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Process Research, Development, and Pilot-Plant Preparation of Clofencet, a Novel Wheat Hybridizing Agent: Lewis Acid-Catalyzed Reaction of Ethyl Diazoacetate with 4-Chlorophenyl Hydrazonoacetaldehyde

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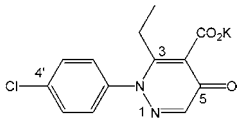
Abstract:

Described are studies directed toward the chemical research and development of an alternative synthesis to 9, the penultimate intermediate of clofencet (1), a novel wheat-hybridizing agent. Retrosynthetic analyses as well as the results obtained from feasibility studies are detailed, leading to the successful development of an alternative process. The key features of the novel route are a method for preparing on-scale ethyl diazoacetate (28) in a safe and effective manner, and the Lewis acid-catalyzed reaction of 28 with hydrazonoacetaldehyde 29, affording β-ketoester 30. The synthesis is completed via propionylation of 30, acid-catalyzed cyclization of 31 to pyridazinecarboxylic acid ester 32, followed by saponification and isolation of carboxylic acid 9. The results and challenges of eight pilot-plant runs are reported. The baseline process developed produced over 45 kg of 9 in 43−45% yield.

Introduction

This account describes the chemical process research and development of an alternative synthesis to **9**, the penultimate form of the novel agrochemical, clofencet[3] (**1**). Employed as a tool to produce hybrid wheat, the application of **1** under specific conditions prevents wheat from normal pollen development without affecting female fertility.[4] This characteristic allows for viable cross-pollination of selected wheat varieties, resulting in an F_1 hybrid with enhanced properties. The hybrid seed produced propagates into wheat that offers benefits such as increased yield, improved disease resistance, and better pest resistance. The result is wheat with greater overall product quality.[4]



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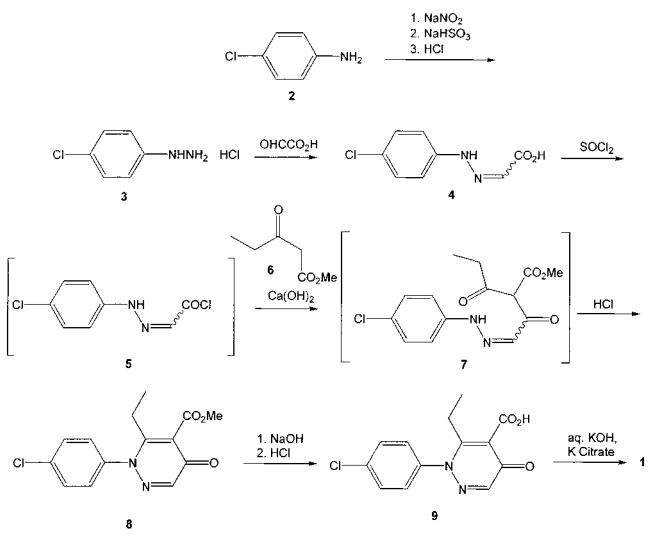
Monsanto acquired the rights for **1**, and accordingly, a process research and development team was formed to evaluate the chemistry shown in Scheme 1. Although this methodology was used to prepare interim quantities of **1**, the following technical issues were identified. The process was (1) too lengthy, (2) gave rise to moderate yields and high waste loads, (3) entailed relatively low payload and long cycle times, (4) required fluid bed drying of **4** (an unstable intermediate), (5) utilized thionyl chloride, (6) involved multiple solids handling operations, and (7) necessitated the use of methyl 3-oxopentanoate (**6**). At a cost of about $16/lb, this was a relatively expensive reagent, contributing approximately 50% to the raw materials cost. Additionally, only one viable commercial supplier of **6** was available. These fundamental issues tied closely with safety, engineering, cost of goods, patent position, resource allocation, raw materials sourcing, business strategy, and the timelines of the business were the epitasis behind the research and development of a new manufacturing route to clofencet.

Scheme 1. **Original route for preparation of 1**



The research began by performing a retrosynthetic analysis[5] on the target molecule. The main structural features of clofencet identified were (1) a 4′-chlorophenyl substituent, (2) a 3-ethyl-2,5-dihydro-5-oxopyridazine ring, and (3) a carboxylic acid salt. This study afforded approximately 15 conceivable synthetic strategies, all focusing on construction of the heterocyclic ring. It was recognized that the aromatic

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(3) The Monsanto brand name for clofencet is Genesis, a registered trademark.

(4) *Benefits of Hybrid Wheat*; Monsanto Technical Report, August 1995.

(5) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley and Sons: New York, 1989.

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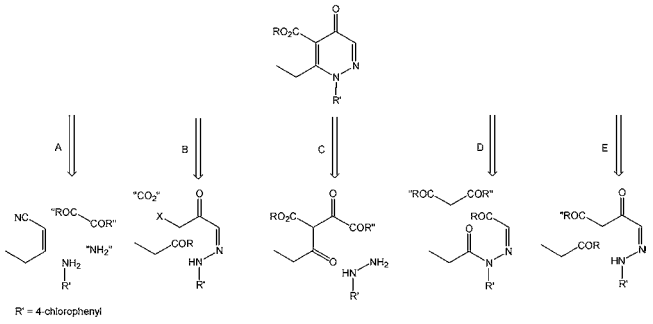
moiety would be derived from either 4-chloroaniline or 4-chlorophenylhydrazine, and that the β-ketocarboxylic acid component provided several potential synthetic strategies. The proposed routes were compared to the enabling chemistry and a cursory cost of goods analysis for each completed. This exercise reduced the number of proposals from 15 to 5. Scheme 2 outlines the bond disconnections that evolved out of this analysis. These five approaches became the focus of our research.

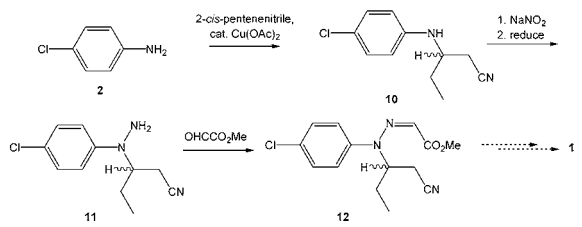
Process Research

The proposed five synthetic strategies were studied in the laboratory. The research centered on quickly performing "killer experiments," i.e., feasibility studies directed toward critical bond connections that would present an expedited assessment of the proposed chemistry. For example, route A (see Scheme 2) envisioned the Michael addition of a 5-carbon unit to 4-chloroaniline, followed by formation of the corresponding hydrazine. Completion of the carboxypyrimidazinone ring would be accomplished via an intramolecular condensation reaction. In this regard, the reaction of 4-chloroaniline (**2**) with 2-*cis*-pentenenitrile[6] was completed (Scheme 3) giving rise to **10** as a well-characterized solid, but in only 20% yield after column chromatography. This was cleanly converted in near quantitative yield with $NaNO_2$ and HCl in ethanol to the corresponding nitrosamine. Reduction of this intermediate to hydrazine **11** failed upon exposure to zinc either in acetic acid or in dilute hydrochloride acid. The conditions produced the corresponding amine, a result of N−N bond cleavage. However, **11** was obtained when the nitrosamine was exposed to zinc and an equivalent of titanium (IV) chloride.[7] Unfortunately intermediate **12**, the product of methyl glyoxylate condensation with hydrazine **11**, proved unstable. This result, in combination with the low-yielding Michael addition reaction, terminated this research effort.

