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Synthesis and Reactivity of Dihalofuranones.

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Background: Halogenated furanones have been found to act as potent quorum sensing inhibitors in several bacterial species. It is believed that dihalofuranones covalently bind to the LuxS enzyme which is necessary for autoinducer-2 synthesis. In addition to their antimicrobial activity, halogenated furanones also possess anti-cancer, antioxidant and depigmentation properties. However, traditional routes to these compounds are low yielding and capricious.

Objective: To investigate higher yielding preparations of *gem*-dihalofuranones and compare their reactivity using Suzuki chemistry.

Methods: Ramirez dibromoolefination of maleic anhydride was optimised using a variety of conditions. A similar route was investigated for the preparation of bromofluorofuranones and dichlorofuranones. The conversion of a dichlorofuranone to the corresponding iodofuranone-derivatives using microwave-assisted Finkelstein chemistry was also studied. Lastly, the reactivity of the different dihalofuranones was compared by Pd-mediated coupling with phenylboronic acid.

Results: A higher yielding, concise synthesis to dibromofuranones was developed using a modified Ramirez reaction. Additionally, a telescoped preparation of dichlorofuranone proved higher yielding than previous approaches. Bromine- and iodine-substituted dihalofuranones proved more reactive than their chlorine-substituted analogues.

Conclusion: Higher yielding routes to bromine-, fluorine-, chlorine- and iodine-containing dihalofuranones were successfully developed. Suzuki couplings of *gem*-dihalofuranones were found to proceed with high stereoselectivity.

Keywords: Quorum sensing; autoinducers; resistance; heterocycles; dihalofuranones; Suzuki coupling.

1. INTRODUCTION

Molecules that interfere with bacterial quorum sensing (QS) and biofilm formation have been investigated as potential alternatives to antibiotics, and may constitute a new generation of antimicrobials.[1-4] QS is a mechanism that enables microbes to regulate gene expression in response to changes in cell population density.[5] The ability of bacteria to communicate *via* QS has a major impact on bacterial virulence. Inhibition of QS represents a useful means of controlling bacterial pathogenicity at a time when antibiotic resistance poses a significant threat to human health.[6] Unlike current bacteriostatic and bactericidal therapies, QS inhibitors could provide a route to treating infections without impacting bacterial cell growth and viability. As QS is not considered an essential process, its inhibition should not result in significant selective pressure for the development of resistance.[7] As such, QS is a novel target in the treatment of bacterial infections, particularly those caused by antibiotic resistant pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *Acinetobacter baumannii* (MDR-AB), multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) and multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA).[6, 8]

Halogenated furanones, originally isolated from the marine algae *Delisea pulchra*, as well as synthetic furanone derivatives, have been found to act as potent QS inhibitors.[9] These furanones interfere with the autoinducer-2 (AI-2) QS system present in several bacterial species (Fig. **1**).[10] It is believed that halogenated furanones, such as *gem*-dibromofuranone **3**, covalently bind to and modify the LuxS enzyme which is necessary for AI-2 synthesis.[11] The inability of the LuxS substrate to subsequently bind to the active site of the enzyme inhibits AI-2 synthesis, thereby blocking biofilm formation and toxin production. In addition to their antimicrobial activity, halogenated furanones also possess anti-cancer, antioxidant and depigmentation properties.[12-14]

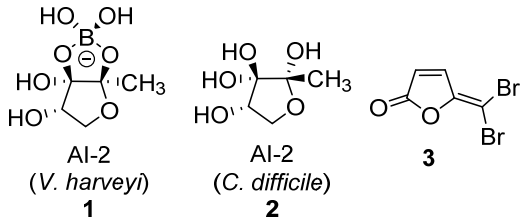
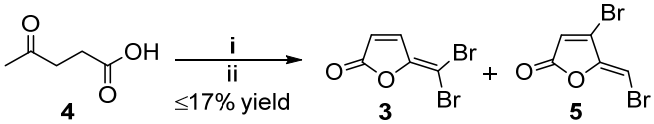


Fig. (1). Autoinducer-2 and dibromofuranone **3**.

In this paper, we describe a convenient one-step synthesis of dibromofuranone **3** and the preparation of related dihalofuranone derivatives. *gem*-Dihalofuranones constitute useful synthetic intermediates for various cross coupling reactions including palladium-catalysed Suzuki, Sonogashira and Stille couplings.[12, 15, 16] The reactivity of the different dihalofuranones is also compared.

