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Development of a Scalable Process for the Insecticidal Candidate Tyclopyrazoflor. Part 3. A Scalable Synthesis of Methyl 3-((3,3,3-Trifluoropropyl)thio)propanoate via Thiol−Ene Chemistry

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ABSTRACT: Optimization of the thiol−ene reaction for the preparation of methyl 3-((3,3,3-trifluoropropyl)thio)propanoate (**4**), a key intermediate in the synthesis of the sap-feeding insecticidal candidate tyclopyrazoflor (**1**), is described. The major challenge with the radical thiol−ene chemistry was control of the regioselectivity between the linear and branched products. Reducing the radical initiation temperature was found to be the key variable in controlling the selectivity. Because of the high cost and storage challenges associated with the use of the room-temperature diazo initiator 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70), a two-component initiator system consisting of benzoyl peroxide and *N*,*N*-dimethylaniline was developed, allowing for radical initiation at temperatures as low as −15 °C. Application of semibatch operation gave 90:1 selectivity favoring the linear product. The overall yield and selectivity of the radical thiol−ene reaction were improved from 78% yield and 11:1 selectivity with azobis(isobutyronitrile) in batch mode to 91% yield and 90:1 selectivity with the two-component system in semibatch mode, further eliminating the need for a fractional distillation purification step.

KEYWORDS: *radical reaction, thiol−ene, selectivity, methyl 3-((3,3,3-trifluoropropyl)thio)propanoate, agrochemicals, insecticide*

INTRODUCTION

Pyrazole derivatives have been actively researched over the past few decades for the development of agrochemicals such as fungicides, herbicides, and insecticides[1] and are also a common structural motif in pharmaceutical targets.[2] Tyclopyrazoflor (**1**) (Figure 1), a pyrazole-containing insecticidal candidate with

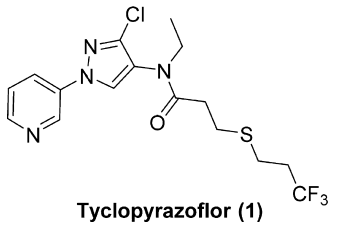

Figure 1. Structure of tyclopyrazoflor (**1**).

excellent activities against sap-feeding pests,[3] was made via amidation of advanced pyridinylpyrazole derivative **7**[4] with acid chloride **6** (Scheme 1). Acid chloride **6** was prepared in two steps from the key intermediate methyl 3-((3,3,3-trifluoropropyl)thio)propanoate (**4**). This report describes the development of a scalable synthesis of **4**.

Tasked with developing a scalable synthesis of **4**, we identified four possible routes (Scheme 2) and evaluated their viability on the basis of the availability and cost of starting materials, the regulation of harmful components, and the inherent selectivity of the reaction being performed. These criteria align closely with the 12 principles of green chemistry proposed by Anastas and Warner.[5] To support field efficacy studies, the product was initially prepared on 100 gram scales using a simple nucleophilic substitution reaction with 3-halo-1,1,1-trifluoropropanes (Scheme 2, Route A); however, these reagents have properties that we attempt to avoid in manufacturing processes.[6] 3-Bromo- and 3-chloro-1,1,1-trifluoropropane are known ozone depletors, while the iodide waste generated from 3-iodo-1,1,1-trifluoropropane poses waste stream complications. The Michael addition between methyl acrylate and 3,3,3-trifluoropropane-1-thiol (Scheme 2, Route B) could be highly selective and atom-efficient, but the cost of the 3,3,3-trifluoropropane-1-thiol starting material made this route impractical.[7] Switching the addition partners to 3,3,3-trifluoropropene and methyl 3-mercaptopropionate for an anti-Markovnikov hydrothiolation (Scheme 2, Route C) eliminated expensive starting materials and led to the development of a radical thiol−ene pathway that eliminated the use of stoichiometric base (Scheme 2, Route D).[8] This report details the development and optimization of the radical thiol−ene addition of methyl 3-mercaptopropionate (**2**) to 3,3,3-trifluoropropene (**3**) to make **4**.