Scheme 2. **Retrosynthetic analysis of 1**

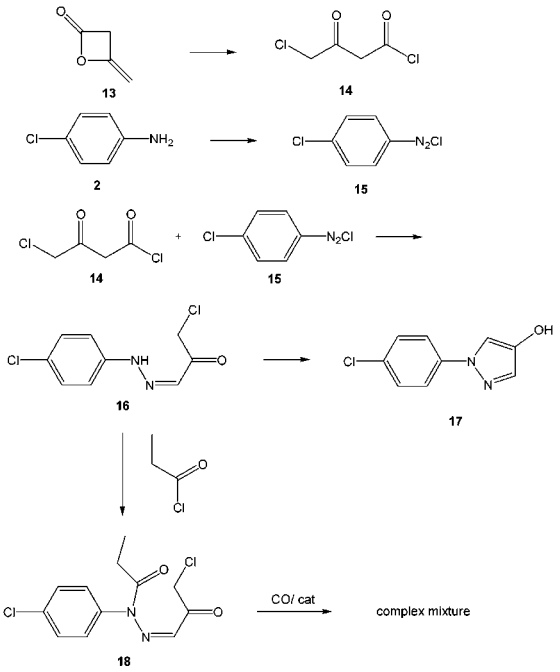


Scheme 3. **Attempted preparation of 1 via 4-chloroaniline Michael addition to 2-*cis*-pentenenitrile**



The "carbonylation," or route B approach (Scheme 4) to **1** proposed building the molecule by first coupling the diazonium salt **15** with a 3-carbon unit such as an α-chloroketoester or acid chloride.[8] Carbonylation of the α-haloketo moiety[9] would then give rise to the corresponding β-ketoester. Propionylation and intramolecular cyclization would complete the proposed formation of the pyrimidazinone ring.

Scheme 4. **Carbonylation approach to 1**

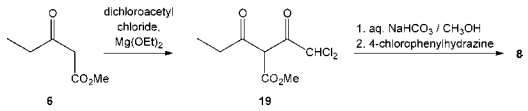


Designing the "killer" experiment for route B began by coupling of γ-chloroacetoacetyl chloride (**14**), prepared from diketene,[10] with *p*-chlorophenyldiazonium chloride (**15**). This performed as anticipated,[8] affording derivative **16** in 90−95% yield. Multiple attempts to carbonylate this intermediate failed, resulting predominately in the formation of hydroxypyrazole **17**.[8] Therefore, propionylation of **16** was carried out successfully, providing the amide **18**. Unfortunately, attempts to perform the key carbonylation reaction on **18** failed, providing a complex product mixture. A series of catalyst and alternative conditions, including attempted displacement with cyanide,[11] were examined, but all failed. Therefore, this approach was abandoned.

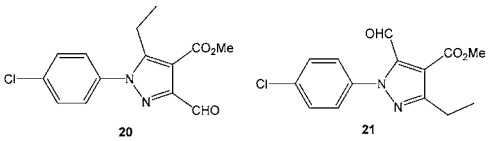
Work directed toward the proposed route C (Scheme 5) entailed coupling dichloroacetyl chloride with **6** to give the corresponding 7-carbon unit **19**.[12] Although this strategy would still involve the use of **6**, the potential advantages over the enabling chemistry would be fewer chemical steps, fewer solids handling, and avoidance of the preparation of an acid chloride.

(6) For β additions of aniline derivatives to *cis*-2-pentenenitrile see: (a) Brudermueller, M.; Witzel, T.; Merger, F. U.S. Patent 5,334,745, 1994. (b) Bradbury, R. H. Eur. Pat. Appl. EP 539066 A1, 1993.
(7) Lunn, G.; Sansone, E. B.; Keefer, L. K. *J Org. Chem.* **1984**, *49*, 3470.
(8) (a) Lamberth, C. *Org. Prep. Proced. Int.* **2002**, *34*, 98. (b) Phillips, R. R. *Org. React.* **1959**, *10*, 143.
(9) Adapa, S. R. *Indian J. Chem., Sect. B.* **1991**, *30B*, 1067.
(10) Gross, M. U.S. Patent 4,473,508 A, 1984.
(11) Martinelli, M. J.; Khau, V. V.; Horcher, L. M. *J. Org. Chem.* **1993**, *58*(20), 5546.
(12) Yallamanchili, G. U.S. Patent 4,962,199, 1990.

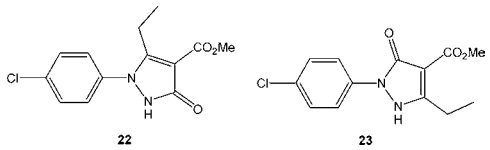
Scheme 5. **Proposed coupling dichloroacetyl chloride with MOP**



The coupling of **6** with dichloroacetyl chloride gave the desired product **19** as a clear, free-flowing liquid in 51% yield after distillation. This was then treated with sodium carbonate in water/methanol to generate in situ the corresponding aldehyde. Immediate reaction of this with *p*-chlorophenylhydrazine hydrochloride gave rise to **8**, but only in 14% yield after chromatography. Interestingly, it was found that pyrazole isomer **20** (or **21**)[13] was also formed. Evidently the desired conversion of **19** to its corresponding aldehyde was incomplete. Reaction of the dichloro adduct **19** with the hydrazine, before aldehyde formation, was evident.



To accentuate in situ aldehyde formation, more base was added. However, lactam **22** (or **23**)[13] was found to be the major product of the reaction under these conditions. Efforts to optimize the formation **8** by manipulation of reagent addition, temperature, solvent, base, and reaction time resulted in a meager yield improvement to 25%. Therefore, this research effort was also terminated.

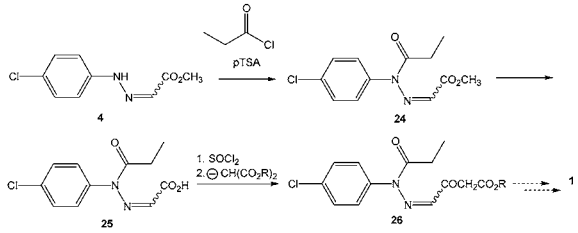


The fourth initiative, approach D (Scheme 6), proposed construction of the carboxypyrimidazinone ring via the methyl glyoxylate derivative **4**. In this regard, treatment with propionyl chloride and a catalytic amount of *p*-toluenesulfonic acid produced **24**. A number of conditions for the transformation of **24** directly to **26** were explored, but the best results were obtained via isolation of **25**. Thus, **24** was saponified with excess $NaHCO_3$ in a 70:30 mixture of methanol/water, affording, after acidification, **25** in 95% yield. The corresponding acid chloride was then prepared in situ by treatment with thionyl chloride in methylene chloride. Reaction of this with the sodium salt of methyl malonate produced **26** in greater than 50% yield. Although this route seemed to have good potential, further studies revealed that the acid chloride analogue of **25** was unstable. The project was therefore halted.

The important breakthrough in the preparation of **9** came via a synthesis strategy that centered on utilizing the Lewis acid-catalyzed coupling reaction of ethyl diazoacetate[14]

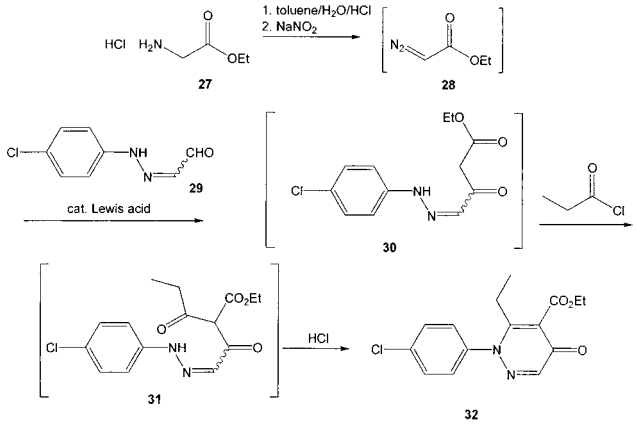
(13) The structure of the isomer produced could not be absolutely discerned from the available data.

