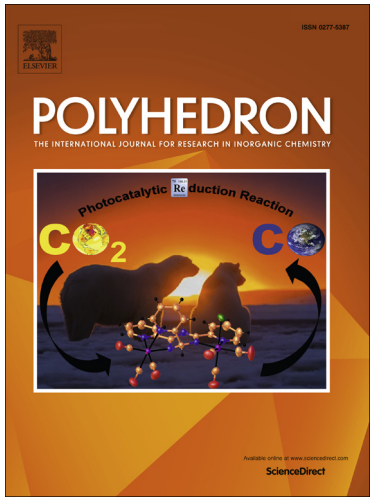

Revisiting the Three Component Synthesis of Isoxazolo[5,4-*b*]pyridines, 4-Aryl-3,7,7-trimethyl-isoxazolo[5,4-*b*]quinolin-5(6*H*)-ones and Related Heterocycles

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Revisiting the Three Component Synthesis of Isoxazolo[5,4-*b*]pyridines, 4-Aryl-3,7,7-trimethyl-isoxazolo[5,4-*b*]quinolin-5(6*H*)-ones and Related Heterocycles.

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Abstract

The one-step three-component microwave assisted synthesis between aromatic aldehydes with tetronic acid or indan-1,3-dione readily formed the Knoevenagel adducts that underwent addition of 3-methylisoxazol-5-amine **1** to form the isoxazolo[5,4-*b*]pyridine products **8**[**a,b,d,e,g**] in 67-90% yield. The multicomponent reaction using dimedone formed the respective addition products 4-aryl-3,7,7-trimethyl-isoxazolo[5,4-*b*]quinolin-5(6*H*)-ones **8**[**c,f,h**] (36-79%). In contrast, the sonication of an aryl aldehyde and dimedone with an equivalent amount of 2-hydroxyammonium formate exclusively generated the Knoevenagel adduct **4c** via **hydro-4c** (Scheme 6). When microwaved either with 3-amino-5-methylisoxazole **1** or 3,4,5-trimethoxyaniline **14** in ethanoic acid-ethylacetate (1:1), tetrahydroacridones **15[a,b]** formed in high yields (88-92%). Importantly, this two-step reaction sequence generates highly reproducible and pure products.

Keywords: Multicomponent Microwave Synthesis, Isoxazolopyridines, Isoxazoloquinolinones, Tetrahydroacridones

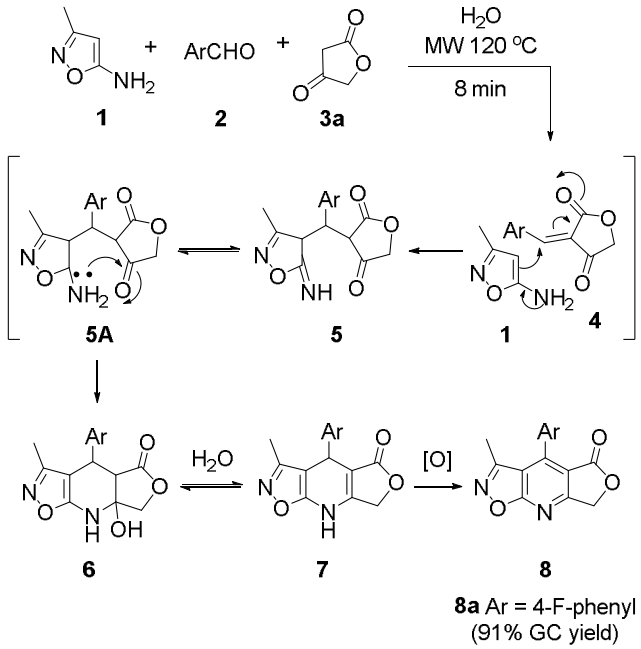
Introduction

The atom efficient and step-economic accessibility of heterocyclic scaffolds particularly pyridine-one containing rings is of medicinal importance and has been actively pursued[1-3]. The three component synthesis of substituted bi- and tri- cyclic pyridine derivatives provides a rapid route for the preparation of a family of potentially bioactive compounds.[4,5] However, Kappe and coworkers[6] demonstrated that the control of chemo- and regioselectivity in multicomponent experimental protocols also influences the product pathway when aryl-aldehydes, dimedone, 5-aminopyrazoles are condensed.