2. RESULTS AND DISCUSSION

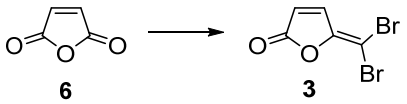
gem-Dibromofuranone **3** was initially synthesised from levulinic acid using a previously published procedure (Scheme 1).[16-18] While this route provided us with access to **3**, it was unreliable. Lowery and co-workers reported issues with both reproducibility and yields during the cyclisation of brominated levulinic acids.[19] They also noted that the sulfuric acid-catalysed cyclisation of brominated levulinic acids could potentially explode upon scale up (e.g. 5g scale). We encountered similar issues with decomposition of dibromofuranone **3** resulting in poor yields. An alternative, higher yielding route to **3**, which avoided the formation of 3,5-dibromofuranone **5** and the difficulties inherent in separating **3** from **5**, was obviously attractive.



Scheme 1. i. Br_2, HBr (cat.), CH_2Cl_2, 0 °C-r.t., 2 h; ii. H_2SO_4, 100 °C, 20 min.

Several methods for the incorporation of the dibromoolefin moiety to maleic anhydride were explored (Table 1). Employing the standard conditions of carbon tetrabromide and triphenylphosphine in dichloromethane saw complete consumption of the starting material but no evidence for the formation of **3** (entry 1).[20] Repeating the reaction in THF resulted in a similar outcome (entry 2). Park found that addition of triethylamine was beneficial for the dibromoolefination of aromatic anhydrides, but its introduction had no effect in our case (entry 3).[21] Likewise, Brown *et al.* reported the zinc-mediated dibromoolefination of aldehydes, but this combination again proved unsuccessful (entry 4).[22] We next investigated a modified Ramirez olefination procedure developed by Lautens and co-workers.[23] The addition of a solution of carbon tetrabromide in dichloromethane to maleic anhydride, followed by the slow addition of triisopropylphosphite, furnished dibromoolefin **3** in 21% yield following purification by column chromatography (entry 5). Switching the solvent to tetrahydrofuran was accompanied by a decrease in yield (entry 6). In an effort reduce side product formation, the reaction temperature was lowered to 0 °C, which resulted in a cleaner reaction but at the cost of unreacted starting material still remaining (entry 7). A compromise approach, where the carbon tetrabromide solution was added at 0 °C and then warmed to room temperature, saw full consumption of starting material and afforded the highest yield of 29% (entry 8). Unfortunately, subsequent attempts at improving the yield by altering the equivalents of carbon tetrabromide or triisopropylphosphite were not fruitful. Although a 29% yield is relatively modest, it compares favourably to the highest previous yield of 17% reported to date.[24] Additionally, this approach avoids the formation of **5**, making isolation much more straightforward. Finally, the cost of maleic anhydride in this one-step route is lower than previous multistep syntheses employing levulinic acid.

Table 1 Optimisation of dibromoolefination conditions



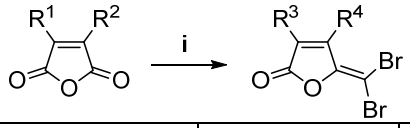
Entry	Reagents	Solvent	Temp	Yield
1	CBr_4, PPh_3	CH_2Cl_2	r.t.	-
2	CBr_4, PPh_3	THF	r.t.	-
3	CBr_4, PPh_3, Et_3N	THF	r.t.	-
4	CBr_4, PPh_3, Zn	CH_2Cl_2	r.t.	-
5	CBr_4, $P(O\text{-}iPr)_3$	CH_2Cl_2	r.t.	21%
6	CBr_4, $P(O\text{-}iPr)_3$	THF	r.t.	17%
7	CBr_4, $P(O\text{-}iPr)_3$	CH_2Cl_2	0 °C	25%
8[a]	CBr_4, $P(O\text{-}iPr)_3$	CH_2Cl_2	0 °C-r.t.	29%

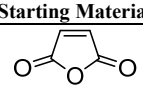
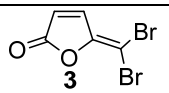
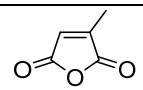
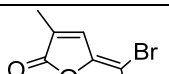
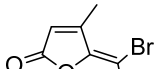
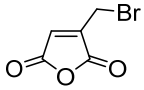
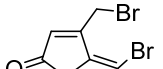
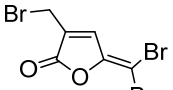
[a]CBr_4 (1.5 eq.), $P(O\text{-}iPr)_3$ (3 eq.), CH_2Cl_2, N_2, 0 °C-r.t., 2 h.