Scheme 6. **Homologation approach to 9**



(**28**) with hydrazone aldehyde **29**[15] to produce *β*-ketoester **30** (Scheme 7). This could then be converted to **9** by way of **32**. One main concern with this strategy, however, was the use of **28** on-scale. Although **28** is an important 2-carbon synthon,[16] application of this reagent on a commercial scale is limited due to safety concerns. Nevertheless, the cursory cost analysis suggested that this chemistry would be very competitive.

Scheme 7. **Preparation of 32 employing the Lewis acid-catalyzed coupling reaction of 28 with hydrazone aldehyde 29**



In our initial experiments to perform the coupling reaction of **28** with hydrazone aldehyde **29**, 10 mol % of anhydrous $SnCl_2$ was utilized in methylene chloride.[14] Only 50% conversion was observed after 2 h. Column chromatography of the reaction mixture gave rise to **30** in 47% yield. Extending the reaction time to 14−16 h and the addition of extra catalyst nearly completed the desired conversion. *β*-Ketoester **30** was then subjected to propionyl chloride in the presence of triethylamine, producing **31**.[17] Exposure of

(14) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258. Also see: (a) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297. (b) Angle, S. R.; Wei, G. P.; Ko, Y. K.; Kubo, K. *J. Am. Chem. Soc.* **1995**, *117*, 8041. (c) Nagao, K. *Synthesis* **1983**, 197. (d) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 4(23), 8084.

(15) (a) Shandurenko, G. V.; Avramenko, G. V.; Stepanov, B. I. *Zh. Org. Khim.* **1980**, *16*(4), 751. (b) Zaitsev, B. E.; Sheban, G. V.; Shandurenko, G. V.; Avramenko, G. V.; Stepanov, B. I. *Zh. Obshch. Khim.* **1982**, *52*(1), 49.

(16) (a) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (c) Mass, G. *Top. Curr. Chem.* **1987**, *137*, 75. (d) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (e) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (f) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (g) Shapiro, E. A.; Dyatkin, A. B.; Nefodov, O. M. *Russ. Chem. Rev.* **1993**, *62*, 447. (h) Padwa, A.; Austin, D. J. *Angew. Chem.* **1994**, *106*, 1881; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797. (i) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091 and references therein. (j) Miller, D. J.; Moddy, C. J. *Tetrahedron* **1995**, *51*, 10811. (k) Moody, C. J.; Morfitt, C. N. *Synthesis* **1998**, 1039.

(17) Less than 3% *N*-propionylated product was present has determined by HPLC analysis.

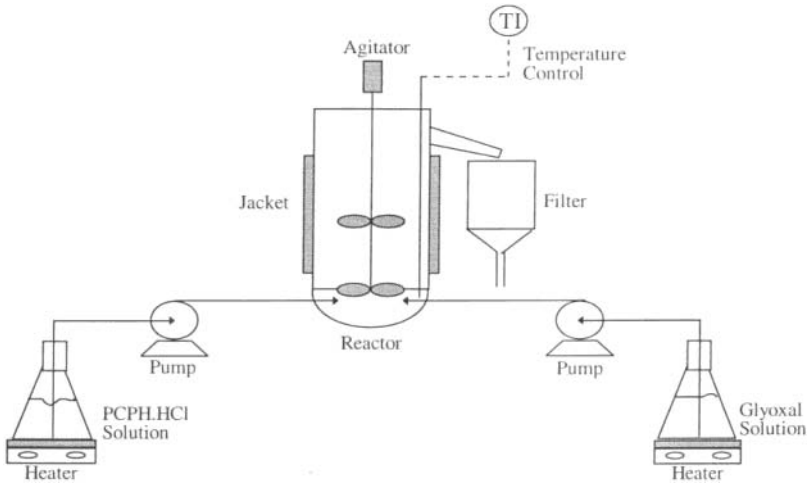


Figure 1. **Continuous process with jacketed reactor.**

the crude **31** to anhydrous $MgCl_2$ gave the ethyl ester intermediate **32** in 89−90% yield after column chromatography. This intermediate was converted to **9** and shown to be identical to an authentic sample. These very promising results led us to focus on the development of the "diazo" approach to **9**.[18]

Process Development

Having completed the "killer experiments," a potential manufacturing route was established utilizing the Lewis acid-catalyzed coupling reaction of **28** with **29**.[14] Our research turned toward four significant efforts to test, optimize, and verify the proposed technology. These objectives were (1) to demonstrate a continuous process for the preparation of hydrazone aldehyde **29**, (2) test the idea that **28** could be prepared cost-effectively and employed safely on-scale, (3) optimize and safely practice the desired **28** and **29** coupling reaction, and (4) define the remaining chemistry and isolation protocol.

Hydrazone Aldehyde 29. Aldehyde **29** was prepared in 92% yield and with 98.5 area % purity via reaction of 4-chlorophenylhydrazine hydrochloride with aqueous glyoxal.[15] The chemistry was sequentially scaled from 100 g to 1 kg without any observable scale-up issues. The reactions were run at 6% payload based on weight of hydrazine to the weight of water. In all cases a thick slurry resulted, requiring efficient mixing throughout the reaction. Preliminary filter tests in a Büchner funnel and in a laboratory centrifuge indicated that filtration of **29** was manageable. Attempts to increase the payload from 6 to 10% were unsuccessful. The mixture was too viscous to stir.

Despite the success of these laboratory studies, two scale-up issues were recognized. First, batch processing as described in the literature would not be cost-effective, because of the large volumes projected for manufacture of **1**. Second, a viable drying procedure would have to be developed as well. With regard to the former issue, a continuous process for the preparation of **29** was devised. Utilizing the reactor shown in Figure 1, the procedure entailed the simultaneous addition of aqueous solutions of *p*-chlorophenylhydrazine hydrochloride (4% aq PCPH·HCl) and glyoxal (4 wt %) to water at 60 °C near the impeller. This interaction, under these conditions, resulted in immediate precipitation of product that was easily isolated via overflow. Aldehyde **29** generated by this method was much easier to filter and to dry compared to product obtained from a batch process. The yield was >90% with an assay of ≥95 wt %. Complete mass balance for hydrazine **3** was obtained when the aqueous phase was analyzed for starting materials.

Two approaches to the on-scale drying issue were studied. The first involved isolation and drying of the solid on the filter. The second scenario entailed transfer of the wet cake to a reactor and azeotropically removing the excess water. The latter approach gave the best results. The solid product was placed in toluene and the water removed at 60 °C at 20 Torr. Product recovery was >98% with an assay of >98%. This protocol afforded **29** with a moisture content of <0.05 wt %.

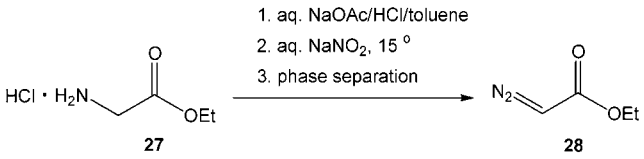
While measuring the melting point of **29**, rapid decomposition accompanied by gas evolution was observed at 150−152 °C. This indicated a potential thermal stability concern. Thus, studies directed toward ascertaining the stability and thermal properties of **29** were completed.

Stability studies found no appreciable change in assay over 6 weeks at 50 or 60 °C. However, at 70 °C, the assay decreased to 92% over the same 6-week period. At 80 °C, rapid decomposition was observed, resulting in the product assay decreasing from >97% to <5% in only two weeks.

Accelerated rate calorimetry found that **29** thermally decomposed at 105 °C. The rate of decomposition was 378 °C/min. The solid was also held at 85 °C for 24 h and the ARC test completed. The onset temperature was identical to that held at ambient temperature. This indicated that the decomposition was not catalyzed by the build-up of a reactive intermediate. This was further confirmed by storing material at 70 °C for 1 month. Again the onset temperature for decomposition was the same (105 °C). The maximum self-heating varied with these samples, probably as a result of sample size. Drop-weight testing also revealed that **29** did not decompose when shocked.

