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Synthesis and Herbicidal Activity of Phenylpyridines – A New Lead

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Abstract: Novel phenylpyridines were synthesized based on molecular modeling oriented design by superposition of herbicidal phenyl-uracils, -indazoles, and diphenylethers. Their preparation follows Suzuki-type coupling conditions of reactive 2-chloro-pyridines with appropriate 2,5-substituted 4-chloro-phenyl boronic acids. Depending on the nature of substituents in the pyridine, and in particular the phenyl group, a large number of derivatives are readily accessible. Besides open-chain phenylpyridines also anellated compounds, such as pyridine-substituted 2H-1,4-benzothiazin-3(4H)-one or 3,4-dihydro-1H-quinolin-2-one, were prepared. Phenylpyridines act by inhibition of protoporphyrinogen-IX-oxidase. Their synthesis will be described in conjunction with structure–activity relationships. Phenylpyridines are highly active against many important broadleaf and grass weed species under pre- and – in particular – post-emergent conditions.

Keywords: Phenylpyridines · Protoporphyrinogen-IX-oxidase inhibitors · SAR · Suzuki-coupling

1. Introduction

Over the past 30 years, the number of herbicides that inhibit the enzyme protoporhyrinogen-IX-oxidase (Protox) has grown from a few experimental compounds to one of the largest classes of patented herbicides; see overview [1]. The reasons for industrial engagement were

- low application rates,
- fast activity,
- broad spectrum against grasses and weeds, and
- residual activity.

The mode of action, which ultimately led to the use of the term 'peroxidizing herbicides' [2], was, however, not discovered until 1987 [3–5]. Their molecular target site is the enzyme protoporphyrinogenoxidase (Protox) of the porphyrin pathway, a key enzyme of chlorophyll biosynthesis. By inhibiting Protox ('PPO-inhibitors'), these herbicides induce protoporphyrinogen IX accumulation – the desired enzyme intermediate. They do so, however, at the wrong place – being exported from the plastid envelop into the cytoplasma, where it is oxidized by autoxidation [3] and herbicide-resistant extraorganellar oxidases [6] into protoporphyrin IX, a very efficient photosensitiser, generating singlett oxygen when exposed to light [2]. The latter destroys cell membranes, the pigments bleach out and the plant becomes brown and necrotic: the plant burns up [7]. Therefore, the light-requiring step – the generation of singlett oxygen – is only a secondary event, resulting from the initial formation of protoporphyrin IX.

Among the early PPO-inhibitors are diphenyl ethers like Blazer® (acifluorfen sodium; Rohm and Haas, BASF) which were followed by N-phenyl-imides, especially phenyl uracils and tetrahydrochlorindazoles like S 275 (Sumitomo) [1].

1.1. *Molecular Modeling*

We became interested in new derivatives based on molecular modeling-oriented design by superposition of herbicidal phenyl uracils, -indazoles and diphenylethers, that lead to biphenyls as a first step (Scheme 1). The latter showed good PPO enzyme- but only poor green-house activity. Introduction of a pyridine nitrogen strongly increased control of undesired plants. As shown in Fig. 1, molecular modeling is very helpful for visualizing and understanding the degree of superposition of uracils and phenylpyridines, with one carbonyl oxygen being imitated by a chlorine atom and the other by the pyridine nitrogen with its free electron pair.

2. Materials and Methods

Phenylpyridine synthesis was achieved by Suzuki-type coupling of reactive 2-chloropyridines with appropriate 4-chlorophenyl-boronic acids. Depending on the nature of groups R^1–R^3 and, especially, R^4 (see Fig. 2), a large number of derivatives are readily accessible [8][9].

