The Synthesis and Biological Activity of 1-Alkyl-4-(3-azacyclobenzoyl)-5-hydroxypyrazole Herbicides

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Abstract: The benzoylpyrazoles belong to a class of herbicides that inhibit the enzyme 4-hydroxy-phenylpyruvate dioxygenase (HPPD). This mode of action is characterized by bleaching due to the disruption of plastoquinone and α-tocopherol biosynthesis. Early studies indicated that the C(3) position of benzoylpyrazoles can accommodate a wide range of functionality. This paper describes synthetic efforts to improve cool season grass weed activity and wheat selectivity by incorporating cyclic moieties attached through nitrogen at this position. The aza substituents were generally installed by nucleophilic aromatic substitution, however, an efficient four-step method was developed for constructing substituted morpholino moieties directly on pre-formed benzoylpyrazoles. The structure–activity relationships revealed that certain piperidino moieties provided good activity on wild oat, while exhibiting selectivity toward wheat. They also showed that excellent levels of activity on wild oat and blackgrass can be achieved with morpholino substituents.

Keywords: Benzoylpyrazoles · Herbicide · Hydroxyphenylpyruvate dioxygenase inhibitors · Morpholines · Piperidines

Introduction

1-Alkyl-4-benzoyl-5-hydroxypyrazoles are highly active novel herbicides that are characterized by an appropriately function-alized benzoyl group attached to an acidic hydroxypyrazole (Fig. 1). These materials are herbicidal because they inhibit the enzyme hydroxyphenylpyruvate dioxygenase (HPPD) in the quinone biosynthesis pathway [1]. Inhibition of this step interrupts the synthesis of plastoquinones and α-tocopherol, which makes the plant unable to protect itself from photo-oxidation. The un-mistakable bleaching symptomology, followed by plant death, is characteristic of this mode of action. Other herbicidal chemistries are known to operate at this site as well, most notably the benzoylcyclo-hexanediones [2] and the benzoylisoxa-zoles [3].

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Interest in these benzoylpyrazoles stems from the broad spectrum activity observed when they are applied pre- or post emergently on broadleaves and grasses and because they are mobile in both plants and soil. Research at Dow AgroSciences and elsewhere [4] in the late 1980s and early 1990s led to a basic understanding of the structure–activity relationships (SAR) of the benzoylpyrazoles (Fig. 1). Small alkyl substituents on the pyrazole were preferred and the best compounds generally had a Cl or Me group at the C(2)-position and a SO_2Me in the (C)4-position of the benzene ring. In contrast to the rest of the molecule, however, the C(3) position was able to ac-commodate many diverse substituents. Sul-fones and alkoxycarbonyls were particular-ly good, as were certain alkoxy substi-tuents. Naturally, we wondered whether nitrogen could replace the electronegative oxygen and provide bioisosteric sub-stituents.

Synthesis of the $3\text{-}NMe_2$ substituted analog (Table 1, entry 1) demonstrated that it was possible to utilize a nitrogen at this location and retain herbicidal activity. A general investigation of the area was there-fore undertaken [5]. Of primary interest to us, however, was the grass activity inherent in these molecules. The $MeOCH_2CH_2NH$ group (entry 2) was found to be quite active
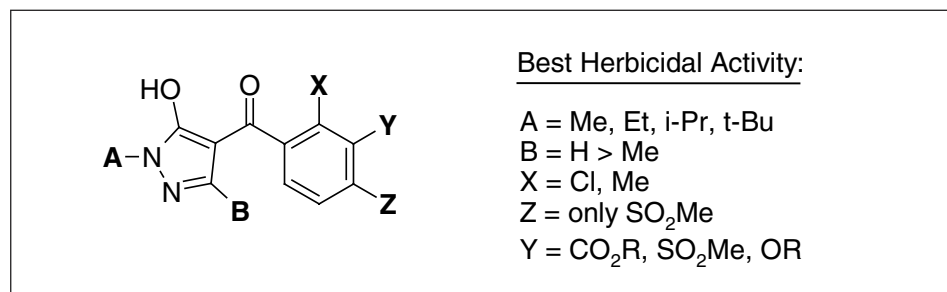