(18) Shah, A. S.; Clark, J. D.; Ma, Y.; Peterson, J. C.; Patelis, L. U.S. Patent 6,025,492, 2000.

Ethyl Diazoacetate (28). Use of commercially available **28** in the β-ketoester-forming reaction gave good results, but additional studies determined that **28** prepared by published procedures[16] was undesirable. These methods use halogenated solvents and gave rise to lower than desired yields. Therefore, extensive work within Monsanto[18] led to the development of a new method of preparation of **28** from ethyl glycinate hydrochloride (eq 1: preparation of **28** from ethyl glycinate hydrochloride).



27 **28**

The procedure was based on a biphasic system of preparation. An aqueous solution of **27** was prepared in a sodium acetate−hydrochloric acid buffer with a pH = 3.5. This pH was found to be optimum. A decrease or increase in pH negatively affected **28** yield. To this solution was then added a predetermined amount of toluene. Typically, solutions prepared in-house ranged from 10 to 11% **28** by weight, with respect to toluene. Working at this concentration addressed in-house safety concerns. On the other hand, extensive studies on the thermostability[19] and detonation properties[20] of **28** suggested that higher concentrations, perhaps up to 30 wt %, may be employed safely.

Once the biphasic system was in place, an aqueous solution of sodium nitrite was added at such a rate that the temperature of the mixture was ≤15 °C. This mixture was stirred for 1−3 h, and the phases were separated. This afforded **28** in yields of 89−92%, which was used without further purification.

***β*-Ketoester 30.** One of the most intriguing techniques reported for preparation of β-ketoesters[21] is the reaction of an aldehyde with ethyl diazoacetate.[14] This homologation may be achieved thermally[22] or by means of Lewis acid,[16,23] zeolite,[24] or alumina[25] catalysis. In a program directed toward preparing β-ketoester **30**,[26] the reaction of aldehyde **29** with **28** was studied extensively.

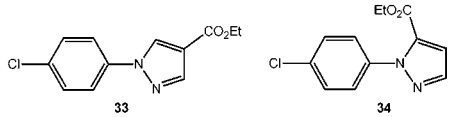
Table 1. **Lewis acid-catalyzed reaction of 28 with 29**

entry[a]	Lewis acid	solvent	time (h)	temp (°C)	product ratio **30**:**33**:**34**[b] (HPLC area %)	**30** (%)[c]
1	BF_3•OEt_2	diethyl ether	2	−5	32:27:4	42
2	$AlCl_3$	toluene	2	0	30:6:1	–
3	$FeCl_3$	CH_2Cl_2	5	25	27:21:2	–
4	$GeCl_4$	CH_2Cl_2	25	22	–	18
5	$ZrCl_4$	cumene	25	22	27:18:1	30
6	$TiCl_4$	toluene	2	−14	–	inc[d]
7	$SnCl_2$	CH_2Cl_2	3	23	30:50:4	47

[a] All reactions were run as 2 wt % of **29** in the listed solvent with 10 mol % Lewis acid and 1.5 equiv of **28**. [b] Ratio determined by HPLC analysis and corrected for relative molar extinction coefficients of 1:1:2.45, respectively.[c] The yields reported are for product isolated via chromatography or by HPLC analysis against an analytical standard of **30**. [d] Incomplete conversion observed due to competing ethyl diazoacetate decomposition.

Our optimization research began by subjecting **28** and **29** to a variety of catalyst in several solvents.[14,16] Some of the results are depicted in Table 1. One difficulty observed was the relative insolubility of **29**[27] in the solvents tested.

In addition to monitoring the desired conversion, another product being formed was pyrazole **33**.[28] Trace amounts of the pyrazole regioisomer **34** were also isolated and identified.[29] The ratio of **30** to **33** to **34**, respectively, is provided in Table 1. Thus, another factor considered in our evaluation was the selectivity of the catalyst for **30**.[30]



33 **34**

Believing the relative insolubility of **29** to be in part responsible for incomplete conversion, a variety of solvents were tested with $SnCl_2$ as the catalyst.[31] A few of the results are summarized in Table 2. Interestingly, $SnCl_2$ was not very effective in most solvents, resulting mostly in incomplete conversion. However, moderate success was obtained in

(19) Clark, J. D.; Shah, A. S.; Peterson, J. C.; Patelis, L.; Kersten, R. J. A.; Heemskerk, A. H.; Gorgan, M.; Camden, S. *Thermochim. Acta* **2002**, *386*(1), 65.

(20) Clark, J. D.; Shah, A. S.; Peterson, J. C.; Patelis, L.; Kersten, R. J. A.; Heemskerk, A. H. *Thermochim. Acta* **2002**, *386*(1), 73.

(21) For alternative β-ketoester preparative methods, see: (a) Clasien, L.; Lowman, O. *Ber.* **1887**, *20*, 651. (b) Schaefer, J.; Bloomfield, *J. Org. React.* **1967**, *15*, 1. (c) Wenkert, E.; McPherson, A. *J. Am. Chem. Soc.* **1972**, *94*, 8664. (d) Balasubrahmanyam, S. N.; Balasubrahmanyam, M. *Organic Syntheses*; Wiley: New York, 1973: Vol. V, p 439. (e) I. Rathko, M. *Org. React.* **1975**, *22*, 423. (f) Pallicciari, R.; Fringualli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959. (g) Ikota, N.; Takamura, N.; Young, S.; Ganem, B. *Teterahedron Lett.* **1981**, *22*(42), 4163. (h) Pallicciari, R.; Natalini, B.; Fringualli, R.; Ceccherelli, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 493. (i) Kocienski, P.; Stocks, M.; Donald, D.; Cooper, M.; Mannera, A. *Tetrahedron Lett.* **1988**, *29*(35), 4481. (j) Benetti, S.; Romagnoli, R.; De-Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065.

(22) (a) Buchner, E.; Curtlus, T. *Ber.* **1883**, *18*, 2371. (b) Schlotterbeck, F. *Ber.* **1907**, *40*, 479, 3000. (c) Dieckmann, W. *Ber.* **1910**, *43*, 1024.

(23) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055.

(24) Sudrik, S. G.; Balaji, B. S.; Singh, A. P.; Mitra, R. B.; Sonawane, H. R. *Synlett* **1996**, 369.

(25) Dhavale, D. D.; Patil, P. N.; Mali, R. S. *J. Chem. Res., Synop.* **1994**, *4*, 152.

(26) (a) Clark, J. D.; Shah, A. S.; Peterson, J. C. *Thermochim. Acta* **2002**, *392*−*393*, 177. (b) Clark, J. D.; Shah, A. S.; Peterson, J. C.; Gorgan, K. M.; Camden, S. *Thermochim. Acta* **2001**, *367*−*368*, 75. (c) Clark, J. D. Proceedings, 28th Annual Conference of the North American Thermal Analysis Society; *Therm. Anal. Appl*. **2000**, 346. (d) Clark, J. D. Proceedings, 27th Annual Conference of the North American Thermal Analysis Society; *Therm. Anal. Appl.* **1999**, 119. (e) Clark, J. D.; Shah, A. *Proceedings of the 9th RC User Forum...USA Scientific and Technical Program*, October 27, 1998.

(27) For example, the solubility of **29** in toluene was measured at approximately 0.70 wt % at 20 °C.

(28) Pyrazole **33** was shown to be identical to material derived from a literature procedure. See: (a) Beck, J. R.; Gajewski, R. P.; Lynch, M. P.; Wright, F. L. *J. Heterocycl. Chem.* **1987**, *24*(1), 267. (b) Holzer, W.; Seiringer, G. *J. Heterocycl. Chem.* **1993**, *30*(4), 865.