2.1. *Synthesis of 3-Chloro-2-(phenyl)-5-(trifluormethyl)-pyridines*

2,3-Dichloro-5-trifluormethylpyridine (**1a**) (Scheme 2) is converted by a sequence of Suzuki-coupling with 4-chloro-phenylboronic acid (**2a**), nitration and Pt/C-catalyzed hydrogenation in N-ethylmorpholine to the pyridyl substituted phenylhydroxylamine **4** with 75% overall yield. The

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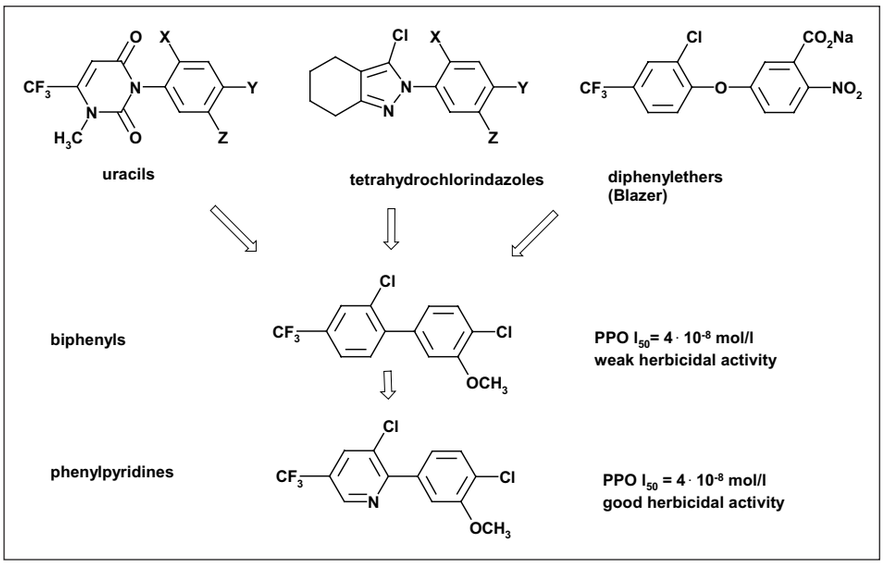


Scheme 1. Phenylpyridines generated by superposition of phenyluracils, indazoles and diphenylethers

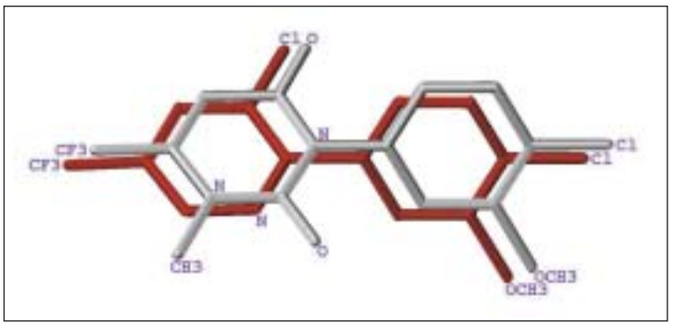


Fig. 1. Superposition of uracils and phenylpyridines

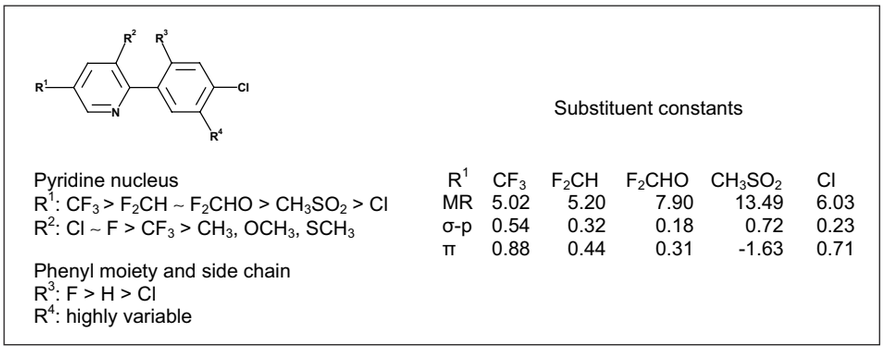


Fig. 2. Structure–activity relationship of the pyridine and phenyl moieties

key step is the following Bamberger rearrangement for the introduction of the fluorine atom into the 2-phenyl position of **5** in 86% yield. The latter is diazotized to the phenol and alkylated to the propargyl ether **7** in 64% yield over both steps.