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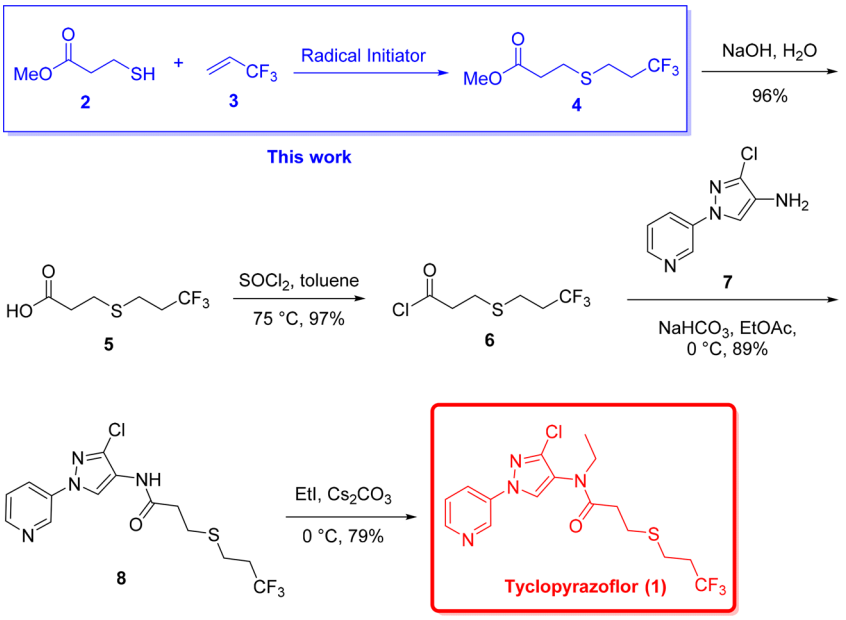
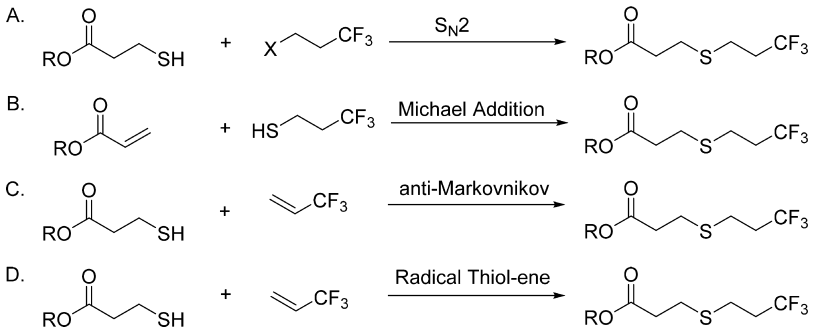
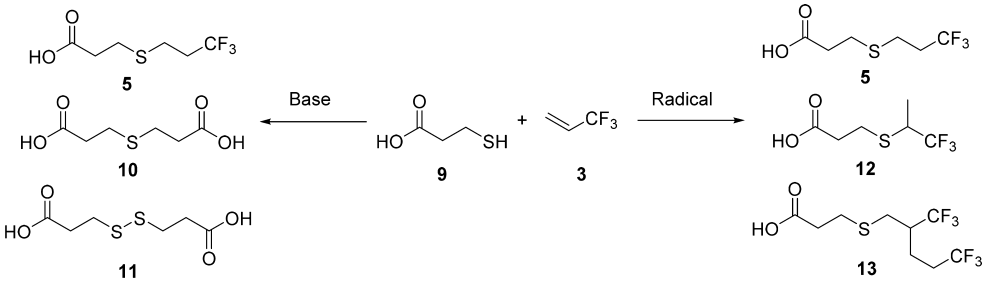
Scheme 1. Route to Tyclopyrazoflor (1)