The reactions of aryl-aldehydes and 1,3-dicarbonyls with 2-aminoazoles have been reviewed by Chebanov and coworkers[7,8] to produce polycyclic substituted 4-aryl-3,7,7-trimethyl-6,7,8,9-tetrahydroisoxazolo[5,4-*b*]quinolin-5(6*H*)-one and 4-aryl-3,7,7-trimethyl-isoxazolo[5,4-*b*]quinolin-5(6*H*)-ones. More recently Chen and Micalizio[9] and also Chung[10] et al. developed an expedient three-component coupling reaction.

Our aim was to utilize 3-methylisoxazol-5-amine **1,** aromatic aldehydes **2a-c** and 1,3-dicarbonyls **3a-c** compounds to prepare isoxazolo-tricylic products by MCRs in water for the rapid synthesis of a range of targets for investigation as nuclear hormone receptor agonists (NR4A). Tu[11, 12a] et al. suggested the reaction proceeds from **2a** and **3a** by the formation of the Knoevenagel addition product **4** that acts as an electrophile for the addition of the 3-methylisoxazol-5-amine **1** to **4** to give **5A**. Then follows the cyclization of **5A**, followed by dehydration/oxidation leading to both the furo[3',4':5,6]pyrido[2,3-*d*]pyrimidine[11] **7** and 4-(4-fluoro-phenyl)-3-methyl-7*H*-1,6-dioxa-2,8-diaza-s-indanen-5-one [12a] **8** as outlined in Scheme 1. The evidence to support the proposed mechanism is based on the reaction between the Knoevenagel adduct **4** and the amine **1** to give the

same yields as achieved in the one pot reaction.[12a] The obvious reaction byproducts include imine formation by condensation of the aryl aldehyde with **1**.



Scheme 1. Tu[12a] et al. MW 3-component synthesis of isoxazolo[5,4-*b*]pyridine **8**.

Results and discussion

The MCR shown in Scheme 1 between **1**, 4-fluorobenzaldehyde (**2a**) and tetronic acid (**3a**) gave 4-(4-fluoro-phenyl)-3-methyl-7*H*-1,6-dioxa-2,8-diaza-s-indacen-5-one (**8a**), a target of particular interest due to the activity of the fused lactone and fluorinated aromatic substituents[6] on the isoxazolo[5,4-*b*]pyridine system. The reported conditions involved the MCR in water at 120ºC (200 W) for 6 min to give **8** in yields above 90%. The authors mentioned that reactions performed in EtOH and AcOH at 90ºC for 10 min gave modest yields of **8a** (54 and 57% respectively), although yields in aqueous media reportedly superseded hydrocarbon solvents under all conditions investigated.[12a]

In our hands, using Tu's reported conditions[12a] on a 1 mmolar scale in a CEM Discover microwave[12b] and **1**, **2a** and **3a** in H_2O (2mL) with microwave heating at 120ºC (200 W) for 6 minutes, upon workup the residue contained the expected product **8a** in < 10% yield (GC-MS) along with 4-fluorobenzoic acid [formed *via* the oxidation of **2a**]. With GC-MS monitoring, the yields of **8a** on a 2 mmol scale at 140ºC in 2 mL EtOH were 45% and in 2 mL AcOH 65% that were similar to published results[12a] along with some observable decomposition products.

The absence of the proposed Knoevenagel intermediate **4** (Scheme 1) during GC-MS reaction monitoring caused concern in that the one-pot reaction may be limited by this condensation step. Reaction of **2a** with **3a** in H_2O (2 mL) at 120ºC (200 W) for 10 min followed by extraction with $CHCl_3$ provided the β-enone **4** in only 60% yield, indicating that both the formation of **4** accompanied by oxidation of the **2a** were responsible for low yields of **8a**. Studies by Zimmer[13] *et al.* discuss the necessity of acidic conditions to catalyze the formation of **4** and to avoid the 2:1 reaction of **3a**:**2a** known to produce the consequent *bis*-Michael addition adduct. To accelerate the formation of the Knoevenagel condensation process and simultaneously avoid aryl aldehyde oxidation, we avoided aqueous conditions and optimized a general reaction medium consisting of

