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Facile synthesis of 6,6,8,6,6-ring fused pentacyclic heterocycles: annelation of quinolines to quinoxalines under PTC condition

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ABSTRACT

An efficient and simple synthesis of pentacyclic quinolonoquinoxalinooxazocines in a one-pot sequence has been performed by unique application of phase transfer catalysis. Preparative simplicity and conceptual novelty of the methodology offer an attractive general application for the synthesis of novel quinoline antibiotics.

1. Introduction

Heterocyclic rings are present as fundamental components in the skeletons of more than half of the biologically active compounds produced by nature.[1] Investigations toward understanding the reactivity of such compounds are therefore gaining significance and expedient syntheses particularly for N-heteroaromatics are much sought after. Among the various heterocyclic skeletal forms, quinolones and quinoxalines are two privileged motifs that are found in the core of several antibiotics presently used in clinical practices such as ofloxacin,[2] norfloxacin,[3] and A-62176[4] on the one hand, and echinomycin, leromycin, and actinomycin[5] on the other hand.

The quinolone drugs are potent inhibitors of lymphocyte apoptosis[6] and often form the framework of DNA intercalating agents,[7] whereas the quinoxaline drugs are known to inhibit the growth of gram-positive bacteria and are also active against various transplantable tumors.[5] The intercalative binding of these drugs is due to the presence of planar linearly fused tri cyclic system.[8] Moreover, tetra, penta, and hexa cyclic compounds containing one or two heteroatoms fused to quinoline ring in a linear fashion are found in natural products as well as in synthetic compounds of biological interest that have antitumor and anticancer properties.[9] Based on these information we contemplated that convergent syntheses of quinolone–quinoxaline hybrid moieties that would yield a fused pentacyclic ring system having two or more heteroatoms might lead to products of enhanced biological efficacy. We also wanted to develop a new methodology that will increase the structural complexity of the molecules while decreasing the number of synthetic steps, and afford high yields coupled with low cost and operational simplicity under environment-friendly mild reaction conditions. In this aspect phase transfer catalysis has long been recognized as a versatile methodology for organic synthesis in industry, academia and in process chemistry.[10] As a part of our ongoing endeavor on phase transfer catalysis for the construction of structurally unique N-heteroaromatics,[11] herein we report the use of this methodology for the synthesis of extended and also expanded polycyclic novel heteroaromatics containing both quinolone and quinoxaline moieties in annelated form.

Our route to the targeted pentacyclic quinolonoquinoxalinooxazocines began with the reaction of 8-hydroxyquinoline (**3a**) and 2,3-bis-(bromomethyl)-6,7-dimethylquinoxaline (**2a**), the alkylating agent effortlessly prepared (Scheme 1) from 1,4-dibromo-2,3-butanedione and phenylenediamine (**1a**). The reaction partners **3a** and **2a** in 1:3 mole ratio were taken in minimum amount of dichloromethane and then treated at room temperature with catalytic amount of tetrabutylammonium bromide (phase transfer catalyst) in the presence of 10% sodium hydroxide solution for several hours.[12] The progress of the reaction was monitored by tlc, which showed that the reaction was complete within 12 hours. Usual work-up followed by chromatographic separation afforded the quinolone (**5a**) with high yield (90%). As we were interested to isolate the putative intermediate quinolinium, the same reaction was performed for a shorter duration to obtain the intermediate quinolinium (**4a**) along with **5a** after chromatographic separation.

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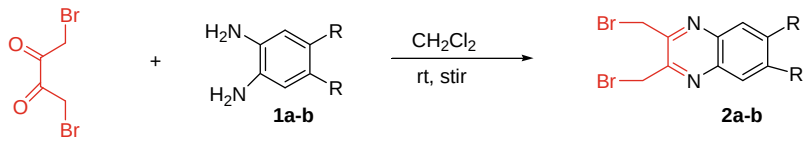


a. R = Me
b. R = H

Scheme 1.