Scheme 2. Synthetic Options for the Preparation of 3-((3,3,3-Trifluoropropyl)thio)propanoate Esters and Acids



Scheme 3. Syntheses of 5 via Base-Promoted Anti-Markovnikov Addition and the Radical Thiol−Ene Reaction of 9 and 3



RESULTS AND DISCUSSION

Initial efforts in this research focused on the direct synthesis of 3-((3,3,3-trifluoropropyl)thio)propionic acid (**5**) to eliminate one step from the synthesis of acid chloride **6**. Starting from 3,3,3-trifluoropropene (**3**) and 3-mercaptopropionic acid (**9**), the anti-Markovnikov addition route did afford a low yield of the desired product **5** in addition to sulfide **10** and disulfide **11** (Scheme 3). In contrast, the azobis(isobutyronitrile) (AIBN)-initiated thiol−ene reaction furnished the desired linear product **5** in good yield with the branched isomer **12** and double addition adduct **13** as the major side products. (Table 1, entry 1). The yield of the double addition adduct **13**, which results from the reaction of the incipient thiol−ene addition radical with another equivalent of **3** before the internal radical is quenched, was significantly reduced by decreasing the amount of 3,3,3-trifluoropropene from 1.8 to 1.0 equiv (entry 2). Switching to a polar aprotic solvent, ethyl acetate (EtOAc), afforded a good yield but had very little effect on the product selectivity (entry 3). Finally, a polar protic solvent, methanol (MeOH), resulted in enhanced selectivity for the single addition product **5** but a significantly lower yield due to low conversion (entry 4).

Attempts to purify **5** from the liquid crude product by fractional distillation were fruitless because of the similar high boiling points of **5**, **12**, and **13**. It was envisioned that these obstacles could be overcome by switching to methyl 3-

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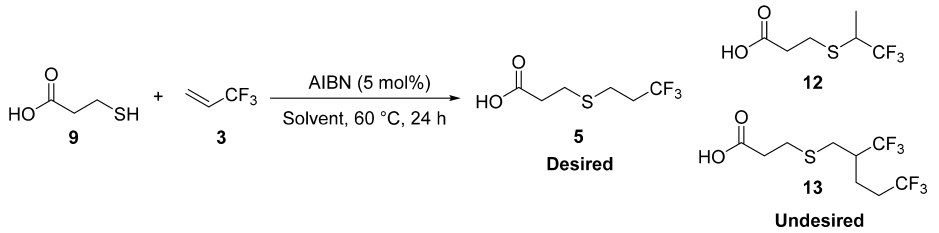
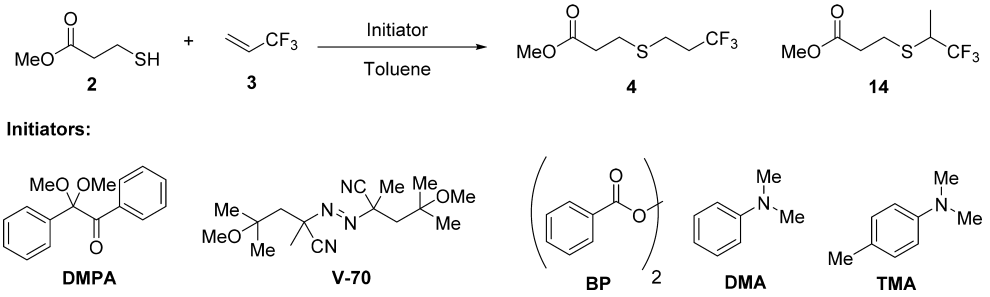
Table 1. Optimization of the Radical-Promoted Thiol−Ene Reaction of 9 and 3



entry	solvent	amount of 3 (equiv)	5:12[a]	5:13[a]	yield (%)[b]
1	toluene	1.8	11:1	14:1	NA
2	toluene	1.0	12:1	43:1	74
3	EtOAc	1.0	11:1	44:1	74
4	MeOH	1.0	12:1	85:1	18

[a]Determined by GC. [b]In-pot yields by quantitative GC analysis. NA: not available.