(29) Pyrazole **34** was shown to be identical to material derived from a literature procedure. (a) Holzer, W.; Seiringer, G. *J. Heterocycl. Chem.* **1993**, *30*(4), 865. (b) El Khadem, H.; Rateb, L.; Mokhtar, H. *J. Chem. Soc., C* **1968**, 1845.

(30) A study of the reaction of **28** with **29** by NMR analysis indicated that **30**, **33**, and **34** form independently, with no build up of a common intermediate. The relative rate of formation of **30** verses **33** was approximately 10:1, respectively. A clean transformation was observed displaying resonances consistent with the reaction of **28** and **29** to products **30**, **33**, and **34** only. No transient α-formyl ester was observed, suggesting that a 1,2-rearrangement similar to that reported by Kanemasa[23] was not in operation.

(31) For the effect of solvents on the reactivity of imines with ethyl diazoacetate see: Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358.

Table 2. **$SnCl_2$-catalyzed reaction of 28 with 29**

entry[a]	solvent	time (h)	temp (°C)	product ratio **30:33:34**[b] (HPLC area %)	**30** (%)[c]
1	toluene	36	23	29:41:10	22
2	xylenes	19	23	20:15:1	15
3	ethylbenzene	18	23	1:20:1	18
4	cyclohexane	23	23	22:6:0	5
5	acetonitrile	3	23	5:1:1	–
6	di-*n*-butyl ether	19	23	0:40:3	61
7	cumene	36	26	0:58:11	54
8	toluene/cumene hydroperoxide	4	22	0:30:1	62

[a] All reactions were run as 2 wt % of **29** in the listed solvent with 10 mol % Lewis acid and 1.5 equiv of **28** present. [b] Ratio determined by HPLC analysis and corrected for relative molar extinction coefficients of 1:1:2.45, respectively. [c] The yields reported are for product isolated via chromatography or by HPLC analysis against an analytical standard of **30**.

Table 3. **Tin (IV)-catalyzed reaction of 28 with 29**

entry[a]	catalyst	mol equiv	reaction temp (°C)	reaction time (h)	ratio[b] 30:33	**30** (%)[c]
1	$SnCl_4$	0.065	15	3	45:1	74
2	$SnBr_4$	0.22	27	14	27:1	56
3	SnI_4	0.13	27	14	11:1	44
4	$PhSnCl_3$	0.07	32	14	30:1	50
5	$BuSnCl_3$	0.4	25	2	30:1	50
6	$MeSnCl_3$	0.07	25	14	30:1	20
7	$Sn(acac)_2Cl_2$	0.12	40	4	33:1	69
8	Bu_2SnCl_2	0.2	44	14	30:1	24
9	Bu_2Sn(maleate)	0.1	55	2	–	0

[a] All reactions were run as 10 wt % of **29** in toluene with 10 mol % Lewis acid and 1.5 equiv of **28** present. [b] Ratio determined by HPLC analysis and corrected for relative molar extinction coefficients of 1:2.95, respectively. [c] The yields reported are for product isolated via chromatography or by HPLC analysis against an analytical standard of **30**.

either di-*n*-butyl ether or cumene. For example, incomplete conversion was observed after 36 h in toluene (Table 2, entry 1) at ambient temperature. However, running the reaction for 36 h in cumene (Table 2, entry 7) resulted in complete consumption of **29**. These observations led us to speculate that trace amounts of peroxide present in either di-*n*-butyl ether or cumene may be oxidizing tin (II) to tin (IV).[32] Indeed, when the reaction was carried out in toluene with 10 mol % of both $SnCl_2$ and cumene hydroperoxide (Table 2, entry 8),[33] **30** was obtained in 62% isolated yield after 4 h. Additionally, the ratio of **30** vs **33** was significantly improved to approximately 97% selectivity for **30**. These developments directed our research toward the use of a Sn (IV)-based catalyst.

Initial experiments preformed with $SnCl_4$ were disappointing because of ethyl diazoacetate decomposition.[34] For example, exposure of **28** to 0.1 mol % $SnCl_4$ at 25 °C led to immediate nitrogen evolution with greater than 50% **28** loss in less than 15 min as determined by gas chromatographic analysis. Moreover, stirring at room temperature for 14 h led to a 63% decrease. Nevertheless, additional experiments found that the extent of ethyl diazoacetate decomposition could be minimized to less than 5% when the reagents were combined at 0 °C.[35]

Employing the aforementioned temperature constraints for interaction of **28** with $SnCl_4$, it was found that reaction of **28** and **29** at 0 °C in toluene afforded **30** in 58% yield after 24 h. Interestingly, performing the reaction at 10 °C gave rise to **30** in 68% yield after 6 h and in 74% after 3 h at 15 °C.

The extent of pyrazole **33** formation was also found to be dependent upon the reaction temperature. At 10 °C, the ratio of **30**:**33** was 33:1. This increased to 45:1, respectively, at 15 °C. On the other hand, warming to room temperature led to a complex product mixture, in which the relative proportion of **30** to **33** reversed to 1:2, respectively.

Other Sn (IV)-based Lewis acids were also surveyed in the attempt to find a catalyst that would provide **30** in higher yields and with better selectivity. The results are shown in Table 3. For example, $SnBr_4$ (entry 2) afforded moderately good results, but a 27:1 ratio of **30** to **33** was obtained. The use of SnI_4 (entry 3) as catalyst increased pyrazole formation, yielding a ratio of 11:1 for **30**:**33**, respectively. Relatively high selectivity for **30** was found with alkyl tin trichloride catalysts such as butyl tin trichloride (entry 5), but the yield of **30** decreased substantially. Interestingly, tin (IV) bis-(acetylacetonate) dichloride (entry 7) gave results comparable to $SnCl_4$, but temperatures as high as 40 °C were required[36] for reaction completion.[37] Other substituted tin catalyst such as dibutyl tin dichloride (entry 8) did not perform well. Therefore, $SnCl_4$ (entry 1) gave the best overall result.

To address safety concerns and further optimize this reaction, thermal stability,[20] reaction calorimetry,[26] and the mode of addition studies were completed. This led to the development of a new work process wherein two reagents were added simultaneously to the cold **28**/toluene solution. On lab scale, this mode of reagent interaction generally provided **30** in 65−74% yield.[26]

Thus, the following general procedure for preparation of **30** was developed. To a dry reactor containing cold (5−10 °C) **28** (1.3−1.44 equiv, 10% in toluene) was charged simultaneously 0.07 equiv of $SnCl_4$, as a 1.0 M solution in toluene, and **29** over a 45−60-min period. The temperature of the slurry was maintained at ≤15 °C throughout. After complete addition, the product mixture was held for 3 h and then used without further purification.

Diketo Ester 31. Initial experiments direct toward reacting **30** with propionyl chloride in the presence of magnesium chloride found that carboxypyrimidazinone **32** formed directly, without the isolation of intermediate **31**. However, subsequent work proved that this approach was very sensitive

(32) For peroxide oxidation of tin (II) to tin (IV) see: (a) Alleston, D. L.; Davies, Alwyn G. *J. Chem. Soc.* **1962**, 2465. (b) Daugherty, N. A.; Niewahner, J. H. *Inorg. Chem.* **1972**, *11*(3), 535. (c) Moravskii, A. P.; Shuvalov, V. F. *Otd. Inst. Khim. Fiz., Kinet. Katal.* **1979**, *20*(2), 314.

(33) The exact nature of the tin species present in solution is not known. See ref 32.

(34) Decomposition via exposure of EDA to $SnCl_4$ gave at least 10 products. Ethyl chloroacetate was the major product formed.

(35) No change in the assay of **29** was observed when it was exposed to catalyst in toluene.

(36) It is assumed that the higher temperature was required for dissociation of the bidentate ligand for the substrate to contact the catalyst.

(37) It has been suggested[14] that the slow reaction and higher payloads of catalyst required for aromatic aldehydes is due to the consumption of the catalyst by the enol form of the β-ketoester produced.