NBS bromination of another Suzuki coupling product **3b** yields a dibromomethyl derivative, which is transferred to the corresponding aldehyde **8** by treatment with sulfuric acid. The acid **9** is obtained in high yield by sodium chlorite oxidation followed by standard esterification (**10**).

To obtain the methyl 2-chloro-3-(phenyl)propanoate **11**, 2-chloro-5-[3-chloro-5-(trifluormethyl)-2-pyridinyl]-4-fluoroaniline **5** is diazotized in a t-butyl nitrite solution in acetonitrile in the presence of methyl acrylate and cupric chloride during 4 h at 0 °C and 12 h at 22 °C to produce after chromatography the propanoic ester **11** in 31% yield.

For the synthesis of the sulfonamide **13**, 2,3-dichloro-5-trifluormethylpyridine (**1a**) is coupled under Suzuki conditions with 4-chloro-2-fluoro-phenylboronic acid (**2c**) to the phenylpyridine **3c,** which is submitted to chlorosulfonylation at 130 °C, followed by reaction with sarcosin-methyl ester hydrochloride in 72% and 68% yield, respectively.

The first step for the synthesis of the 2H-1,4-benzothiazin-3-(4H)-one **17** is nucleophilic displacement of the fluorine atom in **14** with thioglycolic acid to afford the thioether **15** which by reductive cyclization yields the 6-(2-pyridinyl)-2H-1,4-benzothiazin-3(4H)-one **16** in an overall yield of 50%. The latter is alkylated with propargyl bromide in the presence of sodium hydride in DMF, resulting in a yield of 80%.

2.2. Biological Tests

2.2.1. *Greenhouse Experiments*

All the data were taken from screening-type trials in the greenhouse. For post-emergence tests, plants were cultivated in plastic pots of 8.6 cm diameter containing loamy sand with about 1.2% humus as the substrate. The test plants were sown, grown in the test pots to a height of 4–12 cm and then treated with the test compound in a spray chamber at a rate of 31.25 g/ha a.i., formulated as emulsion concentrates. The number of replicates was one and, for comparison, four untreated control pots were included in each test. After the application, the test plants were kept for 18–20 days at 18–27 °C, during which period the plants were maintained and their reaction to the individual treatments was assessed and recorded.

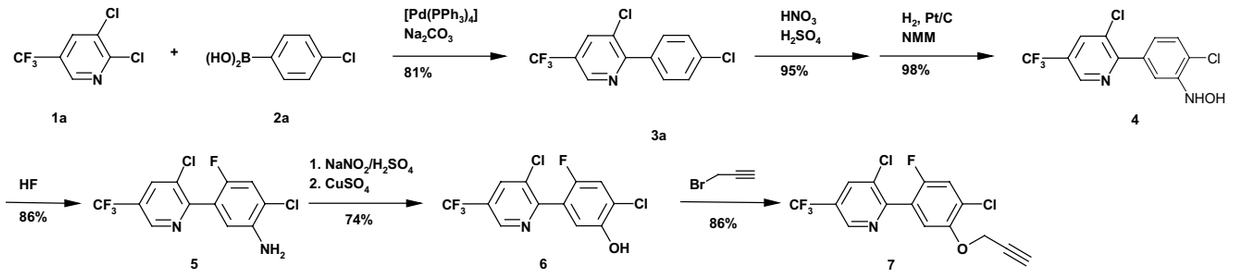
Injury to the plants was assessed on a scale from 0 to 100 in comparison to the untreated controls, with 0 denoting no damage and 100 denoting complete destruction of at least the visible plant parts. Fig. 3 denotes the average injury across three grass species (grey bars) or seven broadleaf species (black bars).