Table 2. Optimization of the Radical Promoted Thiol−Ene Reaction of 2 and 3



entry	initiator	initiator loading (mol %)	temp. (°C)	4:14[a]	yield (%)[b]
1	AIBN	2.5	80	11:1	78
2	AIBN	1	80	11:1	68[d]
3	DMPA[c]	5	35	22:1	71
4	V-70	5	RT	44:1	77
5	V-70	1.75	RT	38:1	86
6	BP + DMA	5[e]	RT	31:1	73
7	BP + DMA	5[e]	8	56:1	86
8	BP + DMA	5[e]	−6	76:1	87
9	BP + DMA	5[e]	−15	95:1	84
10	BP + TMA	5[f]	RT	26:1	71

[a]Determined by GC. [b]In-pot yields by quantitative GC analysis. [c]Initiated with a 366 nm light source. [d]The reaction stalled at 91% conversion. [e]5 mol % BP and 5 mol % DMA were used. [f]5 mol % BP and 5 mol % TMA were used.

mercaptopropionate (**2**) to generate the more volatile methyl ester **4**.[9] The reaction of **2** and **3** with AIBN as the radical initiator in toluene at 80 °C resulted in an 11:1 mixture of linear product **4** and branched product **14** (Table 2, entry 1, virtually identical to that seen for the acid starting material) in a good yield of 78%. This reaction was ultimately scaled to 5 kg of methyl ester **2** with no loss in selectivity (11:1 ratio). A multistage vacuum distillation provided effective separation from the impurities, including the branched isomer with a similar boiling point.[10] It should be noted that a fast exotherm of up to 36 °C was observed on the 5 kg scale when the AIBN-initiated process was run in batch mode with all reagents present.[11]

Reducing the radical initiator loading to 1 mol % had little effect on the reaction selectivity but resulted in somewhat sluggish reactivity, lower conversion, and consequently a lower yield of only 68% (Table 2, entry 2). To test the effect of low temperature on the efficiency and selectivity of the thiol−ene reaction, we envisioned that a photoinitiator would allow access to lower-temperature conditions. With the use of 2,2-dimethoxy-2-phenylacetophenone (DMPA)[12] as the initiator and a reaction temperature of only 35 °C, the reaction proceeded in good yield (71%) with an improved linear/branched selectivity of 22:1 (entry 3). Because of the challenges associated with the scale-up of photochemistry in the available equipment, alternate low-temperature thermal initiators were investigated. Reducing the reaction temperature further to room temperature and using 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70)[13] as the initiator further improved the linear/branched product selectivity to 44:1 (entries 4 and 5). While V-70 provided the desired selectivity and yield, it was less than favorable from a manufacturing perspective because of its high cost and need for special storage conditions (it has a short shelf life at 0 °C and must be stored below −15 °C to extend its lifetime).

The literature suggested that the use of a two-component initiator system, such as benzoyl peroxide (BP) and *N*,*N*-dimethylaniline (DMA),[14] could provide access to radicals at low temperature while maintaining the stability of the initiators during storage. Under normal conditions BP has a half-life of

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10 h at 73 °C, but in the presence of DMA, BP can rapidly decompose at temperatures as low as −15 °C to produce radicals (Table 2, entries 6−9). Systematic lowering of the reaction temperature from ambient to −15 °C resulted in a significant improvement in the linear/branched selectivity (from 31:1 to 95:1) while affording an excellent yield of 84% (entry 9).