Table 4. **Propionylation of 30**

entry	$Ca(OH)_2$[a] (equiv)	DMAP (equiv)	acid chloride (equiv)	reaction temp (°C)[b]	acid chloride add time (min)	conversion[c] *(%)*
1	1.44	0.10	1.34	19−45	<1	>97
2	1.20	0.04	1.15	16−28	<1	∼74
3	1.44	0.15	1.20	13−24	<1	∼70
4	1.50	0.15	1.50	28−38	<1	>97
5	1.40	0.15	1.25	30−45	<1	>95
6	1.40	0.15	1.45	29−45	<1	>97
7	1.05	0.10	0.93	30−40	18	>97
8	1.05	0.10	0.93	31−46	18	>97
9	1.05	0.10	0.93	30−44	18	>97

[a] Stoichiometry based on the number of moles of β-ketoester **30** plus tin (IV) chloride. [b] Temperature range represents the internal pot temperature. [c] Percentage conversion based on consumption of **30**.

to impurities, reaction conditions, and stoichiometry, often leading to incomplete conversion. Therefore, experiments were run with calcium hydroxide, the same catalyst used in the original route. Some of the laboratory results are given in Table 4. It was also found that this unpredictability was due, in part, to competing *O*-propionylation. This intermediate would then revert back to **30** during workup. The inclusion of a catalytic amount 4-*N*,*N*-dimethylaminopyridine (DMAP) rectified the problem. The use of 6 mol % of DMAP, with respect to the β-ketoester **30**, increased the conversion to **31** to a consistent level of >97 area % by HPLC analysis. For example, the original chemistry conditions were repeated along with the inclusion of DMAP (entry 1). This increased the degree of conversion of **31** to >97%. The formation of (*E*)- and (*Z*)-hydrazone isomers was observed by HPLC analysis. Very little **32** was formed. Note in entries 2 and 3 of Table 4, the amount of conversion to product decreased. This was attributed to the lower temperature of reaction before acid chloride addition. Indeed, reproducible results were achieved when crude **30** in the presence of $Ca(OH)_2$ was warmed to approximately 30 °C before acid chloride addition (entries 4−6). Further refinement of the stoichiometry led to a decrease in the equivalents of both propionyl chloride and calcium hydroxide. Therefore, the best protocol entailed warming the reaction mixture containing **30** to 30 °C and adding 0.95−1.05 equiv of anhydrous $Ca(OH)_2$. This was followed with 0.93−1.05 equiv of propionyl chloride. The product mixture was used without further purification.

Ethyl Carboxypyrimidazinone 32. Investigating the cyclization of **31** to **32** was uneventful. Initial experiments engaged *p*-toluenesulfonic acid monohydrate as the acid catalyst. Nearly complete conversion was observed, but the time for cyclization varied from 1 to 5 h. The use of either excess 96% H_2SO_4 or 37% HCl led to the immediate formation of a gummy, inorganic precipitate that complicated reaction workup. This was overcome by diluting the acid solution. It was also found that the rate of reaction was dependent upon the reaction temperature and equivalents of acid. For example, at 30 °C, greater than 5 h was generally required to complete the conversion. At 80 °C, the cyclization reaction was generally complete within 5 min. As little as 0.3 mol equiv of concentrated HCl gave the desired conversion in less than 5 min at 80 °C.

The following general procedure for preparation of **32** was developed for the pilot plant. To the reactor containing the crude solution of diketoester **31** in toluene was charged 2.0−4.0 equiv (with respect to the original hydrazone aldehyde **29** input) of 1.2 N HCl. This was heated to 80 °C and held for 1−3 h. The mixture was cooled to 25 °C, the layers were separated, filter-aid was added, and the organic phase was filtered to obtain **32** as a solution in toluene. Analytical analysis indicated an overall yield of 50% from **29**.

Pyridazinecarboxylic Acid 9. Initial studies of the conversion of the ethyl ester **32** to the corresponding carboxylic acid **9** employed the conditions used in the enabling technology. The crude toluene solution of **32** was exposed to caustic and heated to 60 °C. Isolation of the crude free acid via HCl acidification, followed by 2-propanol lixiviation gave rise to purified **9**. This method afforded product that was 50−70% **9** before lixiviation, and 86−97% pure after a 2-propanol wash. Assays were determined by HPLC analysis. Although this protocol did provide product with, perhaps, a suitable assay, approximately 25% of **9** was lost during the lixiviation process.

It was found that direct addition of 2-propanol to the aqueous product phase, before acidification, minimized loss, producing 83−92% pure **9** in very good yield after acid treatment. The product quality was further increased to ≥97%, with a single, neat 2-propanol wash of the filter cake. Less than 2% product loss was measured in the mother liquor. Therefore, the work process developed for the conversion of **32** to **9** was to add 4.3 equiv of 15% NaOH to the crude **32** solution. The mixture was heated to 60 °C, held at this temperature for a minimum of 1 h, and cooled to ambient temperature. Excess 2-propanol was added, followed by addition of 4.8 equiv of 37% hydrochloric acid solution. The slurry was agitated for 1 h, filtered, and washed with neat 2-propanol and water, affording **9** in 48−52% overall yield from **29** with an assay of ≥97%.

Pilot Plant Campaigns

The aforementioned technology was transferred to Monsanto's Queeny Pilot Plant. The results from eight batches are reported herein. The major equipment utilized were two 100-gal glass-lined reactors, one 30-gal glass-lined reactor, one 100-gal stainless steel reactor, a bag filter system, a Sparkler filter system, and a 1-m^2 Rosenmund filtration device equipped with vacuum for product drying.

Batch 1. The main goal of batch 1 was to gain experience on all the reaction steps using the developed laboratory procedures, applying what was considered conservative operating parameters. Accordingly, the reaction to prepare **28** proceeded as expected. Aqueous sodium nitrite solution was added at a steady rate over a 3-h period, providing **28** in 85% yield from ethyl glycine hydrochloride as determined by GC analysis.

The reactor containing the **28**/toluene solution was cooled to −5 °C, and 0.07 equiv of $SnCl_4$ (as the 1 M solution in toluene) was added over a 30-min period via a small Teflon-

lined electric pump. To this was added **29** over 3 h by way of a 4-in. double-valve charge tube. The temperature of the reaction mixture reached 13 °C for a short period of time during addition. HPLC analysis of the product solution confirmed completion, with a small amount of unreacted **29** present. The estimated yield of **30** was about 60% as determined by HPLC analysis.

The reactor containing **30** in toluene was warmed to 20 °C. To this was charged 0.97 equiv of $Ca(OH)_2$ and 0.1 equiv of DMAP. Propionyl chloride (0.93 equiv) was added via a small pump over 35 min. The reaction mixture was held at 20 °C for 35 min. HPLC analysis indicated that the reaction progressed as expected, giving rise to **31** as (*E*)- and (*Z*)-isomers. Approximately 4% of unreacted **30** was present.

To the crude product **31** was added 2.0 equiv of 1.2 N aqueous HCl, and the mixture was heated to 80 °C. Upon cooling the product to 30 °C, an interface-suspended precipitate was observed for the first time. The decision was made to filter before separation. Unfortunately, two attempts to filter the mixture through a Sparkler filter failed, but a Nutsche filtration was successful, giving rise to a clean, two-phase mixture. The material collected on the filter had a sludge-like consistency.[38]

The separated organic phase was charged with an excess of 15% NaOH, heated to 60 °C, and held at temperature for 2 h. The system was cooled to 25 °C and charged with 2-propanol and 37% HCl. The slurry was then agitated for 1 h and filtered through a 1-m^2, 10-μm Rosemund filter system, and the mother liquor was collected. The solids filtered well and were washed with 1 volume of 2-propanol followed by 1 volume of water. Drying of the cake under reduced pressure provided **9** in 42% yield from **29** with an assay of 97%. The entire batch took approximately 84 h to complete. Thus, the outcome for batch 1 correlated well with bench-scale results with the exception of the difficult filtration.