We also applied this chemistry to other cyclic anhydrides. Employing citraconic anhydride (**7**) as our substrate furnished 3-methyldibromofuranone **9** in 31% yield and novel 4-methyldibromofuranone **10** in 46% yield (Table 2, entry 2). Interestingly, the presence of the methyl group in the starting material led to a significant increase in yield (77% combined) compared to unsubstituted maleic anhydride (entry 1). The dibromoolefin moiety was also incorporated into 3-(bromomethyl)furan-2,5-dione (**8**), which was prepared according to a procedure of Reynaud and coworkers.[25] The presence of an allylic bromide group is often associated with potent QS activity.[9] Ramirez olefination of **8** afforded novel tribromofuranone **11** in 23% yield, while the minor product, tribromofuranone **12**, was generated in <5% yield based on ^{1}H-NMR integrations (entry 3). **12** was not isolated as it is a known compound.[26] In the case of citraconic anhydride (**7**) and 3-(bromomethyl)furan-2,5-dione (**8**), both starting materials were fully consumed and olefination was found to occur

predominantly at the more sterically hindered carbonyl. **9** and **10** were isolated in a ratio of 2:3, while **11** and **12** were produced in a 5:1 ratio.

Table 2 Modified Ramirez olefination of cyclic anhydrides.

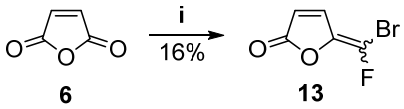


Entry	Starting Material	Product	Yield
1	 **6**	 **3**	29%
2	 **7**	 **9**	31%
		 **10**	46%
3	 **8**	 **11**	23%
		 **12**	<5%[a]

i.CBr_4 (1.5 eq.), P(O-*i*Pr)$_3$ (3 eq.), CH_2Cl_2, N_2, 0 °-r.t., 2 h.

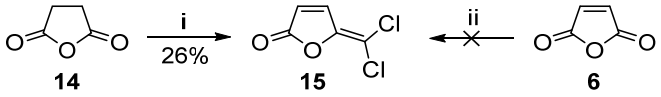
[a]Not isolated.

The antimicrobial potential of fluorine-, chlorine- or iodine-substituted furanones has not hitherto been explored. Incorporation of fluorine *via* the *gem*-difluoroolefination of maleic anhydride using the methods of Xiao *et al.* was unsuccessful.[27, 28] Instead, a Ramirez-type olefination of **6**, with tribromofluoromethane in place of carbon tetrabromide, produced *gem*-bromofluorofuranone **13** as a single isomer of undetermined configuration (Scheme 2). **13** decomposed over time, which was reflected in the low yield of 16%.



Scheme 2. i. CBr_3F (1.5 eq.), P(O-*i*Pr)$_3$ (3 eq.), CH_2Cl_2, N_2, r.t., 2 h.

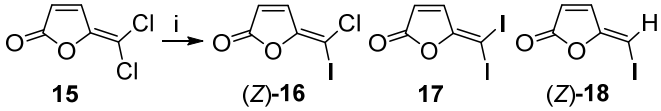
Dichlorofuranone **15** was prepared using a modified procedure of Franzén and co-workers (Scheme 3).[29, 30] Treating succinic anhydride (**14**) with sodium trichloroacetate at reflux for 3 h, followed by addition of concentrated sulfuric acid, produced **15** as the major product. Utilising this telescoped approach, which avoided the isolation of the chlorolevulinic acid intermediate, provided the target compound in a consistent 26% yield compared to those previously reported in the range of 16-20%. By contrast, dichloroolefination of **6** based on our previously optimised methodology, with dichlorodibromomethane replacing carbon tetrabromide, failed to proceed.



Scheme 3. i. $NaOCOCCl_3$, DME, reflux, 3 h then H_2SO_4, 100 °C, 45 min. ii. CBr_2Cl_2 (1.5 eq.), P(O-*i*Pr)$_3$ (3 eq.), CH_2Cl_2, N_2, r.t., 2 h.

Methods for the direct introduction of iodine into dihalofuranone substrates are heretofore undisclosed. We initially attempted to access iodine-containing derivatives *via* halogen-exchange reactions on dibromofuranone **3**, but were unable to isolate the resultant iodofuranones due to product degradation. Similar reactions with dichlorofuranone **15** proved more successful (Table 3). Classical Finkelstein conditions of sodium iodide in anhydrous acetone led to poor conversions of **15**. Heating **15** and excess sodium iodide in anhydrous dimethylformamide to 160 °C under microwave irradiation afforded a mixture of three iodinated products, namely chloroiodofuranone **16**, diiodofuranone **17** and monoiodofuranone **18**. Dimethylformamide was our chosen solvent as its high boiling point allowed for higher temperatures and shorter reaction times when compared to acetone.[31, 32] The product ratios were determined by measuring the integration of the H-4 doublets at 7.74 ppm for **16**, at 7.62 ppm for **17** and at 7.39 ppm for **18**. After three minutes, novel chloroiodofuranone **16** was the predominant product along with limited amounts of diiodofuranone **17** and monoiodofuranone **18** (entry 1). Purification of the crude reaction mixture furnished **16** exclusively as the (*Z*)-isomer in a yield of 43%. The stereochemical configuration of **16** was determined *via* subsequent Suzuki coupling reactions (*vide infra*). Extending the reaction time favoured the formation of both **17** and **18** (entries 2-5). Isolation of **17** was not possible due to its tendency to degrade.