Table 1
Construction of fused pentacyclic quinoliniums and quinolones using 8-hydroxyquinolines (**3a–d**) and 2,3-bis-bromomethyl quinoxaline derivatives (**2a–b**)[a]

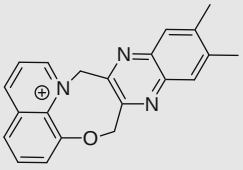
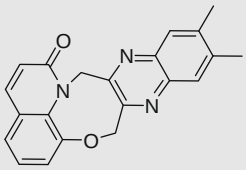
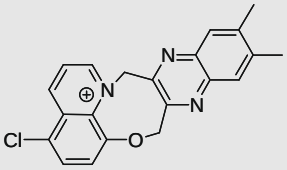
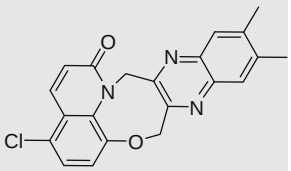
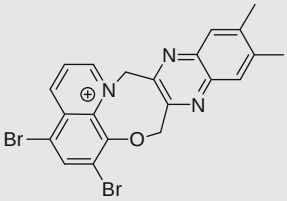
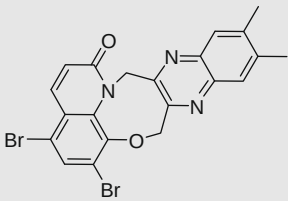
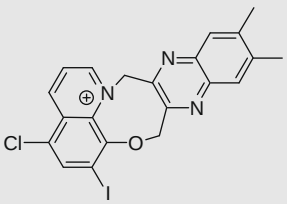
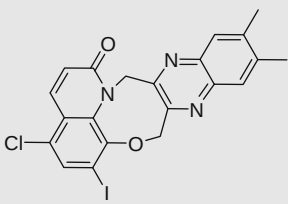
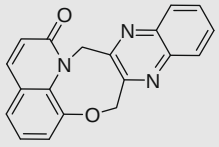
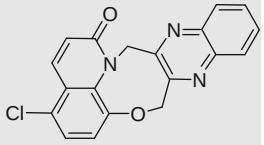
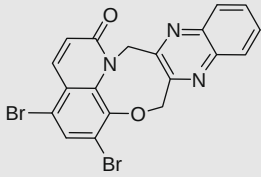
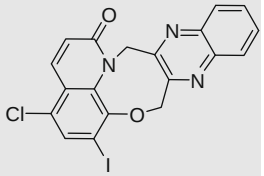
8 HQ (**3a–d**)	Alkylating agents (**2a–b**)	Time (h)	Product[b] (%)[c]	
			Quinolinium[d]	Quinolone
3a	**2a**	4	 **4a** (30)	 **5a** (NI)
3a	**2a**	8	**4a** (50)	**5a** (45)
3a	**2a**	10	**4a** (25)	**5a** (70)
3a	**2a**	12	**4a** (NI)	**5a** (95)
3b	**2a**	4	 **4b** (30)	 **5b** (NI)
3b	**2a**	10	**4b** (30)	**5b** (60)
3b	**2a**	14	**4b** (NI)	**5b** (90)
3c	**2a**	4	 **4c** (25)	 **5c** (NI)
3c	**2a**	8	**4c** (40)	**5c** (50)
3c	**2a**	12	**4c** (NI)	**5c** (90)
3d	**2a**	4	 **4d** (35)	 **5d** (NI)
3d	**2a**	10	**4d** (30)	**5d** (50)
3d	**2a**	14	**4d** (10)	**5d** (70)

Table 1 (*continued*)

8 HQ (**3a–d**)	Alkylating agents (**2a–b**)	Time (h)	Product[b] (%)[c]	
			Quinolinium[d]	Quinolone
3d	**2a**	16	**4d** (NI)	**5d** (80)
3a	**2b**	10	**4e** (NI)	 **5e** (90)
3b	**2b**	12	**4f** (NI)	 **5f** (95)
3c	**2b**	10	**4g** (NI)	 **5g** (88)
3d	**2b**	10	**4h** (NI)	 **5h** (92)

NI = not isolated.

[a] All the reactions were conducted with 8-hydroxyquinoline and bis-bromomethyl quinoxaline derivatives under PTC condition.

[b] All the products are characterized by mass, ^{1}H, ^{13}C NMR.

[c] Isolated yield.

[d] After 4 h unreacted substrates were recovered.