Best Herbicidal Activity:

A = Me, Et, i-Pr, t-Bu
B = H > Me
X = Cl, Me
Z = only SO_2Me
Y = CO_2R, SO_2Me, OR

Fig. 1. Early structure-activity relationships of benzoylpyrazole herbicides established by Dow AgroSciences and others

on broadleaves and warm season grasses, but it was unremarkable on the cool season grass weeds wild oat (AVEFA) and blackgrass (ALOMY). Wild oat and blackgrass are considered to be the most important grass weeds to control in wheat (TRZAS) crops. It was not until this 2-methoxy-ethylamino substituent was 'tied back' into a ring, that there was a dramatic increase in efficacy against these key species (entry 3). We therefore turned our attention to exploring this unique subclass of the benzoylpyrazoles. This paper focuses exclusively on the synthesis of analogs in which cyclic amines have been incorporated at C(3) of the benzoyl ring and the resulting biological activity.
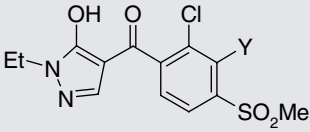
Synthesis

We first synthesized [5] these aminesubstituted materials by taking advantage of the inherent regioselectivity of nucleophilic aromatic substitution on our 2,3,4-trisubstituted benzoic acid starting materials **1** (Scheme 1). The C(3) chlorine is the most labile under the basic conditions of the reaction, because the sulfone is a much more powerful *ortho* director than the carboxylate. The functionalized benzoic acid **2** was then coupled with a 1-alkyl-5-hydroxypyrazole to give a mixture of the corresponding ester and amide. This mixture was subsequently rearranged to the C-acylated product **4** with a catalytic amount of cyanide.
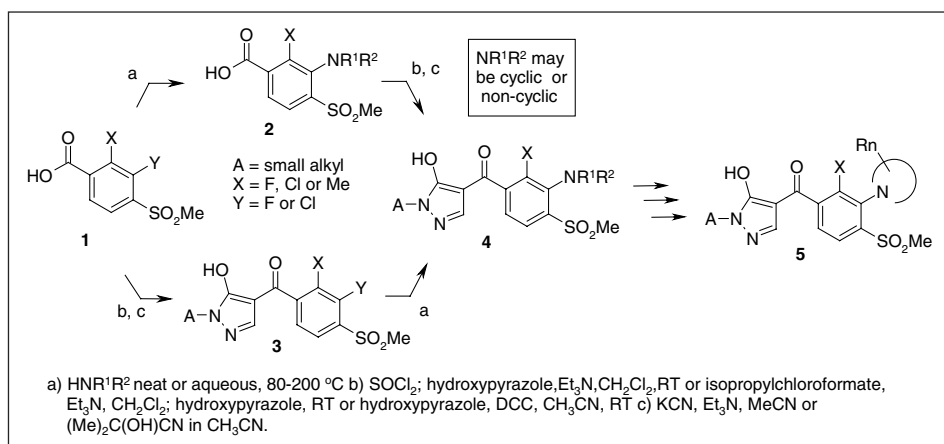
To improve the efficiency of analog synthesis, we considered performing the nucleophilic substitution later in the sequence, directly on a benzoylpyrazole **3** (Scheme 1). We reasoned that a deprotonated hydroxypyrazole moiety was not unlike a carboxylate with respect to activation of the aromatic ring. This approach worked well and was general, although hindered amines tended to give lower yields [6]. Increased heat or the use of the corresponding 3-fluoro version of **1** or **3** could be used to overcome this problem. A number of commercially available cyclic amines were utilized directly in this sequence, although some of the piperidines needed minor modifications [7].