EtOAc:AcOH (1:1, 50 wt.%) as mild acidic reaction conditions. Using our experimental conditions with MW heating at 140ºC for 8 min, we successfully produced **8a** in 90% yield by GC-MS monitoring, (Scheme 2) accompanied by 4-fluorobenzoic acid as the side product. Aqueous work-up involving extraction into hot $CHCl_3$ isolated **8a** as a crystalline solid (53%) and accompanied by an isomer (3%) with identical *m/z* that had a tendency to co-crystallize during recrystallization from EtOH. After successive recrystallizations only a low yield of **8a** (26%) of sufficient purity suitable for bioassay was obtained and the structure was confirmed by X-ray crystallography. The ORTEP diagram in Figure 1 clearly shows the planar isoxazolo[5,4-*b*]pyridine system in **8a**, as expected for the aromatized product having undergone oxidation after cyclization.

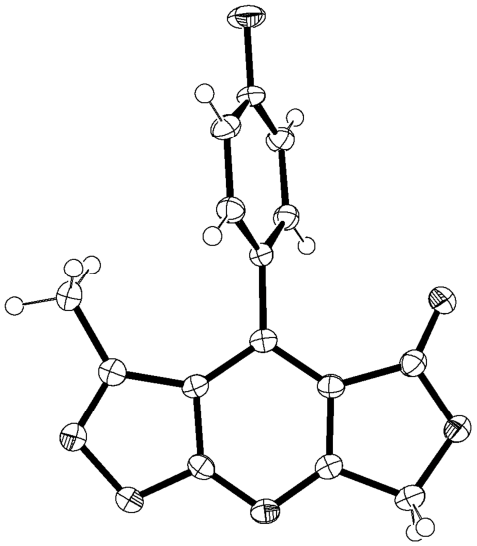
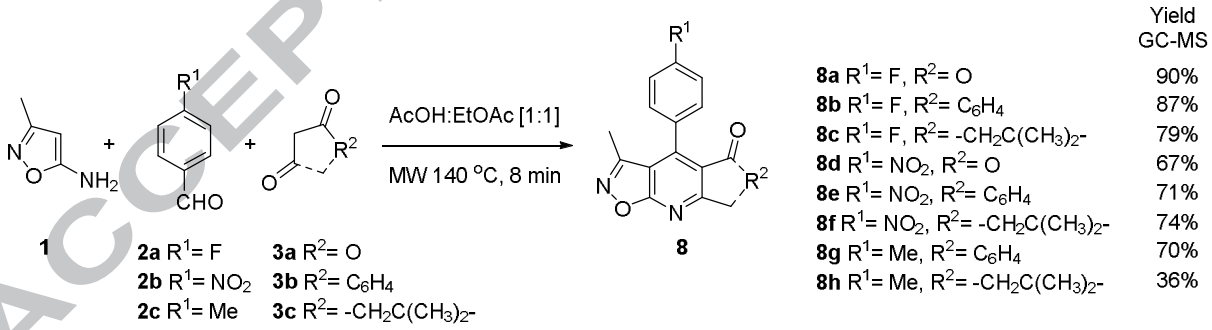


Figure 1. X-ray crystal structure of 4-(4-fluorophenyl)-3-methyl-7H-1,6-dioxa-2,8-diaza-s-indacen-5-one (**8a**) (ORTEP view). Hydrogen atoms have been removed for clarity and displacements ellipsoids are scaled to the 50% probability level.



Scheme 2. MW-assisted MCR synthesis of isoxazolo[5,4-*b*]pyridine and isoxazolo[5,4-*b*]quinolin-5(6*H*)-ones **8a-h**.

