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Synthesis of new tetraalkoxyquinolines from parsley and dill secondary metabolites

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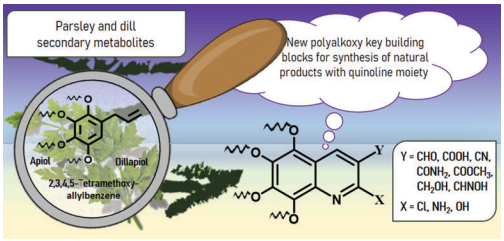
Efficient preparative procedures for the synthesis of 2,3-disubstituted 5,6,7,8-tetraalkoxyquinolines starting from tetraalkoxybenzaldehydes are reported. The latter are available from plant (polyalkoxy)(allyl)benzenes, secondary metabolites of parsley and dill seeds.



Keywords: plant allyltetraalkoxybenzenes, tetraalkoxybenzaldehydes, polyalkoxyquinoline derivatives, Knoevenagel reaction, Curtius rearrangement, Vilsmeier reaction.

Polyalkoxybenzene scaffold not only is found in a wide variety of natural products but also is used as building blocks for a number of active anticancer drugs.[1–7] Recently, effective syntheses of various heterocyclic polyalkoxy derivatives such as analogs of combretastatin A4,[8] podophyllotoxin[9] and glazovianin A[10] were successfully developed in our laboratory using apiol **1** or dillapiol **2** aldehydes[10–12] obtained by ozonolysis from plant (polyalkoxy)(allyl)benzenes **3**.[13]

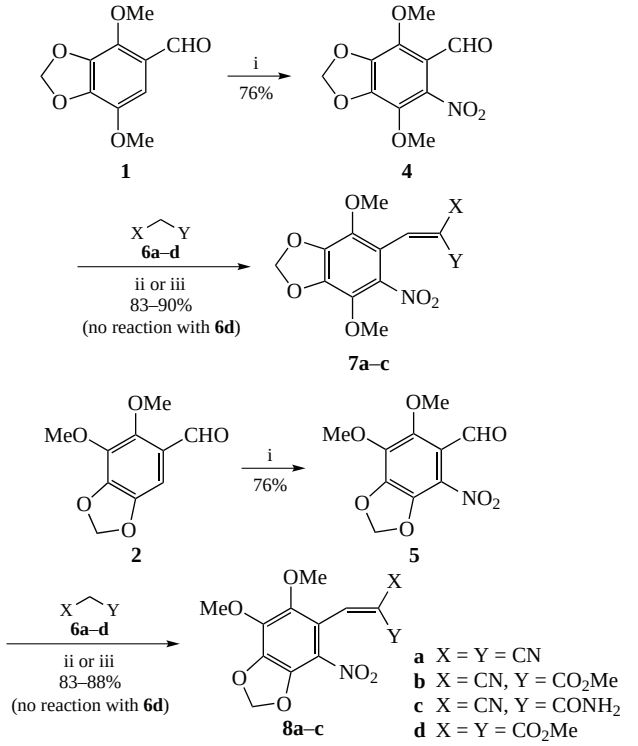
On the other hand, quinolines are found in many natural products and have diverse and potent pharmacological properties.[14,15] Tri- and tetraalkoxy-substituted furanoquinolines exhibit high antitumor activity,[16,17] while natural antitumor antibiotics streptonigrin[18] and lavendamycin[19] include the key quinolinoquinone ring system. Our own interest is to obtain 2,3-disubstituted tetraalkoxyquinolines which are practically poory studied.

Nitration of aldehydes **1** and **2** afforded nitro aldehydes **4**, **5** in good yield[11] (Scheme 1). Their condensation with malonic acid derivatives **6a–c** in methanol with the addition of alumina (for **6a**) or triethylamine (for **6b**,**c**) as catalysts led to the corresponding Knoevenagel products **7a–c** and **8a–c** in good yields. Unfortunately, when the reactions were conducted with dimethyl malonate **6d**, the corresponding products could not be obtained.

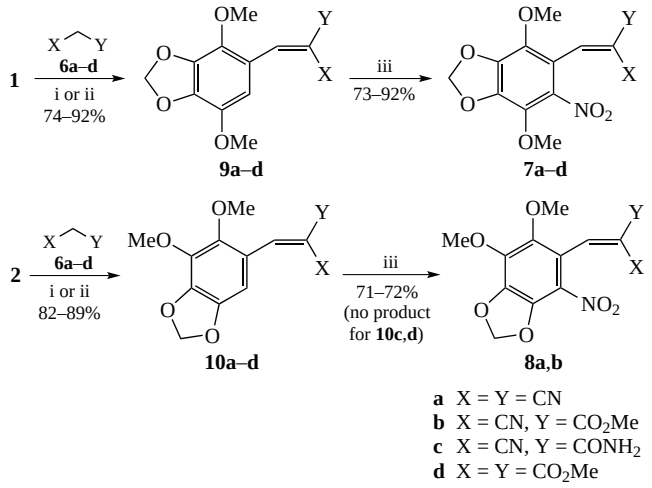
In order to expand the scope of the synthesis of compounds **7**, **8** from aldehydes **1**, **2**, we have explored an alternative route involving the Knoevenagel condensation of aldehydes **1**, **2** with malonic acid derivatives **6a–d**[20,21] followed by nitration (Scheme 2). In fact, the nitration of the Knoevenagel products **9a–d** and **10a**,**b** truly afforded nitro compounds **7a–d** and **8a**,**b**, respectively, in 72–92% yields. However, attempted nitration of **10c**,**d** gave only oily substances.