Batch 2. The plan for preparation of **28** for this batch was to add the aqueous sodium nitrite solution at a steady rate over 1.5 h and maintain the batch at 7 ± 3 °C with a jacket temperature of −8 °C. This strategy was intended to decrease the cycle time of this operation. However, a temperature spike to 11 °C was observed; therefore, the addition rate was extended to a total of 2 h. The reaction was stirred for about 3 h, providing 9.8 wt. % **28** in toluene for a yield of 81%.

For the preparation of **30**, aldehyde **29** was again added over 3 h to the EDA/$SnCl_4$ solution with the jacket temperature set at −8 °C. The ratio of **28** to **29** was increased from 1.3 to 1.44 equiv because of the longer addition time (and expected decomposition of **28**). The batch was held at 7 °C for 2 h after addition of **29** was completed.

The conversion of **30** to diketo ester **31** proceeded as expected. Operationally two design changes were incorporated into the work instructions. First, the agitation was increased from 65 to 84 rpm, and the propionyl chloride was added over 45 min, rather than 35 min. Both changes were made because of the unreacted starting material present in batch 1. Indeed, HPLC analysis indicated that all starting material was consumed.

Cyclization to **32** was complete within 1 h at 80 °C. After stopping agitation for 30 min, the bottom aqueous layer (containing the solids) was removed without filtration until a rag layer was observed. The toluene layer and the rag layer were then filtered through a cartridge filter with a 10-μm glass element. The filtration proceeded without clogging. Examination of the filter showed very little residue.

The conversion of **32** to **9** proceeded without issue. The overall yield from **29** was 40%. Therefore, it appeared that batch 2 proceeded as expected, providing high-quality product.

Batch 3. The goal of batch 3 was to shorten the batch time and improve the yield. We planned to accomplish this by increasing the reagent addition rate and upper temperature limits for the β-ketoester **30** and diketoester **31** reactions.

Unfortunately, a problem arose during preparation of **31**—approximately 28% (HPLC analysis) of unreacted **30** remained. The addition of more reagents did not significantly improve the conversion. This behavior indicated the presence of water in the reaction medium.[40] Nevertheless, this material was processed as is.

The reaction and separation/filtration for the conversion of **31** to **9** was run as in batch 2, and all proceeded as before. Again the separation and filtration was without incident. The product **9** was very crystalline, easy to filter and dry, and had an assay of 98%. The overall yield from **29** was 28%. Thus, despite the incomplete conversion of **30** to **31**, the chemistry proved robust, providing high-quality product, albeit in lower yield.

Batch 4. The goal of batch 4 was to achieve the 40−42% yield of batches 1 and 2. In this regard, **28** was prepared, and a new lot of **29** with a Karl Fisher analysis of < 1% water was utilized. Agitation was increased from 65 to 100 rpm and **29** added over 2.25 h. A normal exotherm was observed during the course of the reaction. The product solution looked very good by HPLC with an estimated yield of 65%.

The conditions utilized in batch 2 for the conversion of **30** to **31** were repeated. However, a substantial amount of **30** was observed again. The batch was maintained at 20 °C for an additional 2 h and more DMAP (50% of the original charge) added. The final result was approximately 15% of unreacted **30**.

The conversion of the crude **31** to **9** proceeded as before. A very crystalline product was obtained in 32% overall yield with an assay of 98%. Thus, once again the robustness of the process was demonstrated, despite incomplete propionylation of **30**.

Batch 5. The primary goal for this batch was to move closer to a "baseline" pilot-plant procedure. Unfortunately, several difficulties were observed. Heat spikes as high as

(38) Analysis of the sludge indicated that the material was composed mainly of Ca and Sn. The exact nature of the species present is not known. However, the literature suggest $CaSn(OH)_6$. See ref 39.

(39) Toptygina, G. M.; Evdokimov, V. I.; Eliseeva, N. A.; Badanin, V. S. Zh. Neorg. Khim. **1978**, *23*(6), 1471.

(40) Water spiking studies indicated a maximum water tolerance level of 0.7% (as measured by Karl Fischer analysis). Water above this level had a dramatic, adverse effect on product conversion.

21 °C were measured during the preparations of **28** and **30**. Incomplete conversion was observed, and the yield of **30** was estimated at only 53%. Once again it was postulated that entrapped water was the problem.

Complete conversion of **30** to **31** was achieved by increasing calcium hydroxide charge from 0.97 to 1.05 equiv. The charge was based on the HPLC estimated yield of **30**. Cyclization of **31** to **32** proved uneventful, but during the saponification, incomplete phase separation was observed for the first time, and a significant amount of "rag layer" formed. It was decided to isolate the rag separately and analyze it for product. Indeed, a significant amount of **32** was present in this mixture. Precipitation, filtration, and purification of **9** were uneventful. The isolated yield of **9**, based on **29**, was 25%. The assay was 99%.

Batch 1−5 Evaluation. The inconsistent performance of the chemistry to this point warranted further evaluation of the process. Hence, the results of each step from all batches were analyzed for best chemical conversion, cycle time, temperature profile, agitation, reagent stoichiometry, etc. For the conversion of **28** and **29** to **30**, this analysis indicated that batches 2 and 4 afforded the best results. However, in both cases the conversion to **30** was incomplete.

To further understand this reaction, several laboratory studies utilizing a Mettler RC1 calorimeter were completed in which dosing conditions were analyzed and optimized.[26] This analysis indicated that the simultaneous addition of both the $SnCl_4$ and **29** to a cold **28** solution would provide optimum performance, giving rise to essentially complete conversion to **30** and with a yield as high as 77%.

The best result for preparation of the diketoester **31** with an excellent cycle time was achieved during batch 5. As stated above, this was accomplished by increasing the molar stoichiometry of the calcium hydroxide. For the remainder of the process, the results seemed fairly consistent from batch to batch with the exception of batch 5. In this instance, it was proposed that the complications derived from the increased $Ca(OH)_2$ charge. The calcium tin hydroxides formed by the reaction of $SnCl_4$ with $Ca(OH)_2$, followed by caustic, caused the rag layer.[38] Therefore, it was decided that the **32** product mixture would be filtered prior to addition of caustic.

Batch 6. The goals of batch 6 were to practice the aforementioned proposals and findings and, of course, to obtain the desired overall chemical yield of above 40%. In fact these objectives were achieved. An ethyl diazoacetate yield of 90−92% was obtained. The dual stream addition of **29** and the $SnCl_4$ in toluene solution was successful in maintaining a pot temperature below 15 °C. The total cycle time on the other hand was too long, a total of 8 h. Nevertheless, the yield of **30** was measured at 62%, substantially higher than, for example, the 53% achieved in batch 5.

Nearly complete conversion of **30** to **31** was achieved with 5% of **30** remaining as determined by HPLC analysis. The adjusted protocol of maintaining a higher pot temperature during addition worked.

To alleviate downstream phase-separation problems, a new filtration system was devised. Seven parallel 1-μm cartridge filters were used to filter solids out of the **32** product solution before the addition of caustic. This approach was successful. HPLC analysis of the resulting toluene solution measured **32** at 48% yield from **29**.

The phase-separation problems observed for the conversion of **32** to **9** in batch 5 were successfully alleviated in batch 6 by the aforementioned filtration and by maintaining a temperature range of 55−60 °C during phase separation. Laboratory studies indicated that the higher temperature minimized emulsion formation.

The precipitation of **9** and the filtration were uneventful. A single static wash with 2-propanol and water gave rise to product with a 97% assay (2% moisture) in an overall yield of 44%. Thus, substantial movement toward defining a baseline pilot-plant procedure was realized.