Our optimized conditions were then applied to reactions involving **2a**, 4-nitrobenzaldehyde (**2b**) and 4-methylbenzaldehyde (**2c**) to monitor the influence of aryl substituents on the yield of **8**. The MCR reactions that gave the highest yields of **8** were the aryl aldehydes with electron

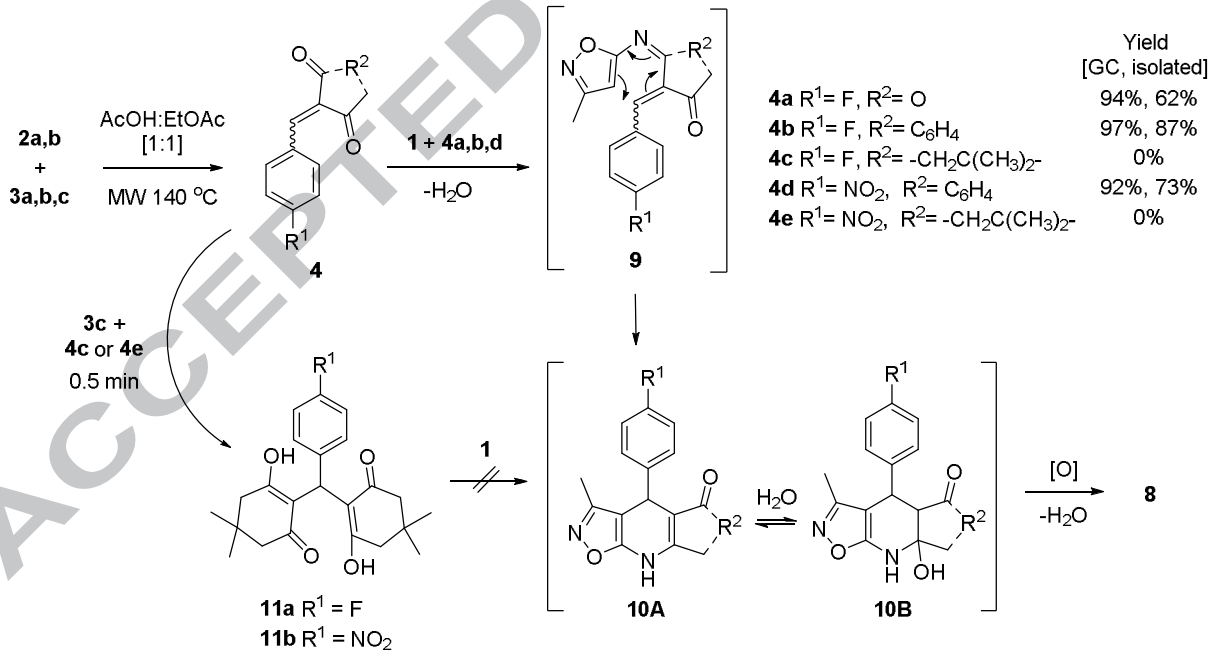
withdrawing substituents (Scheme 2), consistent with the increased aldehyde electrophilic effect, enhancing reactivity and product yields. We found that the nature of the aromatic substituent can influence the reaction between intermediates and the amine nucleophile **1**, resulting in a substantial decreased yield of **8h** (Scheme 2).

Besides **3a**, other 1,3-dicarbonyls were investigated including 1,3-indandione (**3b**) that forms stable Knoevenagel condensation products (Scheme 3), however dimedone (**3c**) has been reported to react with aromatic aldehydes to preferentially form the more stable *bis*-Michael adduct **11**[14] followed by dehydration to produce xanthenedione products **12** under acidic conditions (Scheme 4)[15]. Aldehydes bearing electron withdrawing substituents gave high yields of **8** for reactions involving **3b** and **3c**, despite differences in the reactivity of intermediates formed.

In the one-pot process, side products appeared from undesired reactions between intermediates. We therefore considered that investigations into the reaction mechanisms involved with this family of reactions was warranted in order to determine the merits of MCR compared to a step-wise synthesis.

Mechanisms of condensation reactions

To further investigate the molecular pathway to isoxazolo[5,4-*b*]quinolin-5(6*H*)-ones **8**, the Knoevenagel adducts **4** were prepared by MW irradiation at 140ºC for 8 min (Scheme 3). The condensation of **2a** with **3a** in EtOAc:AcOH [1:1] gave comparable yields to neat AcOH and provided 94% conversion to **4a** by GC-MS analysis (Scheme 3). Reacting **2a** with **3b** gave 97% conversion to **4b** and showed no sign of byproduct formation or decomposition. The same reaction at 273ºC over a 3 min reaction time gave quantitative conversion to **4b** and demonstrated that this intermediate is robust at higher temperatures. Similar results were obtained for the preparation of **4d**.



Scheme 3. Stepwise pathway to product **8**.