The high level of activity obtained with the morpholine ring was particularly intriguing, but investigation was hindered by the paucity of commercially available morpholines. Even more troubling, however, was the generally low yielding and experimentally difficult methods available in the literature for the synthesis of substituted morpholines. This situation, and our recent success at manipulating advanced ben-

Table 1. SAR comparison of ring size and heteroatoms

Entry	Y	GW GR$_{80}$ Post[a] [ppm]	AVEFA GR$_{80}$ Post[b] [ppm]	ALOMY GR$_{80}$ Post[b] [ppm]	TRZAS GR$_{20}$ Post[b] [ppm]
1	NMe$_2$	50	60	295	16
2	NH—CH$_2$CH$_2$OMe	9	45	>250	150
3	N—morpholine (O)	2	2	20	2
4	N—oxazinane (O)	19	31	>125	4
5	N—pyrrolidine	16	16	31	16
6	N—piperidine	15	25	>63	>63
7	N—tetrahydropyridine	19	31	63	8

[a]The concentration of active ingredient that provides an average growth reduction of 80% compared to untreated controls when sprayed post emergently on the following grass species: *Alopecurus mysuroides* (ALOMY), *Avena fatua* (AVEFA), *Digitaria sanguinalis* (DIGSA), *Echinochloa crus-galli* (ECHCG), *Setaria faberi* (SETFA), *Sorghum bicolor* (SORBI). [b]The concentration of active ingredient that provides the indicated percent growth reduction compared to an untreated control when sprayed post emergently on the listed species. The last column is the wheat crop *Triticum aestivum* (TRZAS). [c]Mixture of *cis* and *trans*.

a) HNR^{1}R^2 neat or aqueous, 80-200 ºC b) SOCl$_2$; hydroxypyrazole,Et$_3$N,CH$_2$Cl$_2$,RT or isopropylchloroformate, Et$_3$N, CH$_2$Cl$_2$; hydroxypyrazole, RT or hydroxypyrazole, DCC, CH$_3$CN, RT c) KCN, Et$_3$N, MeCN or (Me)$_2$C(OH)CN in CH$_3$CN.

Scheme 1. General synthetic route to 3-(azacyclo)benzoylpyrazoles

zoylpyrazole intermediates, prompted us to consider an *in situ* approach to the problem (Scheme 2). Typical literature procedures involved the use of protected ethanolamines. It occurred to us, that if we used the benzoylpyrazole itself as a protecting group, we would be working with organic soluble intermediates and no deprotection step would be required. In fact, from earlier work, we already knew that displacement with ethanolamine was facile. The first step

starting from **6** then, was to install a substituted ethanolamine, many of which were commercially available or easily synthesized. Under the reaction conditions, the water soluble imine of the ketone was also formed, but this intermediate was readily hydrolyzed in a separate step before isolation of the product **7**. The second step was a cyclization to the lactone **8** achieved by heating **7** with glyoxal [8]. A selective reduction to the lactol **9** [9] was the third step,