2.2.2. *Test Species*

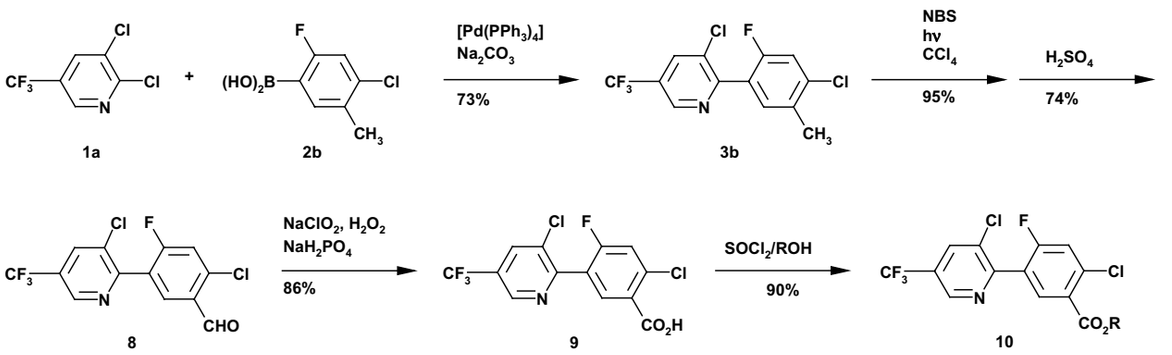
The following plant species were used: Grasses: Alexander grass *(Bracharia plantaginea),* barnyard grass, *(Echinochloa crus galli),* and giant foxtail *(Setaria faberi)*

Broadleaf weeds: velvet leaf *(Abuthilon theophrasti),* redroot pigweed *(Amaranthus retroflexus),* hairy beggarticks *(Bidens pilosa),* common lambs-quarters *(Chenopodium album),* cleavers *(Galium ap-*

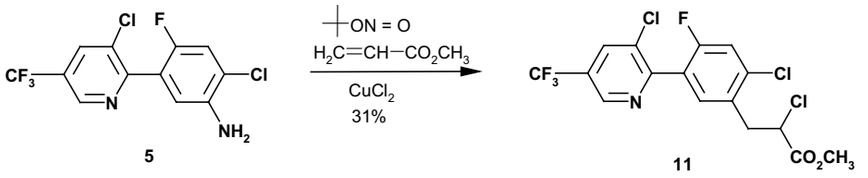
Phenylpyridine ethers



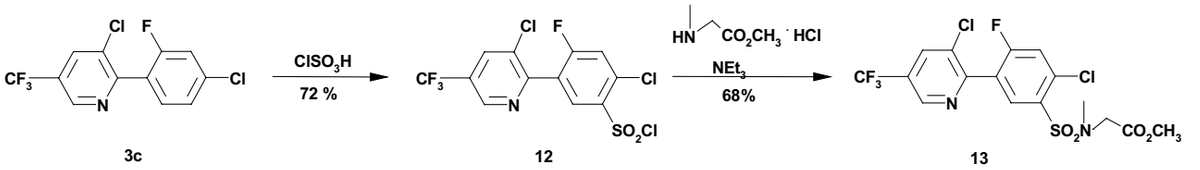
Phenylpyridine carboxylic acid derivatives