Remarkably, attempts to prepare **4c** under the general conditions gave >90% conversion to the *bis*-Michael product **11a** after 30 seconds of MW heating as shown by NMR analysis. Dehydration to the xanthenedione product **12a** was complete upon MW heating for 1.5 min (Scheme 4) and the structure was confirmed by X-ray crystallography. The ORTEP diagram in Figure 2 shows the bent tricyclic ring in **12a** formed upon dehydration of the *bis*-Michael adduct. Both **2a** and **2b** with **3c** formed the xanthenediones **12a** and **12b** and these derivatives were isolated for use in further studies.

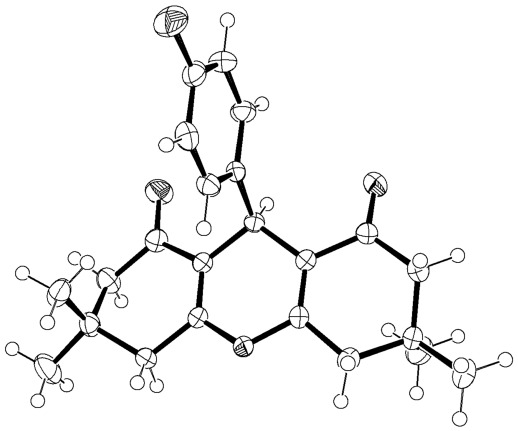
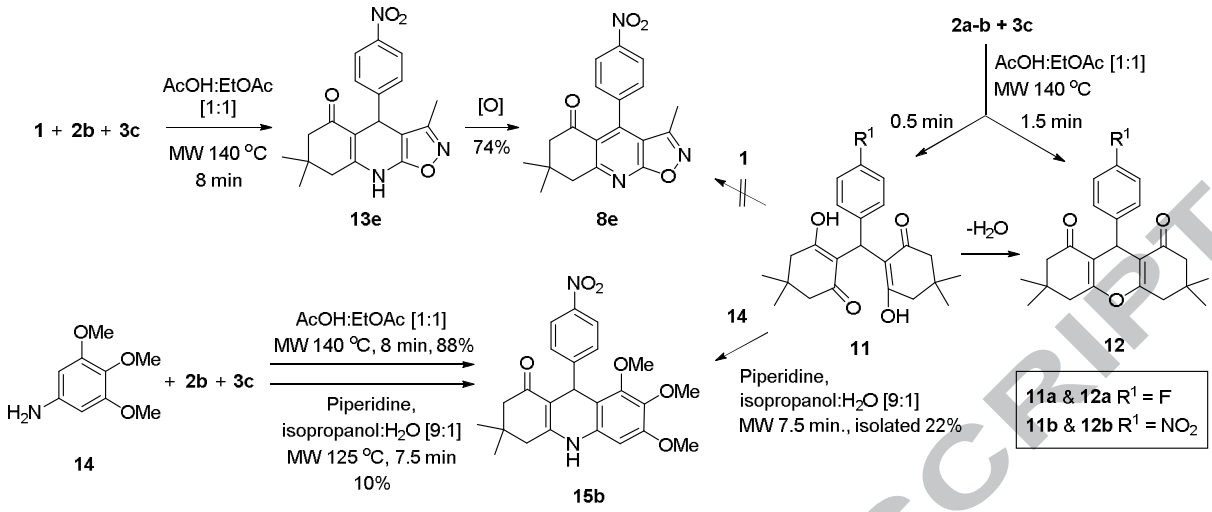


Figure 2. X-ray crystal structure of 9-(4-fluorophenyl)-3,4,5,6,7,9-hexahydro-3,3,6,6-tetramethyl-1H-xanthene-1,8(2H)-dione (**12a**) (ORTEP view). Hydrogen atoms have been removed for clarity and displacement ellipsoids are scaled to the 50% probability level.

