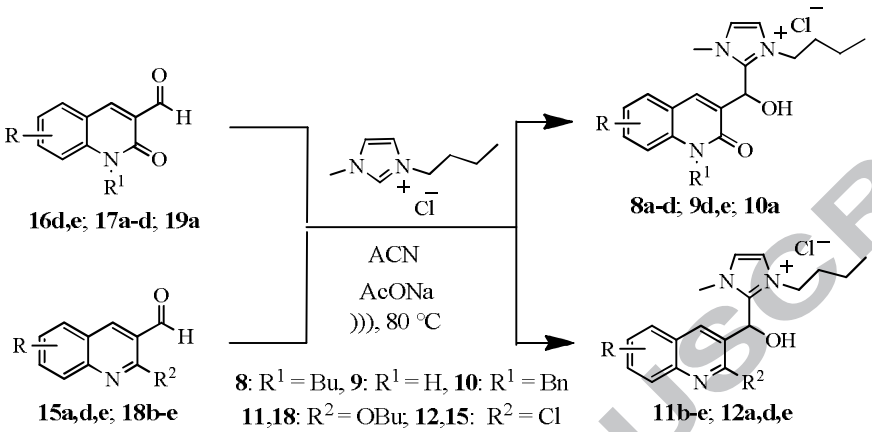
Scheme 2. General procedure for the synthesis of the starting formyl-quinolones **15** and **16**[8,9]

Then, alkylation and benzylation of **16a-e** under mild reaction conditions furnished the key *N*- and *O*-butyl and *N*- and *O*-benzyl quinolines **17**, **18**, **19** and **20** (Scheme 3). In all cases the mixtures of both *N*- and *O*- isomers were easily separated by column chromatography.



Scheme 3. General procedure for the synthesis of the key *N*- and *O*-butyl, and *N*- and *O*-benzyl quinolines **17**, **18**, **19** and **20**

Reaction of these compounds with [BMIM][Cl] under the established conditions led to the formation of adducts **8-12** in acceptable to good yields (Scheme 4).



Scheme 4. Synthesis of the novel hydroxyquinolin-3-ylmethylimidazolium adducts **8-12**

Compounds **8-12** were fully characterized by NMR (^{1}H and ^{13}C) and Electrospray MS techniques. Compounds **8a**, **10a**, **11c** and **12a** produced suitable crystals for X-ray analysis,[10] unambiguously confirming the proposed structures for **8-12**. The thermal ellipsoid plots for **10a** and **11c** are shown in Figure 2. In the solid-state, for **10a** and **11c** planes generated from the imidazolium and quinoline rings bisect each other with dihedral angles (88.16° and 86.72° respectively). This orientation is likely to reduce steric repulsion with the methyl and butyl substituents of the imidazolium ring. The unit cells clearly show the presence of one water molecule along with one chloride ion per molecule.