While the conditions shown in Table 2 achieved high selectivity, a significant exotherm (estimated at −22 kcal/mol) was observed during the investigations. Although the heat was efficiently removed on a small scale (25 g in a 100 mL Parr reactor), we calculated that >100 min would be required to remove all of the heat of reaction for a 300 gal glass-lined vessel, and larger production-scale reactors would require multiple hours. Switching from a batch process to a semibatch process would allow for efficient control of heat generation. In order to enable a semibatch process, a constant supply of radicals would need to be generated in the reactor. This was achieved by continuously adding BP to a reactor containing the aniline activator (Figure 2). Ultimately *N*,*N*,4-trimethylaniline

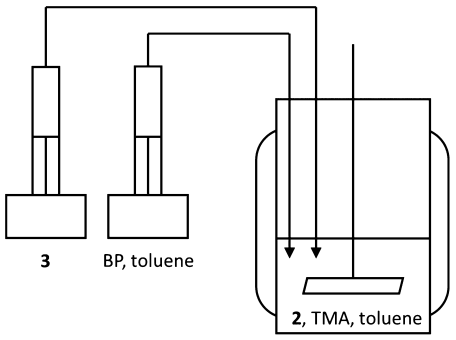


Figure 2. Diagram of the semibatch process for the preparation of **4** via radical-initiated thiol−ene reaction.

(TMA) was selected for further optimization as the aniline activator because it increased the reaction rate by 10-fold, allowing for shorter semibatch reactions.

A semibatch process was investigated in which TMA (5 mol %) and **2** were preloaded into a 300 mL autoclave reactor that was cooled to 0 °C. Two Isco syringe pumps were used to deliver **3**[15] and a solution of BP in toluene into the reactor over 2 h (Table 3). It was found that increasing the reactant concentration gave higher conversion, improved the selectivity, and allowed for reduced BP loadings, with 80 wt % **2** and **3** (1:1.05) being the optimal conditions (entry 3). These conditions were successfully demonstrated on a 1.5 kg scale using a 1 gal reactor at −5 °C, affording an in-pot yield of 91% with 50:1 selectivity favoring the desired linear adduct **4**. The purity of the product was acceptable, which obviated the need for further purification by fractional distillation.

CONCLUSIONS

The thiol−ene reaction proved to be an efficient and low-cost method for the synthesis of methyl 3-((3,3,3-trifluoropropyl)-thio)propanoate (**4**). The main side product of this chemistry, the branched isomer **14**, was controlled by reducing the radical initiation temperature. The two-component initiator system consisting of BP and DMA or TMA proved to be an efficient means of accessing radicals at low temperatures and improved linear/branched selectivity of this reaction while also providing a low-cost and scalable route. A semibatch process was successfully developed to afford excellent yield, selectivity, and effective control of the exotherm, enabling the development of a scalable process that eliminated the need for a challenging fractional distillation separation.

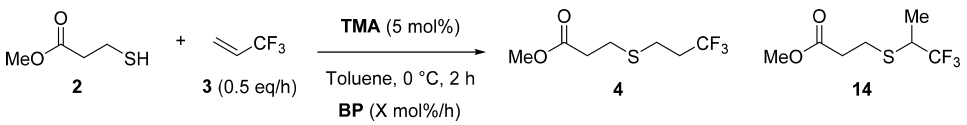
EXPERIMENTAL SECTION

General. All of the reagents were commercially available and used as purchased without further purification. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Ultrashield 400 NMR spectrometer. GC analysis was performed on an Agilent 7890A GC system with an Agilent DB-5MS column (30 m × 0.25 mm × 0.25 μm, P/N 122-5532) using the following conditions: heater, 250 °C; flow rate, 2 mL/min; injection volume, 1 μL; oven program: 50 °C for 2 min, ramp to 280 °C at 20 °C/min, hold at 280 °C for 8 min; internal standard, octanophenone.

Representative Procedure for the Preparation of 4 Using AIBN (Batch Mode). A 10 gal 316 stainless steel (SS) reactor was charged with methyl 3-mercaptopropionate (5007 g, 41.67 mol), AIBN (170 g, 1.04 mol), and toluene (8410 g) and cooled to 5 °C. 3,3,3-Trifluoropropene (3843 g, 40.01 mol) was added as a liquefied gas, and the reactor was heated to 80 °C over 1 h. After 20 h at 80 °C, the pressure was slowly ramped down to 50 mmHg to remove toluene, giving crude **4** (8200 g, 11:1 linear/branched, 82.2 wt % purity, 78% yield).