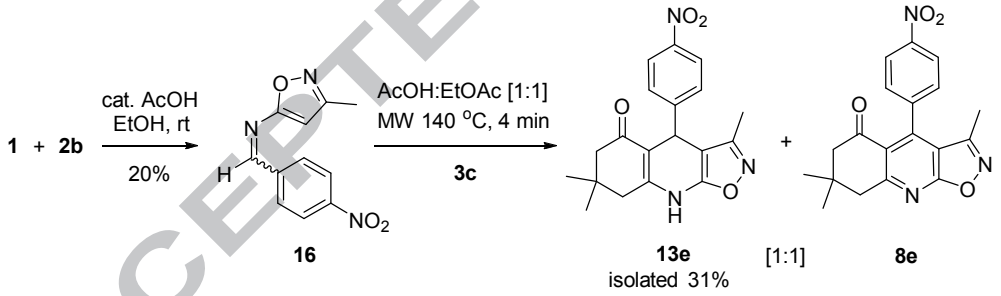
The reaction between **1** and **4a** occurred spontaneously in $CDCl_3$ and was monitored by ^{1}HNMR analysis whereby a water layer was visible suggesting this was the result of the condensation reaction. The water of condensation was confirmed during ^{1}HNMR studies, appearing as a broad singlet at 2.05 ppm. However, neither Tu's **5A** (Scheme 1) or the *bis*-Michael adduct were detected by ^{1}H NMR or GC-MS analysis. Further ^{1}HNMR monitoring revealed the H_2O condensation byproduct had hydrated **10A** forming a white precipitate in $CDCl_3$ and from analysis in D_6-DMSO gave the structure **10B** (Scheme 3) that was corroborated by HRMS data. This was also confirmed by using trifluoroacetic acid to revert **10B** to **10A** in D_6-DMSO with reaction monitoring by ^{1}HNMR**.**

Previous MCR studies have shown that *bis*-Michael adducts **11** participate as intermediates in the preparation of 12-aryl-8,9,10,12-tetrahydro-7H-benzo[b][4,7]phenanthrolin-11-ones[14] and tetrahydroacridones.[10] The microwave reaction of **1** and **11b** in EtOAc:AcOH (1:1) returned only a mixture of **1** and **12b**, whereas studies conducted in neutral media with catalytic amounts of piperidine as described by Chung *et al.*[10] returned complex mixtures. The base catalyzed reaction between **11a** and 3,4,5-trimethoxyaniline (**14**) in ^{i}PrOH:H_2O (9:1) with MW irradiation at 125 ºC (100 W) for 7.5 min produced the tetrahydroacridone **15** isolated in 22% yield (Scheme 4). This indicates that the nucleophilicity of the amine **1** is too weak to react with the *bis*-Michael adduct **11**. Furthermore, the comparative product yields derived by the acid or base MW assisted routes to **15** found that our EtOAc:AcOH (1:1) conditions provided 88% and the base catalyzed medium 10% yield (Scheme 4).



Scheme 4. Acidic/Basic microwave-assisted reaction pathways to **8e** and **15b**.

We also investigated the obvious alternative condensation pathway between **1** and **2b** that resulted in formation of the imine (**16)** as shown in Scheme 5. Studies by Ma *et al.*[16] reported that imines act as an intermediate in the MCR preparation of spiro{isoxazolo[1,3]dioxanopyridine}-4,6-diones. When **16** was microwaved for four minutes with **3c** in EtOAc:AcOH [1:1] two condensation products formed in a 1:1 ratio that were identified as **13e** and **8e** from which **13e** could be recrystallized in 31% yield (Scheme 5). Noteworthy is that longer MW reaction times yielded **8e** as the sole product. The structure of **13e** was confirmed by X-ray crystallography. The ORTEP diagram in Figure 3 shows a tetrahedral geometry around the benzylic carbon, as expected for the unoxidised heterocyclic product **13e**.



Scheme 5. The imine reaction conditions and pathway that produced a 1:1 mixture of **13e** and **8e**.