in which the lactone was reduced with diisobutyl aluminum hydride in the presence of the hydroxypyrazole. An extra equivalent of this reagent was necessary for the initial deprotonation. The propensity of benzoylpyrazoles to chelate certain metal ions (iron is best known, but also aluminum and copper) made a strong acidic work-up necessary. If this was not done, it was actually possible to isolate the tribenzoylpyrazolate aluminum salt by column chromatography! The fourth and final step was to replace the hydroxyl of the lactol **9** with a variety of nucleophiles or simply reduce it with triethylsilane to obtain the final target **10**. For simple alcohols, HCl was a sufficient catalyst, but more complex alcohols, as well as methylmercaptide and cyanide, required $BF_3 \cdot Et_2O$.
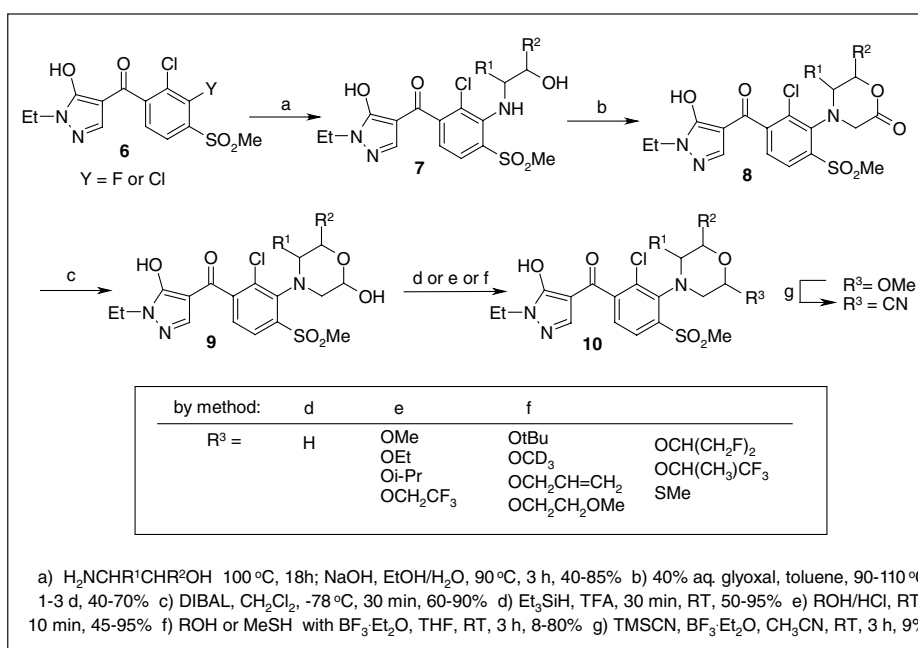
1,3 Oxazine analogs were synthesized *via* the corresponding 3-amino-1-propanol intermediate by cyclization with formaldehyde or phosgene. Attempts at the synthesis of 5- and 7-membered oxazocycles were unsuccessful [10].

Biological Activity

The outstanding activity of the morpholino substituted benzoylpyrazole prompted us to investigate a number of other cyclic amines (Table 1). We found that morpholine was the best, but pyrrolidine and piperidine (entry 5 and 6) still showed respectable activity on wild oat coupled with a modest amount of wheat selectivity. The 1,2,5,6-terahydropyridine and 1,3-oxazine analogs (entry 4 and 7) also showed activity on wild oat, but with no hint of safety toward wheat. Thiomorpholine, 4-methyl- and 4-acetyl-piperazine, 2-oxo-1,3-oxazine (cyclic carbamate) and homopiperidine (7-membered ring) were all inactive at these rates.

Because very few substituted pyrrolidines or morpholines were commercially available, our research program first focused on piperidines, with the intent of improving wild oat activity and wheat selectivity (Table 2). A series of methyl substituted piperidines revealed that certain 3-methyl substituted compounds (entry 3 and 6) retained wild oat activity and the wheat selectivity. Taken together (entry 1, 3, 4, and 6), the results are consistent with the hypothesis that wheat selectivity depends, at least partially, on metabolism at the C(4) of the piperidine ring. Unfortunately, all other piperidine substituents were not selective toward wheat, although 3-Cl, 3-MeO and 3-EtO (entry 7, 10, and 11) were active on wild oat.