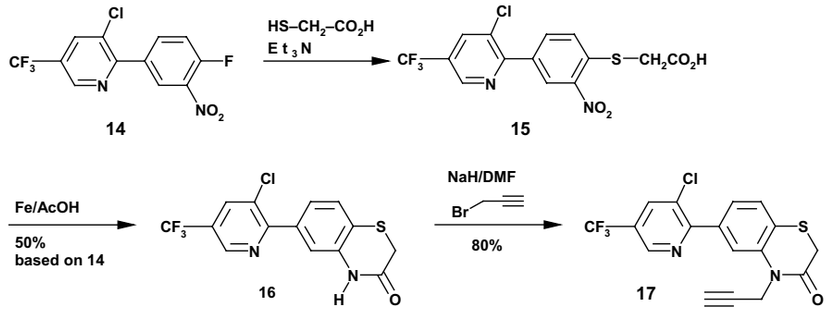
Phenylpyridine propanoic esters



Phenylpyridine sulfonamides



Anellated phenylpyridines



Scheme 2. Synthesis of phenylpyridines

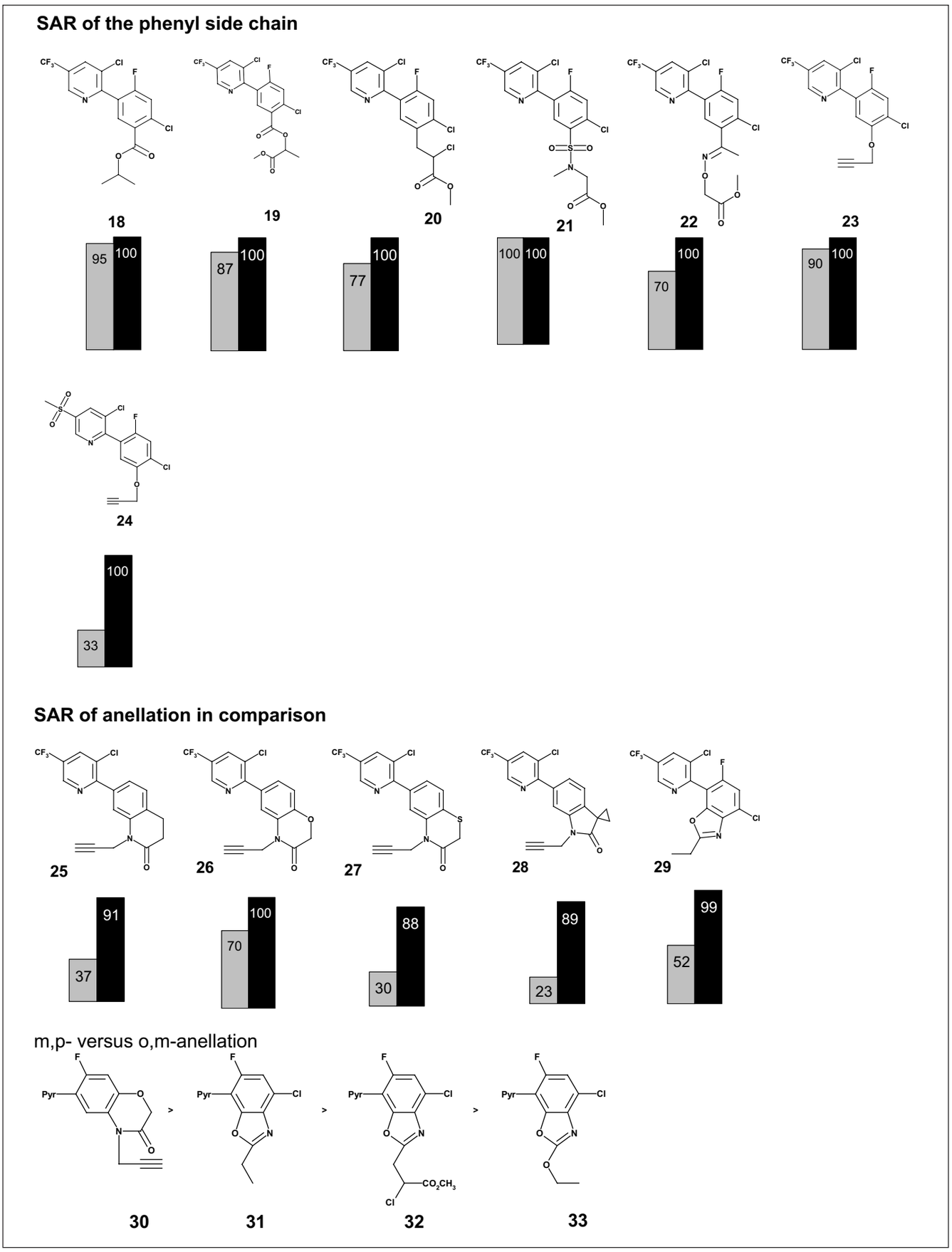


Fig. 3. Structure–activity relationship of the side chain and type of anellation. Grey bars: injury to grass species, black bars: injury to broadleaf species.