Batches 7 and 8. The conditions and charges for these batches were identical to batch 6. Yields of 90 and 92%, respectively, were measured for **28**. The conversion of **28** and **29** to β-ketoester **30** also proceeded as planned. Assay of the resulting product mixture indicated that this process afforded **30** in approximately 62% from **29**. Diketoester **31** formation also was uneventful with the amount of unreacted **30** remaining below 5%. Cyclization, saponification, precipitation, filtration, and drying protocols followed those observed for batch 6, giving **9** in 45 and 43% yield, respectively. Thus, within the operation of Monsanto's Queeny Pilot Plant, a baseline procedure with reproducible results was achieved.

Conclusions

Described were the studies directed toward the research and development of an alternative process to **9**, a penultimate intermediate to the novel agrochemical clofencet (**1**). Retrosynthetic analyses as well as the results obtained from feasibility studies were detailed. This led to the successful development of an alternative process to **9**, employing as the key reaction the Lewis acid-catalyzed reaction of ethyl diazoacetate with hydrazone aldehyde **29**, affording β-ketoester **30**.

The results and challenges of eight pilot-plant runs were reported. Findings such as changing the mode of reagent addition and modifying phase-separation protocols gave rise to a reproducible baseline pilot-plant procedure. 2-(4-Chlorophenyl)-3-ethyl-2,5-dihyro-5-oxo)-4-pyridazinecarboxylic acid (**9**), the penultimate free acid of clofencet, was successfully prepared in four consecutive steps in 43−45% overall yield.

Experimental Section

General. Microanalyses were performed by Galbraith Laboratories. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were recorded on either a Unity Inova Varian 300 MHz or Unity Inova Varian 400 MHz spectrometer in deuteriochloroform and deuteriodimethyl sulfoxide with chloroform and dimethyl sulfoxide, respectfully, used as the internal reference. ^{1}H NMR descriptions are reported as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

Melting points were determined using a Laboratory Devises Mel-Temp Instrument equipped with a Fluke 51 thermocouple. Thin-layer chromatography was performed on EM Science 0.25 nm Silica Gel 60, glass-backed plates with F_{254} indicator. UV light was utilized for visualization. Flash chromatography was performed on Universal Scientific silica gel.

The actual charges of substrates and reagents are given below. The molar amounts and assay of materials are calculated based on the use of analytical standards. 4-Chlorophenylhydrazonoacetaldehyde (**29**) utilized in the pilot-plant campaign was purchased from Dynamit Nobel GmbH of Germany and used without further purification.

Safety. Operators employed a full-face respirator, neoprene gloves with a 4H glove liner, and in a level C Saranex suit with rubber boots during all operations. Sodium nitrite is a strong oxidizer and should be transferred with adequate ventilation. Sodium acetate trihydrate is irritating to the eyes, skin, and respiratory tract. Tin (IV) chloride in toluene is flammable and very corrosive. See ref 26 for EDA safety concerns.

Ethyl Diazoacetate (28). A clean PE carboy (75.7 L) containing water (21.64 kg) and equipped with an air-operated drum mixer was charged with sodium nitrite (14.36 kg, 208.1 mol). Stirring was continued until a solution resulted.

A glass-lined, jacket reactor (378.5 L) equipped with an overhead stirrer, a bottom drain valve, two thermocouples, and a nitrogen inlet with a jacket temperature of 10.0−15.0 °C was charged with water (28.23 kg) and the agitator set to 100 rpm. To this was charged sodium acetate trihydrate (4.82 kg, 35.4 mol), ethyl glycinate hydrochloride (25.14 kg, 180.4 mol), and toluene (146.55 kg, 1590 mol), making sure that a solution was formed with each addition. To this biphasic solution was added 37% HCl (2.29 kg, 62.8 mol) at such a rate that the internal temperature remained within 10.0−15.0 °C. The aforementioned sodium nitrate solution was then added over a 90-min period, while maintaining a temperature of between 13 and 15 °C. After the reaction was complete, the agitator was shut down, and the phases were allowed to separate. The aqueous phase (72.4 kg, pH = 3.65) was removed. Assay of the organic phase (165.2 kg) gave rise to a 10.9 wt % (90%) solution of ethyl diazoacetate in toluene.

(4-[(4-Chlorophenyl)-(1-hydrazinyl-2-ylidene)]-3-oxo) Butanoic Acid Ethyl Ester (30). To a clean, dry PE carboy (18.9 L) equipped with a nitrogen inlet was added toluene (6.76 kg) and tin (IV) chloride (1.78 kg, 6.85 mol). The glass-lined, jacket reactor containing the ethyl diazoacetate solution was cooled to −5 °C and the agitator speed set to 100 rpm. The reactor was then charged simultaneously with hydrazonoacetaldehyde **29** (19.3 kg, 106 mol) and the aforementioned tin (IV) chloride solution at such a rate as to maintain an internal temperature of 9.0−15.0 °C. After the addition was complete, the reaction was held at 10 °C for 4 h. Analytical analysis of the organic phase indicated a yield of 71.6% with a β-ketoester-to-pyrazole ratio of 27:1. The crude product mixture was used directly without further purification. The product **30** may be obtained by quenching with water and crystallization of the organic phase concentrate with diethyl ether and hexane. Obtain is a yellow solid: mp 100−101.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.28 (AA′BB′, 4H), 4.21 (q, J = 7.2 Hz, 2H), 3.89 (s, 2H), 2.46 (s, 1H), 1.29 (t, J = 7.2 Hz, 3H). $C_{12}H_{13}N_2O_3Cl$: Calcd: C, 53.64; H, 4.88; N, 10.42. Found: C, 53.76; H, 4.90; N, 10.49.

Diketo Ester 31. The reactor containing the β-ketoester **30** in toluene was warmed to 20 °C, the agitator set at 120 rpm, and the reactor charged with calcium hydroxide (7.6 kg, 102.6 mol), 4-(dimethylamino)pyridine (1.3 kg, 10.55 mol), and propionyl chloride (0.1 kg, 98.8 mol). The reaction mixture was held at 20 °C for 40 min, then filtered. The crude product mixture was used directly without further purification.

2-(4-Chlorophenyl)-3-ethyl-2,5-dihyro-5-oxo)-4-pyridazinecarboxylic Acid Ethyl Ester (32). Into the reactor containing the crude diketoester **31** in toluene was charged 1.2 N HCl (68.3 kg, 214 mol). This was heated to 80 °C and held for 3 h. This was cooled to 55−60 °C, the layers were separated, filter aid (0.23 kg) was added, and the organic phase was filtered through a parallel series of seven, 1-μm filters to obtain the organic phase (196 kg). Analytical analysis indicated an overall yield of 53.3% from **29**. Unreacted **30** = 4.9%, pyrazole **33** = 5.4%. Yellow solid: mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.49 (AA′BB′, 4H), 4.47 (q, 2H), 2.63 (q, 2H), 1.44 (t, 3H), 1.14 (t, 3H).

2-(4-Chlorophenyl)-3-ethyl-2,5-dihyro-5-oxo)-4-pyridazinecarboxylic Acid (9). To the organic phase from the previous reaction was charged 15% NaOH (121.7 kg, 457 mol). The mixture was heated with agitation to 60 °C and held at this temperature for 2 h. The mixture was cooled to 25 °C. 2-Propanol (65.6 kg, 1093 mol) and 37% HCl (50.8 kg, 515.2 mol) were charged sequentially. The slurry was agitated for 1 h and then filtered through a 1-m^2, 10-μm Rosemund filter system. The mother liquor (286 kg) was collected and the cake washed with isopropyl alcohol (16.5 kg) followed by water (16.7 kg). Drying of the cake under reduced pressure provided 15.1 kg (45%) of **9** with an assay of 97.1% as a tan/yellow solid. The product was shown to be identical to an authentic sample.

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