Reduction of nitro compounds **7a**,**d** with zinc dust in acetic acid resulted in 2-aminoquinolines **11** and **15**, respectively. The similar reactions with **7b**,**c** gave the mixtures of quinolin-2-one **12** and the corresponding 2-aminoquinolines **13** and **14** (Scheme 3). Unlike derivatives **7a–d**, reductive cyclization of nitro compounds **8a–c** proceeded more selectively to furnish 2-aminoquinoline derivatives **16a–c** as single products, although in moderate yields.

Another route to tetraalkoxylated quinolines was based on the Vilsmeier cyclization of acetanilides with DMF and $POCl_3$.[22] Initially, polyalkoxybenzoic acids **17a–d** were synthesized by oxidation of the corresponding aldehydes.[13] Our approach to acetanilides **18a–d** was predicated upon a novel cascade of

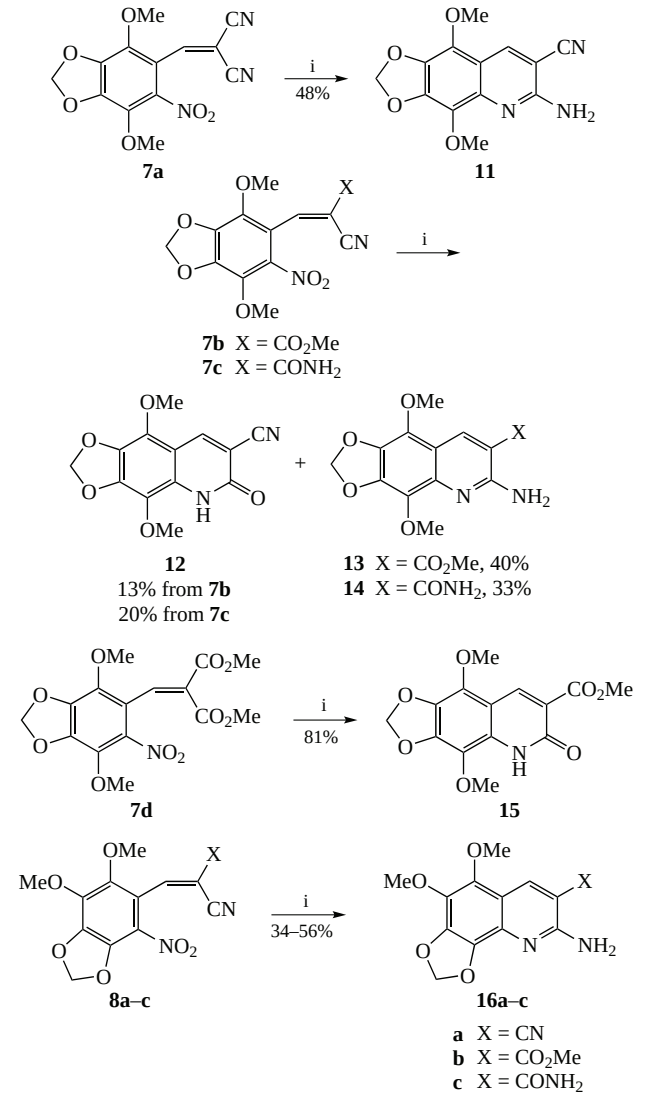


Scheme 1 *Reagents and conditions*: i, HNO_3 (98%), $CHCl_3$, 0–5 °C (ref. 11); ii, Al_2O_3, MeOH, 20–25 °C, 4 h (for **6a**); iii, Et_3N, MeOH, reflux, 2–4 h (for **6b**,**c**).

