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A short and efficient preparation of methyl-[1,2,4]oxadiazolium derivatives with plant-inducing activity

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We have developed a concise and efficient synthetic method leading to a structurally diverse array of salicylic acid and oxadiazolium derivatives, starting from commercially available halogenated phenols.

System acquired resistance (SAR) of a plant is the induction of a transient long-distance defense response to a fungal or bacterial attack that is distinct from the local production of phytoalexins.[1] Chemicals that promote SAR are potential control agents with long-term persistence. Salicylic acid (**1**) is an inducer of antifungal proteins and is proposed to activate the expression of SAR genes in plants.[2] Acibenzolar (**2**) may operate in a similar manner to natural defense activators. It does not possess fungicidal activity *per se* but induces resistance to a wide range of pathogens (Fig. 1).

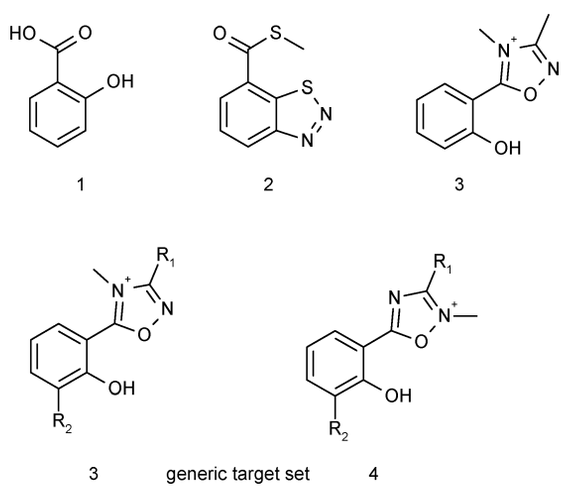


Fig. 1 SAR active molecules.

Recently we discovered a new lead structure **3**, acting as a plant inducer. In order to explore this interesting biological activity and to evaluate the scope of our findings, we have established a novel diversity-oriented synthetic approach to the compound classes **3** and **4** (Fig. 1). Based on the earlier work of Ryabukhin and co-workers,[3–6] a flexible and highly convergent approach, utilizing cheap starting materials and therefore allowing an agrochemical application, was developed.

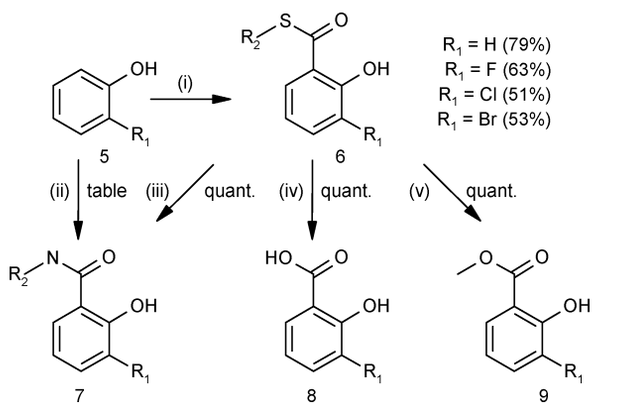
The starting point of our synthesis was the Lewis acid mediated addition of isocyanates (R_2 = Me) to phenols as described by Picollo and co-workers.[7] The reaction proved to be robust and worked with a range of halogenated phenols and isocyanates producing the desired meta-halogenated salicylamides **7** (Scheme 1, Table 1).

Similarly successful was the BCl_3–$AlCl_3$ mediated *ortho*-exclusive Friedel–Crafts type reaction of **5** with methylthiocyanate.[8] In the presence of 1.2 equivalents of BCl_3 and 1 equivalent of $AlCl_3$, phenols **5** reacted smoothly to produce thioesters **6** in acceptable yields. The obtained thioesters **6**, proved to be very versatile intermediates for the rapid synthesis of either *meta*-halogenated salicylic acids **8** or esters **9**,[9] as well as for amides **7** (R_2 = H), not easily accessible with the isocyanate condensation pathway (Scheme 1, Table 1). Compounds **8** and **9** were found to be excellent SAR active compounds by themselves, supporting the suspected importance of the "salicylic acid like" motif present in a potential SAR active molecule.

Table 1 Conversion of phenols **5** to salicylamides **7**

Entry	R1	R2	**7** (%)[a]	Path	Mp/°C
1	H	H	79	(i), (iii)	144
2	F	H	63	(i), (iii)	151
3	Cl	H	51	(i), (iii)	174
4	Br	H	53	(i), (iii)	162
5	H	Me	88	(ii)	113
6	F	Me	81	(ii)	148
7	Cl	Me	94	(ii)	166
8	Br	Me	87	(ii)	132

[a] Isolated yields.



Scheme 1 *Reagents and conditions:* (i) I. MeNCS, BCl_3, $AlCl_3$, dichloroethane, rt, 4 h; II. 6 M HCl, rt, 10 min; (ii) MeNCO, $AlCl_3$, toluene, rt, 12 h; (iii) $(R_2)NH_2$, dichloromethane, rt, 6 h; (iv) LiOH, H_2O, 5% MeOH, rt, 6 h; (v) LiOH, H_2O–MeOH 1 : 1, rt, 6 h.

The 4-oxo-1,3-benzoxazinium salts **9** were obtained by a one-pot acylation–dehydration approach in good overall yields.[10] Following Ryabukhin's protocol,[4,5] the recyclization of the perchlorates **10** with hydroxylamine and sodium acetate in boiling glacial acid gave the desired oxadiazolium compounds **3** (Scheme 2, Table 2).