Our intent with respect to the highly active morpholine ring, was to incorporate a substituent that would allow selective metabolism to occur in wheat. The biological data (Table 3) revealed that excellent activity on both wild oat and blackgrass could be retained with small alkyl substituents (entry 1–7). Reasonable activity on wild oat was also obtained with a 2-MeO group (entry 11), but this was lost very quickly with increasing size of the alkoxy substituent. (entry 13–15). A modest recovery in this trend was made with the CF_3CH_2O group (entry
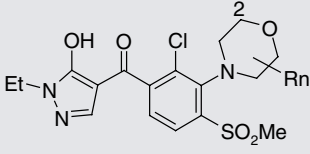
16) which was attributed to the ability of the fluorines to destabilize the incipient free radical typically formed during metabolism of an alkoxy group [11]. It was also interesting to note that the overall loss in activity engendered by a 2-MeO group was mitigated by the presence of a 6-Et substituent (entry 11, 25, and 26). Stereochemical effects across the morpholine ring were insignificant (entry 25 and 26, 27 and 28, 29 and 30), though a significant effect was

a) $H_2NCHR^1CHR^2OH$ 100 °C, 18h; NaOH, $EtOH/H_2O$, 90 °C, 3 h, 40-85% b) 40% aq. glyoxal, toluene, 90-110 °C, 1-3 d, 40-70% c) DIBAL, CH_2Cl_2, -78 °C, 30 min, 60-90% d) Et_3SiH, TFA, 30 min, RT, 50-95% e) ROH/HCl, RT, 10 min, 45-95% f) ROH or MeSH with $BF_3 \cdot Et_2O$, THF, RT, 3 h, 8-80% g) TMSCN, $BF_3 \cdot Et_2O$, CH_3CN, RT, 3 h, 9%

Scheme 2. Synthesis of substituted 3-morpholinobenzoylpyrazoles

Table 2. SAR comparison of substituted piperidine substituents

Entry	R_n	GW GR$_{80}$ Post[a] [ppm]	AVEFA GR$_{80}$ Post[b] [ppm]	ALOMY GR$_{80}$ Post[b] [ppm]	TRZAS GR$_{20}$ Post[b] [ppm]
1	H	15	25	>63	>63
2	2-Me	64	>125	125	12
3	3-Me	49	63	250	100
4	4-Me	35	55	>63	16
5	3,3-diMe	250	>250	>250	>250
6	3,5-diMe [c]	56	25	>250	63
7	3-Cl	23	25	>250	4
8	3-OH	81	50	250	31
9	3-(=O)	197	>250	>250	>250
10	3-MeO	51	14	240	4
11	3-EtO	60	31	>250	10
12	3-CO$_2$Et	231	>250	>250	20
13	4-(=O)	125	>125	>125	125
14	4-MeO	88	85	>250	45

[a]The concentration of active ingredient that provides an average growth reduction of 80% compared to untreated controls when sprayed post emergently on the following grass species: ALOMY, AVEFA, DIGSA, ECHCG, SETFA, SORBI. [b]The concentration of active ingredient that provides the indicated percent growth reduction compared to an untreated control when sprayed post emergently on the listed species. [c]Mixture of *cis* and *trans*.

noted between a pair of diastereomeric branched fluoroalkoxy substituents (entry 18 and 19). In the end, however, no selectivity toward wheat was observed in any of the analogs.
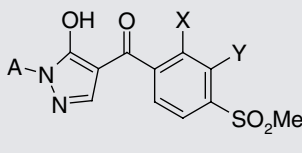
The Most Effective 3-Azacyclobenzoylpyrazoles

To highlight the biological effect of incorporating cyclic amines at the C(3) position of benzoylpyrazoles in this paper, substitution at all other positions was held constant. Our overall research program, however, was directed at optimizing these novel substituents in concert with the rest of the molecule (Table 4). The most effective molecule with respect to overall activity on the key cool season grass weeds wild oat and blackgrass (entry 1), was in fact an unsubstituted morpholino analog. The best wild oat compound with the greatest selectivity toward wheat (entry 2), however, contained a 3-methylpiperidino moiety.