Four batches of crude product **4** (31 200 g, 85.6 wt % purity) were combined and charged to a 10 gal 316 SS reactor equipped with a 60″ tall, 4″ diameter column packed with GOODLOE high-efficiency structured packing. The material was distilled under vacuum (∼5 mmHg at the top of the column) with a 10:1 reflux ratio. Fractions of desired purity were combined to give **4** (26 530 g, 95 wt %, 94% recovery). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.82, (td, J = 7.3, 0.7 Hz, 2H), 2.75−2.68 (m, 2H), 2.63 (td, J = 7.2, 0.6 Hz, 2H), 2.47−2.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

Table 3. Optimization of the Semibatch Process for the Preparation of 4 via Radical-Initiated Thiol−Ene Reaction



entry	reactant concentration (wt %)[a]	BP addition rate (mol %/h)	4:14[b]	conv. (%)[c]	yield (%)[d]
1	50	2.5	75:1	74	48
2	60	1	87:1	75	57
3	80	0.5	90:1	99	91

[a]Combined concentration of **2** and **3** relative to the mass at the end of the additions. [b]Determined by GC. [c]Refers to loss of the starting material **2**. [d]In-pot yields by quantitative GC analysis.

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172.04, 125.93 (q, J = 277.2 Hz), 51.86, 34.68 (q, J = 28.6 Hz), 34.39, 27.06, 24.11 (q, J = 3.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.53.

Representative Procedure for the Preparation of 4 Using BP/DMA (Batch Mode). A 2 L autoclave reactor was charged with methyl 3-mercaptopropionate (376.4 g, 3132.2 mmol), toluene (635.1 g), and benzoyl peroxide (Luperox A75, 75 wt % BP wet with water, 50.1 g, 155.12 mmol active). The reactor was sealed and purged with nitrogen, and the cooling coil was set at −20 °C. 3,3,3-Trifluoropropene (303.0 g, 3154.6 mmol) was added by transfer cylinder, and the resulting mixture was stirred overnight for effective cooling prior to reaction initiation. The in-pot temperature reached 1 °C after cooling overnight. Dimethylaniline (19 g) was added by transfer cylinder. After 1.5 h, more dimethylaniline (18.3 g) was added, and an exotherm was observed (18 °C temperature rise). After 19 h, the reactor was emptied, and its contents were quantified (1353 g, 38.5 wt % active, 520 g active, 77%, 55:1 linear/branched by GC).

The organic layer was divided evenly between two 1 L reactors, and 10 wt % NaOH was added (170 g each). The mixtures were stirred at 350 rpm for 2 h and then allowed to settle. The aqueous layers were removed, and to each reactor was added 130 g of 2 N HCl, after which the mixtures were stirred for 20 min. The organic layers were combined and quantified (1226 g, 42.5 wt %, 521 g active, 77%). The toluene was distilled off at atmospheric pressure, and the product was distilled overhead under vacuum (83−88 °C, 6 mmHg), giving **4** as a colorless oil (493 g, 94.4 wt % active, 466 g active, 89% recovery, 69% yield).