Almost equivalent amounts of the quinoliniums and quinolones could be isolated after 8 h of the reaction; however, with increased time period, the yield of the isolated quinolinium decreased with gradual increase in quinolone formation (Table 1). It is worthy of mention that on termination of the reaction after 4 h only the quinolinium (30%) was isolated. After optimization of the reaction parameters for the generation of **5a**, the scope of this chemistry was then extended to differently substituted 8-hydroxyquinolines, viz. 5-chloro- (**3b**), 5,7-dibromo-(**3c**) and 5-chloro-7-iodo-(**3d**), and 2,3-bis-(bromomethyl)-quinoxaline derivatives **2a**,**b**. The results summarized in Table 1 reveal that the quinolones can be prepared in high yields in all the cases. It is presumed that the pathway for the formation of the quinolones proceeds through the intermediate quinolinium, formed from 8-hydroxyquinoline by intramolecular O-N-dialkylation. The conversion of the quinoliniums to quinolones might have been initiated by nucleophilic attack of hydroxide ion onto the electrophilic C-2 carbon of the quinolinium salts forming the intermediates **I** (Scheme 2), which then transformed to quinolones via oxidative pathway as described earlier.[11] The mass and ^{13}C NMR spectral data of all these quinoliniums and quinolones are well in agreement with the proposed structures but some ambiguity was observed in the ^{1}H NMR spectra of the quinoliniums.[13] The protons of the CH_2 groups in **5a–h** are nonequivalent and resonate in different aliphatic regions as doublets. Though three protons of two CH_2 groups in **4a–d** gave rise to separate doublets in aliphatic region, one of the two protons of the N–CH_2 resonates in the aromatic region (7.7–7.8 ppm). The downfield shift to the aromatic region is probably due to the near parallel orientation of the C–H bond with the *p*-orbitals of the aromatic ring(s), allowing greater overlap. There are reports that in the cases of quinolinium or isoquinolinium benzyl bromides the protons of the –CH_2 group usually resonate as a singlet at δ 6.05–6.70.[14] Single crystal X-ray analyses of quinolinium **4d** and quinolone **5f** unambiguously established the proposed structures (Fig. 1).

2. Conclusion

In summary, we have developed a new strategy for the construction of structurally novel polycyclic N-heteroaromatics having quinoxaline and quinolone moieties in one-pot sequence and demonstrated a unique application of phase transfer catalysis. The procedure offers a broad synthetic feasibility of synthesizing newer heteroaromatic systems having potential biological activity.

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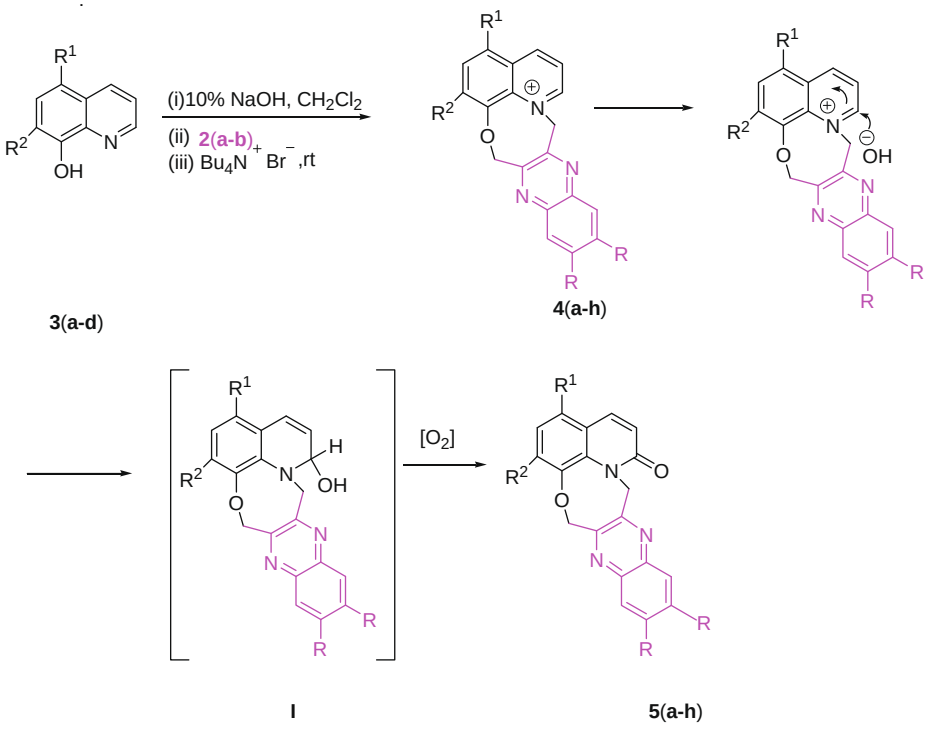