Entry	R_n	GW GR_{80} Post[a] [ppm]	AVEFA GR_{80} Post[b] [ppm]	ALOMY GR_{80} Post[b] [ppm]	TRZAS GR_{20} Post[b] [ppm]
1	H	2	2	20	2
2	3-Me	7	3	31	2
3	3-i-Pr	7	10	31	<4
4	2-Me	6	3	25	1
5	2-Et	5	7	14	2
6	2-i-Pr	10	63	31	4
7	2,6-diMe[c]	4	4	12	<4
8	2-Ph	51	8	250	5
9	2=(O)	>250	>250	>250	>250
10	2-OH	>62	>62	>62	>62
11	2-MeO	63	31	50	12
12	2-CD$_3$O	6	8	78	1
13	2-EtO	>125	>125	>125	>125
14	2-i-PrO	>125	>125	>125	>125
15	2-t-BuO	>63	>63	>63	>63
16	2-CF$_3$CH$_2$O	45	50	125	4
17	2-(CH$_2$F)$_2$CHO	70	103	200	5
18	2-CF$_3$(Me)CHO (1)[d]	40	54	100	5
19	2-CF$_3$(Me)CHO (2)[d]	4	3	31	<2
20	2-MeOCH$_2$CH$_2$O	58	125	>250	31
21	2-CH$_2$=CHCH$_2$O	199	>250	>250	31
22	2-MeS	1258	>250	>250	10
23	2-CN	33	31	125	12
24	2-MeO, 5-Me[c]	19	20	50	4
25	*cis*-2-MeO, 6-Et	6	8	8	4
26	*trans*-2-MeO, 6-Et	16	12	14	4
27	*cis*-2-MeO, 6-i-Pr	26	30	100	<16
28	*trans*-2-MeO, 6-i-Pr	98	30	100	<16
29	*cis*-2-MeO, 6-Ph	16	25	63	3
30	*trans*-2-MeO, 6-Ph	30	14	63	10

[a]The concentration of active ingredient that provides an average growth reduction of 80% compared to untreated controls when sprayed post emergently on the following grass species: ALOMY, AVEFA, DIGSA, ECHCG, SETFA, SORBI. [b]The concentration of active ingredient that provides the indicated percent growth reduction compared to an untreated control when sprayed post emergently on the listed species. [c]Mixture of *cis* and *trans*. [d] Separated but unassigned diastereomer.

Table 3. SAR comparison of substituted morpholino substituents

Entry	A	X	Y	GW GR_{80} Post[a] [ppm]	AVEFA GR_{80} Post[b] [ppm]	ALOMY GR_{80} Post[b] [ppm]	TRZAS GR_{20} Post[b] [ppm]
1	i-Pr	Me	(morpholino)	1	2	3	3
2	Me	Cl	(3-Me-piperidino)	139	50	>250	>250

[a]The concentration of active ingredient that provides an average growth reduction of 80% compared to untreated controls when sprayed post emergently on the following grass species: ALOMY, AVEFA, DIGSA, ECHCG, SETFA, SORBI. [b]The concentration of active ingredient that provides the indicated percent growth reduction compared to an untreated control when sprayed post emergently on the listed species.

Table 4. Optimized 3-azacyclobenzoylpyrazoles

Summary

A practical and general approach to 3-azacyclobenzoylpyrazoles has been developed based on aromatic substitution by amines. The efficiency of analog synthesis was markedly improved by performing the substitution on advanced benzoylpyrazole intermediates. Problems related to the preparation of substituted morpholino analogs were solved by a four-step *in situ* procedure based on glyoxal cyclization. Unsubstituted or small alkyl substituted morpholino substituents were found to provide the greatest activity on the key cool season grass weeds wild oat and blackgrass. On the other hand, significant wheat selectivity with respect to wild oat was observed with a piperidino moiety if there was a small alkyl group incorporated at C(3) of that ring.

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[6] The lower yields are largely due to the competing formation of the corresponding pyrazolobenzpyran, in which the hydroxypyrazole cyclizes onto the C(2) of the benzoyl when there is a leaving group present.

[7] Hydroxypiperidines were modified by standard methylation, oxidation and chlorination procedures.

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