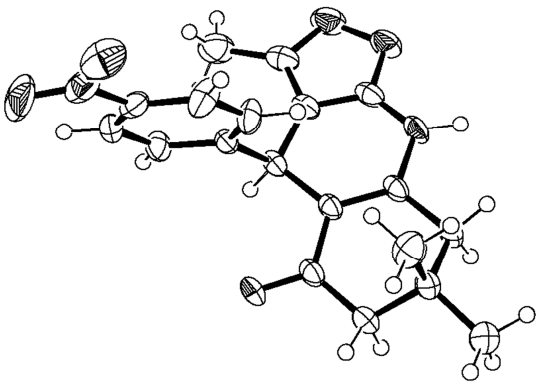
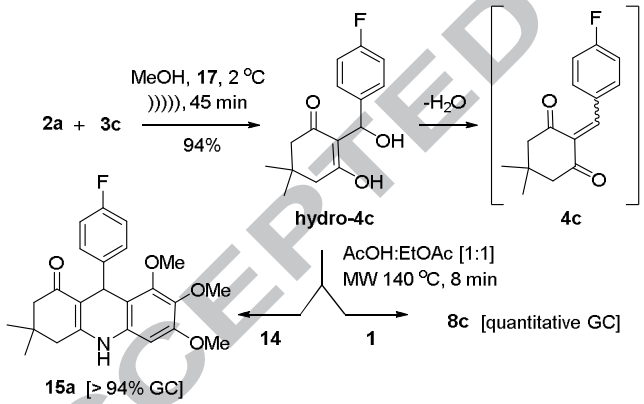


Figure 3. X-ray crystal structure of *3,7,7*-trimethyl-4-(4-nitrophenyl)-4,7,8,9-tetrahydroisoxazolo[5,4-*b*]quinolin-5(6*H*)-one (**13e**) (ORTEP view). Hydrogen atoms have been removed for clarity and displacement ellipsoids are scaled to the 50% probability level.

The failure to isolate dimedone-Knoevenagel adducts turned our attention to the utilization of the ionic liquid buffer 2-hydroxyethylammonium formate (**17**) that had previously been used in Knoevenagel condensations.[17] The sonication at 2 °C of a mixture of **2a** and **3c** in methanol with **17** for 45 minutes followed by solvent evaporation generated the required Knoevenagel adduct **hydro-4c** in 94% yield. Attempts to isolate **hydro-4c** by column chromatography led to decomposition and the product proved to be unstable during analysis in $CDCl_3$ and D_6-DMSO, but was characterized by NMR in CD_3OD. Freshly prepared **hydro-4c** underwent Michael addition with **1** or **14** when microwaved for eight minutes in EtOAc:AcOH [1:1] to provide products **8c** in 74% [quantitative GC] or **15a** [> 94% GC] (Scheme 6).



Scheme 6. Two-step three-component microwave synthesis of 4-fluorophenyl-3,7,7-trimethyl-isoxazolo[5,4-*b*]quinolin-5(6*H*)-one **8c** and 3,3-dimethyl-9-[4-fluorophenyl]-1,2,3,4,9,10-hexahydro-11,12,13-trimethoxy-]-acridine-1-one **15a**.

Conclusion

We have found that the three-component MW assisted reaction pathway between aromatic aldehydes, 1,3-cyclocarbonyls with 3-methylisoxazol-5-amine to furnish isoxazolo[5,4-*b*]pyridine, 4-aryl-3,7,7-trimethyl-isoxazolo[5,4-*b*]quinolin-5(6*H*)-one or 4-aryl-3,7,7-trimethyl-6,7,8,9-tetrahydroisoxazolo[5,4-*b*]quinolin-5(6*H*)-one products, **8a-h** always requires the formation of the Knoevenagel adduct before undergoing Michael addition with the amine; whereas the *bis*-Michael

adducts **11a,b** (Scheme 4) were unreactive with this amine. This was further confirmed whereby only the two-step synthesis sequence via the ionic liquid assisted generation of the dimedone-Knoevenagel adduct (**hydro-4c**, Scheme 6) provided the respective tricyclic products upon microwave irradiation with the amines **1** or **14**.

Appendix A. Supplementary Data

CCDC 1452875 (**8a**), CCDC 1452873 (**12a**) and CCDC 1452874 (**13e**) contains the supplementary crystallographic data. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB12 1EZ, UK; fax; (+44) 1223-336-033; or email: deposit@ccdc.cam.ac.uk.

Acknowledgements

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Abstract: The one-step three-component microwave assisted synthesis between aromatic aldehydes with tetronic acid or 1,3-indandione readily produced Knoevenagel adducts that underwent addition of 3-methylisoxazol-5-amine (**1**) to form the isoxazolopyridine products (**8**). With dimedone, the Knoevenagel adduct was generated using 2-hydroxyammonium formate and then reacted with **1** to give pure products.