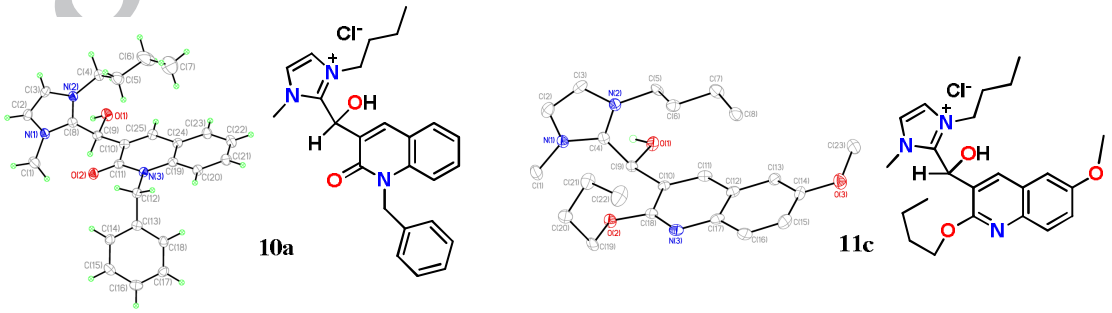
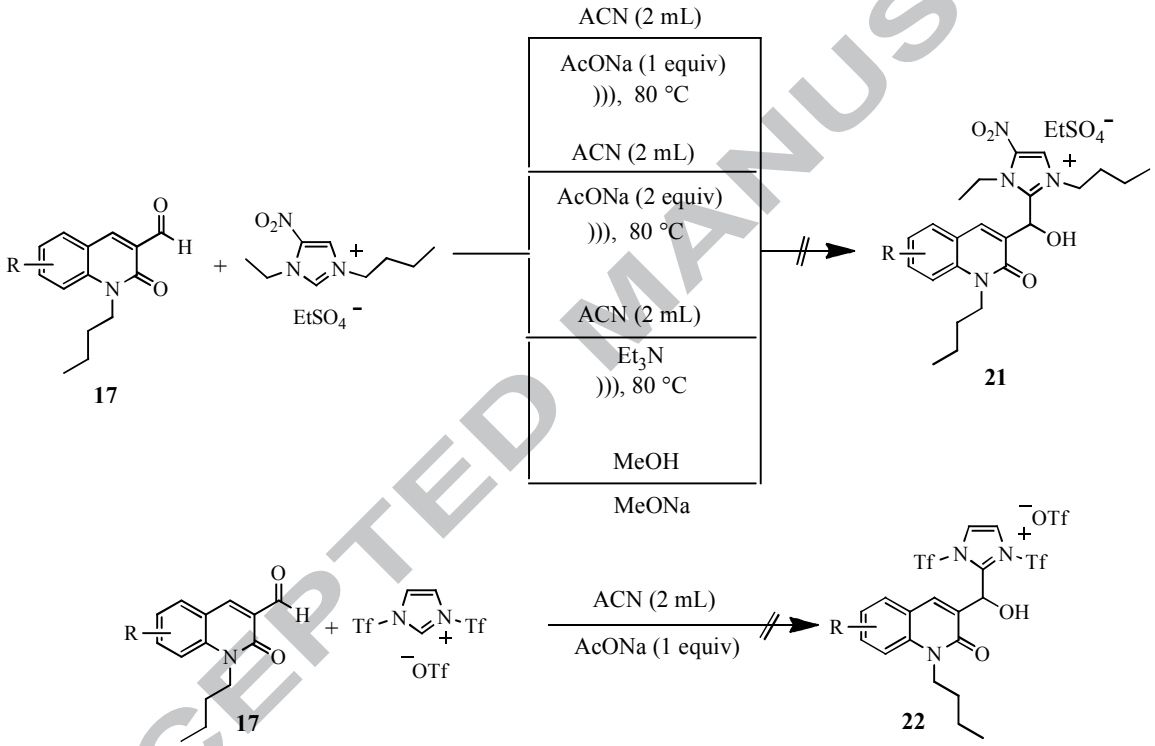


Figure 2. Thermal ellipsoid plots of **10a** and **11c** with 50% probability ellipsoids. Hydrogen atoms, chloride anions, and water molecules have been omitted for clarity.

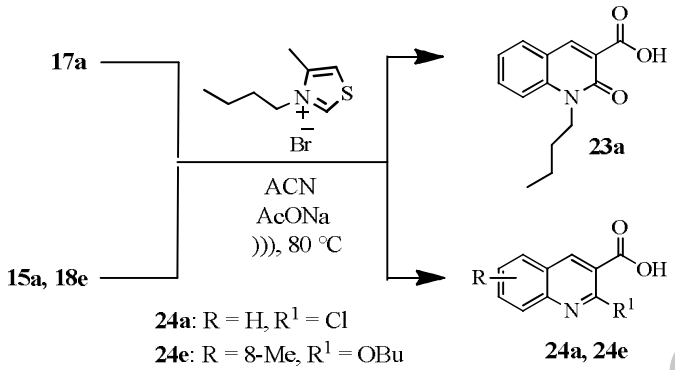
Formation of hydroxyquinolin-3-ylmethylimidazolium adducts **8-12** reflect the *in situ* formation of NHC-carbenes under mild conditions and their subsequent coupling with the quinolone- and quinoline-aldehydes **15-19**.[11]

A number of attempts were made to couple **17** with other imidazoliums, employing AcONa, Et_3N, or MeONa/MeOH as base but none of these conditions led to the formation of adducts **21** or **22** (Scheme 5). Therefore the use of sodium acetate and [BMIM][Cl] appear crucial for the success of these C-C bond forming reactions.