Table 3 Microwave-assisted halogen exchange reactions.



Entry	Time	Product Ratios

	(min)				
		15	**16**	**17**	**18**
1	3	6	88	4	2
2	10	3	67	14	16
3	20	2	38	23	37
4	30	1	19	23	37
5	60	0	0	0	100

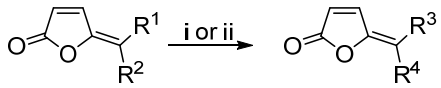
i. NaI (10 eq.), DMF, M.W., 160 °C.

Purification of the reaction mixture after 60 minutes led to the isolation of **18** as a single isomer in 12% yield (entry 5). The formation of **18** is not solvent dependent, as the same product was generated when anhydrous dimethylformamide was replaced with 2-butanone. A 2D NOESY correlation between H-4 and H-6 confirmed the configuration of (*Z*)-**18** (see Supplementary Material). In our hands, (*Z*)-**18** was generally unstable and partially isomerised to (*E*)-**18** in $CDCl_3$ after ten hours at room temperature.[33, 34]

The differences in reactivity of dibromofuranone **3**, dichlorofuranone **15** and chloroiodofuranone (*Z*)-**16** as coupling partners were next investigated (Table 4). Reports of Suzuki couplings with *gem*-dihalofuranones are limited and no such examples have been described for **15** or **16**.[12] Room temperature coupling of **3** and phenylboronic acid furnished monoarylated furanone (*Z*)-**19** as a single isomer in 32% yield after 24 hours, along with small amounts of diarylated analogue **20** (entry 1). Increasing the equivalents of the boronic acid and raising the temperature to 100 °C favoured formation of **20** (entry 2). Dichlorofuranone **15** proved to be a less reactive substrate overall and afforded monoarylated chlorofuranone (*Z*)-**21** in 50% yield after 48 hours (entry 3). Exclusive formation of the *Z*-isomer is in line with previous palladium-catalysed couplings of various *gem*-dichloroolefins.[35, 36] None of the diarylated product was detected, in contrast to the comparable reaction of dibromofuranone **3** (entry 1). Finally, chloroiodofuranone (*Z*)-**16** displayed higher reactivity than dichlorofuranone **15** which was reflected in shorter reaction times and higher yields (entry 4). (*E*)-**21** was recovered in 66% yield after 20 hours at room temperature.

The stereochemical configuration of the Suzuki products was determined using 2D NOESY. No correlation was present between H-4 and the aromatic protons for (*E*)-**21**, in contrast to (*Z*)-**21**. Additionally, in the case of (*E*)-**21**, H-4 appeared considerably downfield at 8.00 ppm whereas the chemical shift of H-4 for (*Z*)-**21** was lower at 7.47 ppm. We had previously observed this marked difference in the chemical shifts of H-4 for similar (*E*)- and (*Z*)-isomers in other studies. As (*E*)-**21** was the sole product of the palladium-catalysed coupling of chloroiodofuranone **16**, **16** was likewise assigned a *Z*-configuration. Accordingly, this chemistry facilitates the preparation of either of the two geometric isomers (entries 3 and 4).

Table 4 Suzuki coupling reactions of dihalofuranones.



Entry	R^1	R^2	i or ii	Temp (° C)	Time (h)	R^3	R^4	Product	Yield
1	Br	Br	i	r.t.	24	Ph	Br	(*Z*)-**19**	32%
						Ph	Ph	**20**	7%
2	Br	Br	ii	100	4	Ph	Ph	**20**	82%
3	Cl	Cl	i	r.t.	48	Ph	Cl	(*Z*)-**21**	50%
4	Cl	I	i	r.t.	20	Cl	Ph	(*E*)-**21**	66%

i. Phenylboronic acid (1.1 eq.), $Pd(OAc)_2$ (3 mol%), SPhos (2 mol%) K_3PO_4 (2 eq.), toluene, N_2.
ii. Phenylboronic acid (3 eq.), $Pd(OAc)_2$ (1 mol%), SPhos (2 mol%), K_3PO_4 (3 eq.), toluene, N_2.

CONCLUSION

gem-Dihalofuranones have significant potential as quorum sensing inhibitors of autoinducer-2. We have described a concise preparation of dibromofuranones *via* direct Ramirez olefination of cyclic anhydrides. A higher yielding, telescoped synthesis of dichlorofuranone is also outlined. Halogen-exchange reactions with dichlorofuranone provide access to iodine-containing derivatives. Subsequent Suzuki couplings proceed with high stereoselectivity depending on the nature of the dihalofuranone substrate.

CONFLICT OF INTEREST

Declared none.

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SUPPLEMENTARY MATERIAL

Full experimental procedures are provided in the Supplementary Material.

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