In order to access the oxadiazo-4-ium compounds **4**, we planned to benefit from an observation made by Ryabukhin and co-workers.[4]

In the course of studying the alkylation behavior of **11** (R = H) by treating it with Me_2SO_4, they observed selective *N*(2)-methylation. The findings were explained with an intramolecular H-bridge of the phenolic H towards N(4). Indeed, boiling of intermediates **11** in neat Me_2SO_4 gave rise to a 1 : 4

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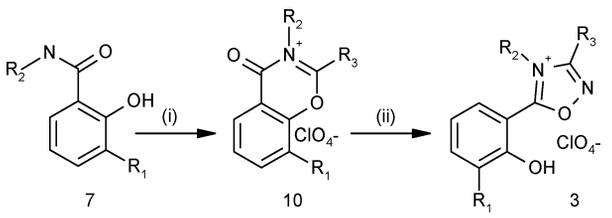
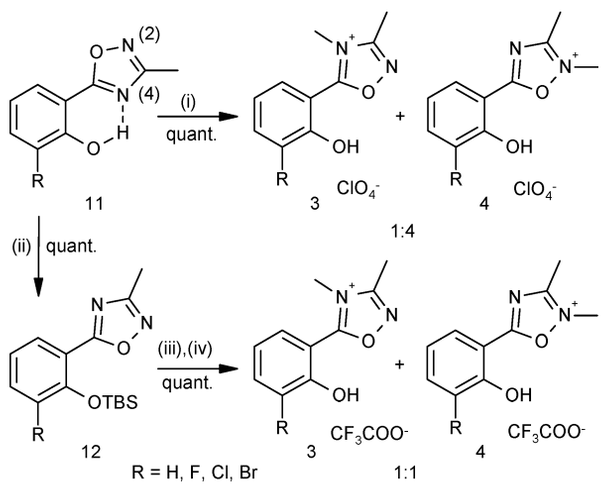
Table 2 Cyclization/recyclization of salicylamides **7**

Entry	R_1	R_2	R_3	**10** (%)[a]	**3** (%)[a]
A	H	H	Me	91	95
B	F	H	Me	68	72
C	Cl	H	Me	63	76
D	Br	H	Me	51	71
E	H	Me	Me	87	59
E	F	Me	Me	74	54
G	Cl	Me	Me	60	56
H	Br	Me	Me	65	58

[a] Isolated yields.



Scheme 2 *Reagents and conditions:* (i) Ac_2O, $HClO_4$, 72 h, rt; (ii) $NH_2OH{\cdot}HCl$, NaAc, AcOH, 2 h, rt.



Scheme 3 *Reagents and conditions:* (i) I. Me_2SO_4, 110 °C, 4 h; II. $HClO_4$, AcOH, rt; (ii) TBSTrf, Hünig's base, CH_2Cl_2, rt, 8 h; (iii) Meerwein's salt, CH_2Cl_2, rt, 12 h; (iv) CF_3COOH, 1% H_2O, 80 °C, 4 h.

mixture of both regioisomers **3** and **4** (Scheme 3). Recrystallization from AcOH–ether furnished pure oxazolium derivatives **4**. To verify the H-bridge influence, compounds of the type **11** were silylated prior to the methylation, using TBSTrf and Hünig's base. Meerwein's salt in dichloromethane was found to be the reagent of choice for the methylation reaction. For comparison reasons the obtained reaction mixtures were subsequently desilylated in CF_3COOH containing 1% of H_2O. A 1 : 1 N(2) : N(4) selectivity was found in all the investigated cases, supporting the H-bridged theory by Ryabukhin.

In summary, we have developed a concise and efficient synthetic methodology leading to a structurally diverse array of oxadiazolium derivatives,[11] starting from commercially available halogenated phenols. The strategy also involves a new and rapid access to all meta-halogenated salicylic acids, compounds of high synthetic value.

Notes and references

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11 All new compounds were completely characterized and gave satisfactory spectral and analytical data. Selected data: Compound **10f** (R_1= F, R_2 = R_3 = Me): ^{1}H-NMR (CD_3CN) δ: 3.12(s, 3H); 3.80(s, 3H); 7.81(dt, 1H); 7.97(td, 1H); 8.08 (d, 1H); ES-MS *m/z* 411(M^{+1}); Mp: 202–205 °C (diethylether). Compound **11f** (R_1 = F, R_2 = H, R_3 = Me): ^{1}H-NMR (CD_3CN) δ: 2.58(s, 3H); 7.06(dt, 1H); 7.48(dd, 1H); 7.80(d, 1H); ES-MS *m/z* 196(M^{+1}); Mp: 120–122 °C (H_2O). Compound **3f** (R_1 = F, R_2 = R_3 = Me): ^{1}H-NMR (CD_3CN) δ: 2.52(s, 3H); 3.61(s, 3H); 6.98(dt, 1H); 7.35(dd, 1H); 7.61(d, 1H); 7.80(br s, 1H); ES-MS *m/z* 209(M^{+1}); Mp: 178–180°C (AcOH). Compound **4f** (R_1 = F, R_2 = R_3 = Me): ^{1}H-NMR (CD_3CN) δ: 2.59(s, 3H); 4.11(s, 3H); 6.92(dt, 1H); 7.38(dd, 1H); 7.65(d, 1H); 7.80(br s, 1H); ES-MS *m/z* 209(M^+); Mp: 152–156°C (AcOH).