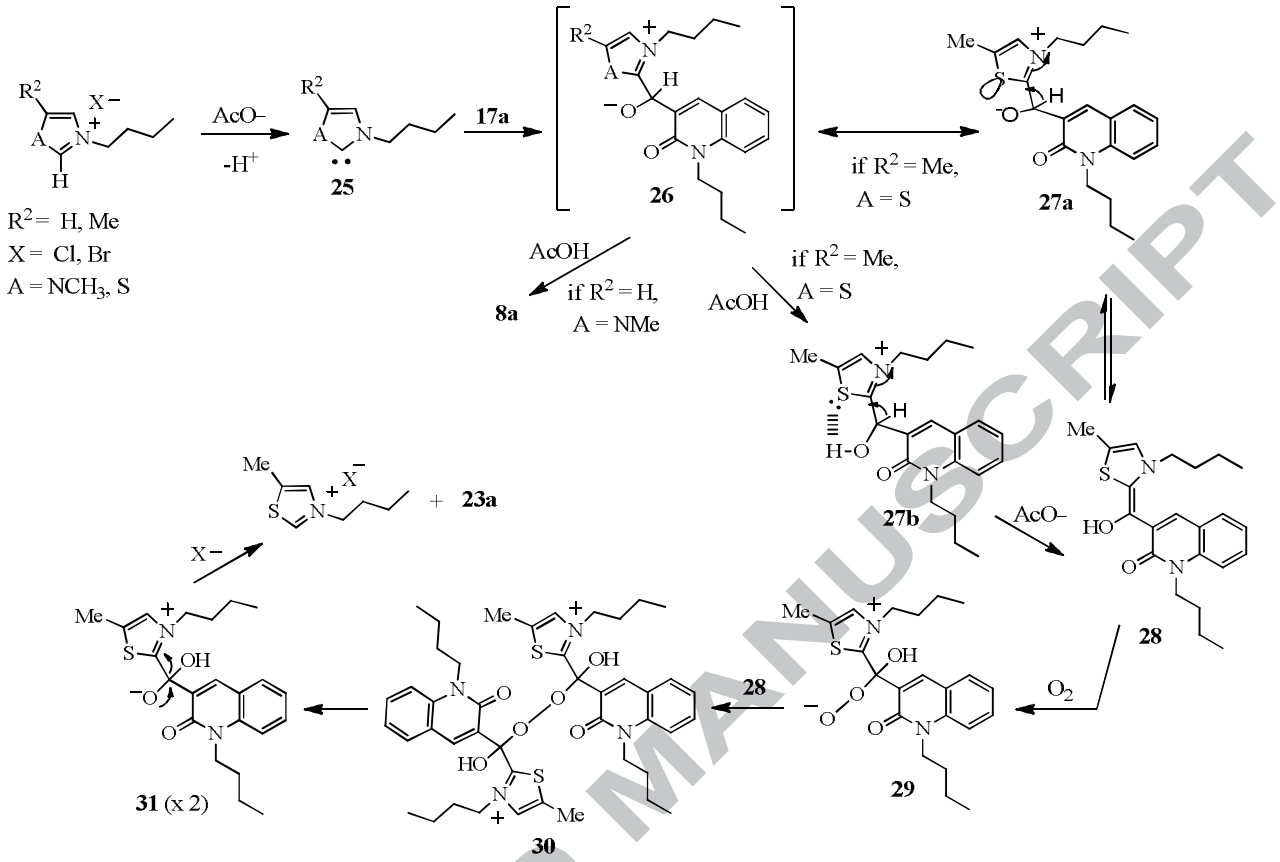
Scheme 5. Attempted coupling with other imidazoliums under various conditions

In an effort to extend this chemistry to other azolium salts, formyl-quinolone **17a** and 3-butyl-4-methylthiazolium chloride were allowed to react under similar reaction conditions. Contrary to expectation, the quinolone carboxylic acid **23a** was obtained instead of the thiazolium type adduct **8a** (Scheme 6). The same behavior was observed when aldehydes **15a** and **18e** were tried, affording the corresponding carboxylic acids **24a** and **24e**. Structure **24e** was unambiguously confirmed by X-ray analysis (see Supplementary Information).



Scheme 6. Synthesis of quinolone carboxylic acids **23-24** mediated by the thiazolium salt.

Formation of the imidazolium adducts **8-12** as well as the quinolone-based carboxylic acids **23-24** should be supported by the formation of a common zwitterionic species **26** generated by the addition of the corresponding imidazolium (R^2 = H, A = NMe) or thiazolium (R^2 = Me, A = S) carbenes **25**[12] to the aldehydes **17a** and their analogues (Scheme 7). In the case of imidazolium derivatives rapid protonation of species **26** would lead to the isolated adduct **8a** and its analogues. For the thiazolium derivatives, formation of a highly reactive Breslow type intermediate **28** and its subsequent oxidation mediated by molecular oxygen[13] could account for the formation of the carboxylic acid **23a** and its analogues. In this sense, the selective formation of the Breslow intermediate **28** for the thiazolium derivatives may be associated with the ability of sulfur to expand its valence shell thus activating the proton migration process in the CHO^- functionality of **26** via the key species **27a**. When "A" = NMe in **26**, the stabilized species **27a** is not produced and a rapid protonation of the CHO^- functionality leads to the isolated hydroxyl derivative **8a**. Alternatively, an H-bonded species **27b** may form and act as precursor to **28**.