parine), tall morning glory *(Pharbitis purpurea),* and ladysthumb *(Polygonum persicaria)*

3. Results and Discussion

3.1. *Structure–Activity Relationships (SAR)*

3.1.1. *Pyridine Moiety*

Electron-withdrawing substituents in the pyridine moiety (Fig. 2) change the herbicidal activity of the phenylpyridines in question. In position R^1 trifluoromethyl roughly has the same steric requirement and lipophilicity as chlorine, but due to its stronger electron-withdrawing properties is herbicidally much more active. Difluoromethylderivatives and methyl sulfonyl are in between, either because of less electron-withdrawing character and lipophilicity or as a result of just too much bulkiness in the methyl sulfonyl case [11][12]. Additionally, in position R^2 electron-withdrawing substituents are required. Chlorine and fluorine show comparable herbicidal activity, better than trifluoromethyl and superior to methyl and ether substituents, which are excessively electron-donating.

3.1.2. *Phenyl Moiety*

In the phenyl moiety (Fig. 2) herbicidal activity decreases in the R^3 position on passing from fluorine to hydrogen and chlorine by about a factor of 3 to 4. The R^4 position, on the other hand, is highly flexible.

3.1.3. *SAR of the Phenyl Side Chain*

The phenyl side chain in position R^4 (Fig. 3) is highly variable and at a rate of 31.25 g/ha a.i. shows the same herbicidal activity on broadleaf weeds, irrespective of the electronic and steric character of the chosen chain. But differences become evident upon examination of grass activity. The most active is the sulfonamide side chain **21,** followed by esters like **18** and **19** and the ether **23.** With propanoic esters **20** and oximes **22** grass activity falls into the 70% range. The methyl pyridyl sulfon **24** has insufficient grass activity.

3.1.4. *SAR of Anellation in Comparison*

When anellation in the 3,4-phenyl position is investigated, the 1,4-benzoxazin-3-one heterocycle **26** is about twice as strong on grasses as the 3,4-dihydro-1H-quinolin-2-one type **25** or the related 1,4-benzothiazin-3-one **27.** Lowest grass activity is shown by the 1,3-dihydro-indol-2-one type **28.** Predetermined breaking points in the heterocyclic nucleus – prone to metabolization – apparently decrease herbicidal activity. The (1,4-benzoxazin-3-one-6-yl)-pyridine *m,p*-anellation **30** is herbicidally more active than the (benzoxazole-7-yl)-pyridine derivative **31** with *o,m*-anellation.

4. Conclusion

Novel phenylpyridines were conceived based on molecular modeling-oriented design – superposition of herbicidal N-phenylimides and diarylethers. Their synthesis *via* Suzuki-coupling is the method of choice for obtaining high yields.

Phenylpyridines are potent inhibitors of protoporphyrinogen-IX oxidase in plants, where they constitute a new herbicidal lead. They have strong herbicidal activity against a broad range of grasses and broadleaf weed species. Structure-activity relationship studies show that the optimum substitution pattern of the pyridine ring is 3-chloro-5-trifluormethyl. The phenyl ring should be 4-chloro-2-fluoro-substituted with an additional (high variable) substituent in the 5-position.

Most active side chains in the 5-position of the phenyl ring are the N-methyl-N-(alkoxy-carbonyl)alkyl sulfonamides, the alkyl and (alkoxycarbonyl)alkyl carboxylates, as well as the propargyl ether. Among the benzanellated derivatives, the (1,4-benzoxazin-3-one-6-yl)-pyridine substitution shows the strongest herbicidal activity. Phenylpyridines are also very good pre-emergent herbicides (data not shown).

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