a.R = Me, $R^1 = R^2 = H$
b.R = Me, R^1 = Cl, R^2 = H
c.R = Me, $R^1 = R^2$ = Br
d.R = Me, R^1 = Cl, R^2 = I
e.R = $R^1 = R^2$ = H
f. R = R^2 = H, R^1 = Cl
g.R = H, $R^1 = R^2$ = Br
h.R = H, R^1 = Cl, R^2 = I

Scheme 2.

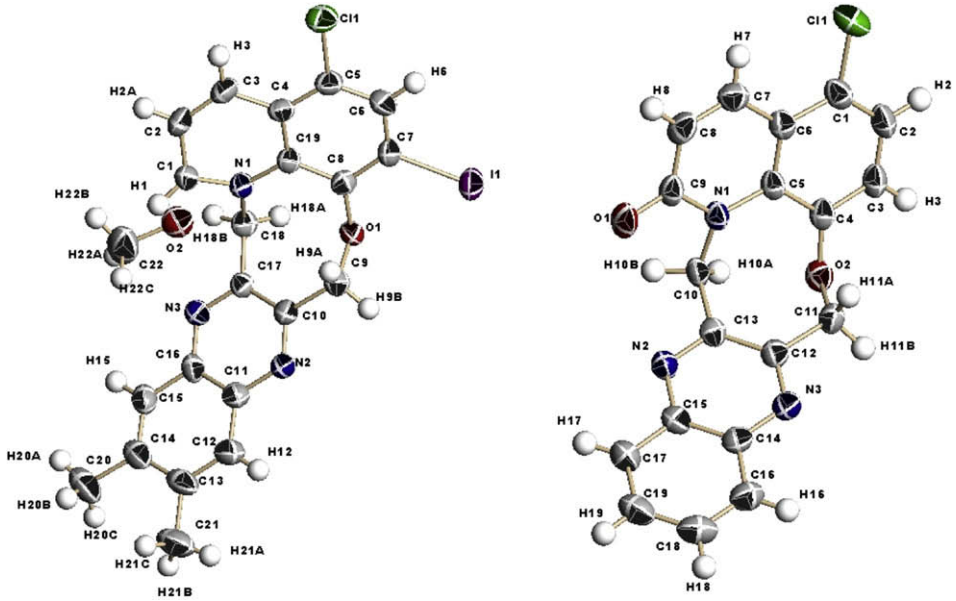

Figure 1. ORTEP representations of compounds **4d** (cationic part with solvent MeOH, left) and **5f** (right), the displacement ellipsoids are drawn at a probability of 50%.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.103.