Scheme 7. Suggested mechanistic pathways for the formation of the imidazolium adduct **8a**, the carboxylic acid **23a,** and their related structures.

In summary we have discovered a facile one-pot approach for the preparation of a library of hydroxyquinolin-3-ylmethylimidazolium adducts in high yields by reacting various substituted quinoline-3-carbaldehydes and 2-oxoquinoline-3-carbaldehydes with [BMIM][Cl] under mild conditions by using sodium acetate/MeCN under ultrasound irradiation. Attempted extension of this methodology to thiazolium adducts led instead to quinoline-3-carboxylic acids.

Supplementary Information (see footnote on the first page of this article)**:** Complete experimental procedures and characterization data for the products **8-12** and **23-24** are given. CCDC 1001927-1001931 contain the supplementary crystallographic data for this paper. These

data can be obtained free of charge from the Cambridge Crystallographic Data Center via ccdc.cam.ac.uk/data_request/cif.

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References

1. (a) Egan, T.J. *J. Inorg. Biochem.* **2006**, *100*, 916–926; (b) Sahu, N.P.; Pal, C.; Mandal, N. B.; Banerjee, S.; Raha, M.; Kundu, A. P.; Basu, A.; Ghosh, M.; Roy, K.; Bandyopadhyay, S. *Bioorg. Med. Chem.* **2002**, *10*, 1687–1693.
2. (a) Miniyar, P. B.; Barmade, M. A.; Majan, A. A. *J. Saudi Chem. Soc.* **2014**, in press. http://dx.doi.org/10.1016/j.jscs.2013.12.004. (b) Ahmad, M.; Rizvi, S. U. F.; Siddiqui, H. L.; Ahmad, S.; Parvez, M.; Suliman, R. *Med. Chem. Res.* **2012**, *21*, 2340–2348. (c) Mugnaini, C.; Nocerino, S.; Pedani, V.; Pasquini, S.; Tafi, A.; De Chiaro, M.; Bellucci, L.; Valoti, M.; Guida, F.; Luongo, L.; Dragoni, S.; Ligresti, A.; Rosenberg, A.; Bolognini, D.; Cascio, M. G.; Pertwee, R. G. Moaddel, R.; Maione, S.; Di Marzo, V.; Corelli, F. *Chem. Med. Chem.* **2012**, *7*, 920–934; (d) Bilodeau, M. T.; Fraley, M. E.; Hartman, E. D. *Expert Opin. Investig. Drugs* **2002**, *11*, 737–745; (e) Abonia, R.; Cortés, E.; Insuasty, B.; Quiroga, J.; Nogueras, M.; Cobo, J. *Eur. J. Med. Chem.* **2011**, *46*, 4062–4070; (f) Abonia, R.; Castillo, J.; Cuervo, P.; Insuasty, B.; Quiroga, J.; Ortíz, A.; Nogueras, M.; Cobo, J. *Eur. J. Org. Chem.* **2010**, *45*, 317–325.
3. See for example: (a) Wasserscheid, P.; Welton (eds), "Ionic Liquids in Synthesis", Wiley-VCH, Weinheim, Germany, 2003; (b) Malhotra, S. V. (ed) "Ionic Liquids in Organic Synthesis", ACS. Symp. Ser. 950, ACS, Washington DC, 2006; (c) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, Jr, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green.Chem.*, **2007**, *9*, 411–420; (d) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H.

G. *Chem. Rev*. **2008**, *106*, 2015–2050; (e) Chiappe, C.; Pearaccini, D. *J. Phys. Org. Chem*. **2005**, *18*, 275–297; (f) Greaves, T. L.; Drummond, C. J. *Chem. Rev*. **2008**, *108*, 206–237.

4. See for example: (a) Ennis, E.; Handy, S. T. *Cur. Org. Syn*. **2007**, *4*, 381–389; (b) Chu, Y.; Cheng, J.-P. *J. Org. Chem*. **2007**, *72*, 7790–7793; (c) Zhou, H.; Zhang, W.-Z.; Liu, C.-H.; Qu, J.-P.; Lu, X.-B. *J. Org. Chem*. **2008**, *73*, 8039–8044; (d) Fevre, M.; Pinaud, J.; Leteneur, A.; Gnanou, Y.; Vignolle, J.; Taton, D. *J. Am. Chem. Soc*. **2012**, *134*, 6776–6784; (e) Kelemen, Z.; Holloczki, O.; Nagy, J.; Nyulaszi, L. *Org. Biomol. Chem*. **2011**, *9*, 5362–5364; (f) Duong, H. A.; Tekavec, T. N.; Arif, A. M.; Louie, J. *Chem.Comm*. **2004**, 112–113; (g) Holbrey, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. *Chem.Comm.* **2003**, 28–29.