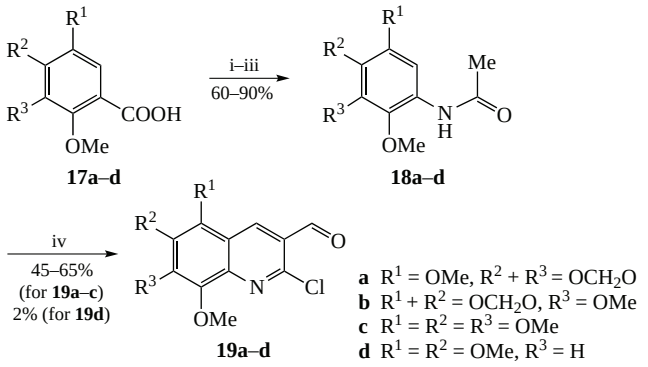


Scheme 2 *Reagents and conditions*: i, Et_3N, MeOH, reflux, 1–4 h (for **9a–d**, **10a–c**); ii, piperidine/AcOH, toluene, reflux, 3 h (for **9a–d**, **10d**); iii, $CHCl_3$, HNO_3 (98%), Ac_2O, 0–5 °C.

transformations *via* one-pot procedure comprising the Curtius rearrangement followed by acylation with acetic anhydride (Scheme 4). The action of diphenylphosphoryl azide on acids **17a–d**, acidic rearrangement of the intermediate acyl azides to isocyanates, followed by hydrolysis led to aniline hydrochlorides. Final acetylation of anilines was performed without isolation of the anilines to get the corresponding acetanilides **18a–d**. The



Scheme 3 *Reagents and conditions*: i, Zn, AcOH, 20–110 °C, 30 min.

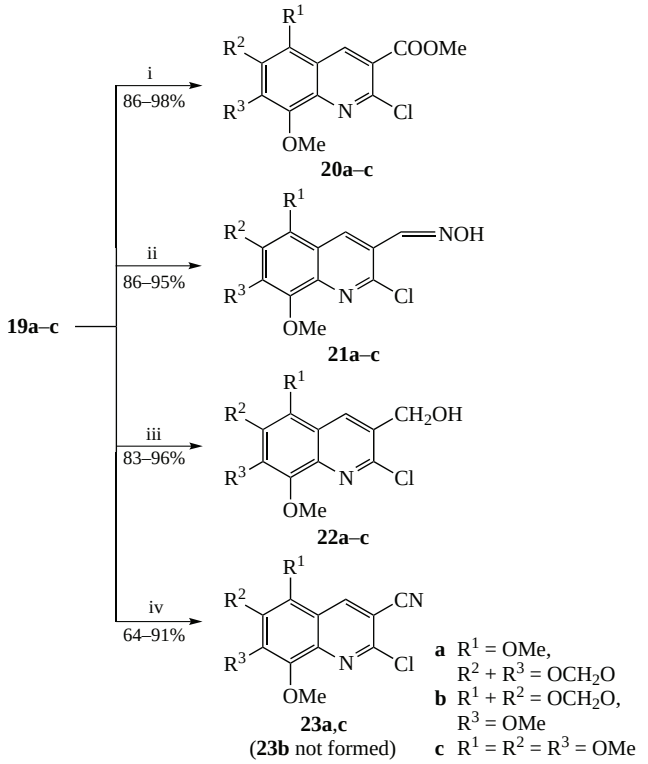


Scheme 4 *Reagents and conditions*: i, Et_3N, DPPA, 0–20 °C, 1 h; ii, HCl, 80 °C, 1 h; iii, Et_3N, Ac_2O, 20 °C, 2 h; iv, Me_2NCHO, $POCl_3$, 90 °C, 2 h.

Vilsmeier-type cyclization of acetanilides **18a–d** to previously unknown polyalkoxysubstituted 2-chloroquinoline-3-carbaldehydes **19a–c** was performed according to literature procedure[22,23] (see Scheme 4). However, the cyclization of acetanilide **18d** gave a complex mixture of products, and the desired compound **19d** was isolated only with 2% yield.

With the required compounds **19a–c** in hand, our efforts were aimed to prepare new tetraalkoxyquinoline derivatives (Scheme 5). Oxidation of aldehydes with iodine in methanol[24] yielded methyl esters of acids **20a–c**. The condensation with hydroxylamine hydrochloride[25] afforded oximes **21a–c**. Interestingly, condensation of **19b** with hydroxylamine hydrochloride gave a *E*/*Z* isomer mixture, which was detected by NMR. Reduction of aldehydes with $NaBH_4$ afforded the desired alcohols **22a–c** in high yields. Oxidation of **19a**,**c** with iodine in the presence of excess of ammonia[26] led to nitriles **23a**,**c**. However, under identical conditions nitrile **23b** could not be obtained from **19b**.

In conclusion, using developed preparative methods a number of building blocks containing 2,3-disubstituted tetraalkoxyquinoline fragment were synthesized starting from apiol aldehyde **1**, dillapiol aldehyde **2**, and 2,3,4,5-tetra-



Scheme 5 *Reagents and conditions*: i, I_2, K_2CO_3, MeOH; ii, $NH_2OH{\cdot}HCl$, Et_3N, EtOH; iii, $NaBH_4$, MeOH; iv, NH_3, I_2, THF.

methoxybenzaldehyde. Due to high syntethic potential, these compounds may be regarded as key substances in many syntheses of quinoline-contaning natural products and their analogs.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.013.

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