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12. *General reaction procedure for the Synthesis of fused penta cyclic quinolinium* cations (**4a**–**d**): Appropriate amount of 8-hydroxyquinoline derivatives (**3a**–**d**) (3.3 mmol) were dissolved in 50 mL of dichloromethane in a 250 mL RB flask followed by the addition of 50 mL of 10% aqueous NaOH solution, and were stirred at room temperature for about 30 min. Quinoxaline dibromides (**2a**–**b**) (10 mmol, 1:3 ratio with respect to the substrate) was added successively to the stirred solution and stirring continued for 10 min. Finally, a catalytic amount of tetra butyl ammonium bromide (phase transfer catalyst) (322.4 mg, 1 mmol) was added to the solution and the reaction mixture was stirred at room temperature. During the course of reaction, TLC was performed after every 1 h to monitor the progress of the reaction and after 4 h the reaction was stopped for isolation intermediate quinolinium only. Then the contents of the reaction mixture were poured to a separating funnel; the organic layer was separated followed by extraction of the aqueous layer with dichloromethane (3×25 mL). The entire aqueous layer was further extracted with *n*-butanol (50 ml) for collecting the rest amount of compounds. Then, all the organic layers were mixed together, washed thoroughly with water until free from alkali, dried over sodium sulfate, and evaporated to dryness in a rotary evaporator under reduced pressure. The residue was chromatographed over silica gel (100–200 mesh), eluted with a mixture of chloroform–methanol in different ratios yielded the respective fused quinolinium cations (**4a**–**d**).
General reaction procedure for the synthesis of fused penta cyclic quinolones (**5a**–**h**): Following similar protocols as for quinolinium cations (**4a**–**d**) the reaction was continued for further time period. TLC studies revealed that the conversion of quinolinium cations to quinolones used to take 12–16 h for completion of the reaction. The content of the reaction mixture was then worked up as was done for the quinolinium cations. The chromatographic separation was carried out over silica gel (100–200 mesh), eluted with a mixture of petroleum ether and chloroform in different ratios yielded the respective fused quinolones (**5a**–**h**).
13. (a) *Spectral data of* **4a**: Quinolinium **4a** was obtained from the column, eluted with 1% methanol–chloroform, and was crystallized from a chloroform–hexane mixture to give the corresponding quinolinium cation as white needles in 30% yield. Mp: 218–220 °C; R_f (1% MeOH–$CHCl_3$) 0.42; IR (KBr, cm^{-1}) ν 3465, 3402, 3036, 1528, 1369, 1125, 762; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.41 (3H, s, Me), 2.50 (3H, s, Me), 5.57 (1H, d, J = 16.2 Hz), 6.05 (1H, d, J = 13.8 Hz), 6.23 (1H, d, J = 15.6 Hz), 7.72 (1H, d, J = 13.8 Hz), 7.74 (1H, s), 8.01 (1H, t, J = 7.8 Hz,), 8.18 (1H, dd, J_1 = 6.0 Hz, J_2 = 8.4 Hz), 8.22 (1H, d, J = 7.8 Hz), 8.26 (1H, s), 8.31 (1H, d, J = 7.2 Hz), 9.20 (1H, d, J = 7.8 Hz), 9.81 (1H, d, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): 20.0 (CH_3), 20.1 (CH_3), 65.7 (CH_2), 79.3 (CH_2), 123.0 (CH), 127.1 (CH), 127.7 (CH) 128.1 (CH), 130.6 (CH), 131.2 (CH), 131.9 (C), 132.8 (C), 139.6 (C), 140.5 (C), 141.9 (C), 143.0 (C), 145.2 (C), 148.6 (CH), 149.3 (C), 151.0 (C), 151.3 (CH). ESI-MS: m/z 328 $[M]^+$, HRMS: calcd 328.1450 $[M]^+$; found 328.1443; (b) *Spectral data of* **5a**: Quinolone **5a** was obtained from the 25% chloroform–petroleum ether fraction and was crystallized from chloroform–petroleum ether mixture to give quinolone as yellowish needle crystal in 95% yield. Mp: 240–242 °C; R_f (75% petroleum ether–$CHCl_3$) 0.48; IR (KBr, cm^{-1}) ν 3448, 2915, 1670, 1562, 1432, 1135, 1104, 841; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (6H, s, Me), 5.35 (1H, d, J = 15.9 Hz), 5.89 (1H, d, J = 16.2 Hz), 6.12 (1H, d, J = 13.5 Hz), 6.63 (1H, d, J = 13.2 Hz), 6.72 (1H, d, J = 9.6 Hz), 7.15 (1H, t, J = 7.8 Hz,), 7.27 (1H, m), 7.43 (1H, m), 7.54 (1H, d, J = 9.3 Hz), 7.66 (1H, s), 7.90 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.2 (CH_3), 20.4 (CH_3), 48.1 (CH_2), 78.7 (CH_2), 122.4 (CH), 123.3 (CH), 125.1 (CH) 125.6 (CH), 127.0 (CH), 127.7 (C), 128.6 (CH), 133.2 (C), 138.7 (CH), 139.9 (C), 140.6 (C), 141.4 (C), 146.9 (C), 148.5 (C), 150.5 (C), 150.9 (C), 162.4 (C, CO). ESI-MS: m/z 344 $[M+H]^+$, 366 $[M+Na]^+$, HRMS: calcd 366.1218 $[M+Na]^+$; found 366.1193.
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