5. Abonia, R.; Insuasty, D.; Castillo, J.; Insuasty, B.; Quiroga, J.; Nogueras, M.; Cobo, J. *Eur. J. Med. Chem.* **2012**, *57*, 29–40

6. For representative examples see: (a) Nandi, G. C.; Rathman, B.; Laali, K. K. *Tetrahedron Lett.* **2013**, *54*, 6258–6263; (b) Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett.* **2012**, *53*, 4212–4215; (c) Narayanan Kumar, G. G. K. S.; Laali, K. K. *Org. Biomol. Chem*. **2012**, *10*, 7347–7355; (d) Vrazic, D.; Jereb, M.; Laali, K. K.; Stavber, S. *Molecules* **2013**, *18*, 74–96; (e) Narayanan Kumar, G. G. K. S.; Laali, K. K. *Tetrahedron Lett.* **2013**, *54*, 965–969; (f) Nandi, G. C.; Laali, K. K. *Tetrahedron. Lett.* **2013**, *54*, 2177–2179; (g) Prebil, R.; Laali, K. K.; Stavber, S. *Org. Lett.* **2013**, *15*, 2108–2111.

7. To a solution of the respective quinolones (**16d,e**; **17a-d** and **19a**) or the quinolines **15a,d,e** and **18b-e** (1 equiv) in acetonitrile (3 mL), 3-butyl-1-methylimidazolium chloride (1.3 equiv) and AcONa (1.0 equiv) were added. The mixture was subjected to ultrasound irradiation at 80 ^{o}C during 1-7h. The completion of the reaction was monitored by TLC. After solvent was removed under reduced pressure, the resulting solid was dissolved in H_2O and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was washed with hexanes to afford products **8-12**. Representative data for **8a**: White solid. 89% yield, mp, 110-111 °C, IR (cm^{-1}, CH_2Cl_2): ν 3410 (OH), 1589 (C=C), 1651 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s,1H), 7.74 (dd, J = 7.8, 1.5 Hz, 1H), 7.63 (t, J = 8.7 Hz, 1Hz),

7.39 (d, *J* = 8.6 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.36 (d, *J* = 1.8 Hz, 1H), 4.24 (s, 3H), 4.23 – 4.08 (m, 4H), 1.76 – 1.59 (m, 3H), 1.45 – 1.39 (m, 3H), 1.20 – 1.12 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.71 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 146.7, 138.4, 136.7, 136.7, 136.4, 131.2, 129.8, 128.7, 122.8, 120.3, 114.2, 61.0, 48.1, 42.2, 36.8, 31.8, 29.5, 20.5, 19.5, 13.8, 13.3. Electrospray MS (CH_3OH, *m/z*): 368 (M^+- Cl), 771 (cation/molecule cluster).

8. (a) Meth-Cohn, O.; Narine, B. *Tetrahedron Lett*. **1978**, *19*, 2045–2048; (b) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans.* **1981**, *1*, 1520–1530.

9. Abonia, R.; Castillo, J.; Cuervo, P.; Insuasty, B.; Quiroga, J.; Ortíz, A.; Nogueras, M.; Cobo, J. *Eur. J. Org. Chem*. **2010**, 317–325.

10. Single crystals suitable for single X-ray diffraction were obtained from compounds **8a**, **10a**, **11c** and **12a** from DCM solutions at ambient temperature. Crystallographic data were collected at 100(2) K on a Bruker Smart APEX AXS CCD area diffractometer using Mo-Kα X-ray radiation (λ = 0.71073 Å).

11. Formation of NHC carbene from [EMIM][OAc] and its application as an organocatalyst for benzoin condensation and other transformations have been reported (see ref 4).

12. (a) Piel, I.; Pawleczyk, M. D.; Hirano, K.; Frohlich, R.; Glorius, F. *Eur. J. Org. Chem*. **2011**, 5475–5484; (b) Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 7120–7124; (c) Kelemen, Z.; Hollóczki, O.; Nagy, J.; Nyulászi, L. *Org. Biomol. Chem.*, **2011**, *9*, 5362–5364.

13. Raghunadh, A.; More, S. S.; Chaitanya, T. K.; Kumar, Y. S.; Meruva, S. B.; Rao, L. V.; Kumar, U. K. S. *Beilstein J. Org. Chem.* **2013**, *9*, 2129–2136 and references cited therein.