Representative Procedure for the Preparation of 4 Using BP/TMA (Semibatch Mode). Methyl 3-mercaptopropionate (900 g, 7.49 mol) and *N*,*N*,4-trimethylaniline (50 g, 0.37 mol) were charged into a 1 gal Hastelloy C reactor with a peristaltic pump through a 1″ headspace addition port. A 10 wt % solution of benzoyl peroxide (Benox A-75, 75 wt % BP wet with water, 27.2 g, 0.084 mol active) in toluene (184 g) was prepared by mixing for 30 min to dissolve the solids. The entire mixture was charged into the Isco pump (including the water phase, which settled to the bottom). The reactor was inerted with nitrogen and cooled to −5 °C. 3,3,3-Trifluoropropene (755 g, 7.86 mol) was added at 0.5 equiv/h with concomitant addition of the benzoyl peroxide solution at 0.5 mol %/h with the reactor closed (no pressure control on the reactor or venting during operation). After addition of the reagents was complete (135 min, BP solution only during the last 15 min), the feed lines were purged with nitrogen. The reactor was allowed to mix for 1 h following addition, after which the jacket set point was changed to 20 °C and the reactor was left overnight. The mixture was discharged from the reactor and quantified by GC analysis (1952 g, 75.4 wt %, 91% in-pot yield, 50:1 linear/branched).

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Author Contributions

The manuscript was written through contributions of all authors. All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Lamberth, C. Pyrazole Chemistry in Crop Protection. *Heterocycles* **2007**, *71*, 1467. (b) Kramer, W.; Schirmer, U.; Jeschke, P.; Witschel, M. *Modern Crop Protection Compounds*; Wiley-VCH: Weinheim, Germany, 2012.

(2) For recent examples, see: (a) Curtis, N. R.; Davies, S. H.; Gray, M.; Leach, S. G.; McKie, R. A.; Vernon, L. E.; Walkington, A. J. Asymmetric Fluorination Approach to the Scalable Synthesis of a SYK Inhibitor. *Org. Process Res. Dev.* **2015**, *19*, 865. (b) Chekal, B.; Damon, D.; LaFrance, D.; Leeman, K.; Mojica, C.; Palm, A.; St. Pierre, M.; Sieser, J.; Sutherland, K.; Vaidyanathan, R.; Van Alsten, J.; Vanderplas, B.; Wager, C.; Weisenburger, G.; Withbroe, G.; Yu, S. Development of the Commercial Route for the Manufacture of a 5-Lipoxygenase Inhibitor PF-04191834. *Org. Process Res. Dev.* **2015**, *19*, 1944. (c) Cole, K. P.; Campbell, B. M.; Forst, M. B.; McClary Groh, J.; Hess, M.; Johnson, M. D.; Miller, R. D.; Mitchell, D.; Polster, C. S.; Reizman, B. J.; Rosemeyer, M. An Automated Intermittent Flow Approach to Continuous Suzuki Coupling. *Org. Process Res. Dev.* **2016**, *20*, 820. (d) Mulder, J. A.; Gao, J.; Fandrick, K. R.; Zeng, X.; Desrosiers, J.; Patel, N. D.; Li, Z.; Rodriguez, S.; Lorenz, J. C.; Wang, J.; Ma, S.; Fandrick, D. R.; Grinberg, N.; Lee, H.; Bosanac, T.; Takahashi, H.; Chen, Z.; Bartolozzi, A.; Nemoto, P.; Busacca, C. A.; Song, J. J.; Yee, N. K.; Mahaney, P. E.; Senanayake, C. H. Early Development Scale-Up of a Structurally-Challenging 5-Lipoxygenase Activating Protein (FLAP) Inhibitor. *Org. Process Res. Dev.* **2017**, *21*, 1427. (e) Wilsily, A.; Mennen, S. M.; Cosbie, A.; Milne, J. E. Synthesis of the Hydrazinyl Pyridine Intermediate: Phase-Appropriate Delivery. *Org. Process Res. Dev.* **2017**, *21*, 1286. (f) Akin, A.; Barrila, M. T.; Brandt, T. A.; Dechert-Schmitt, A. R.; Dube, P.; Ford, D. D.; Kamlet, A. S.; Limberakis, C.; Pearsall, A.; Piotrowski, D. W.; Quinn, B.; Rothstein, S.; Salan, J.; Wei, L.; Xiao, J. A Scalable Route for the Regio- and Enantioselective Preparation of a Tetrazole Prodrug: Application to the Multi-Gram-Scale Synthesis of a PCSK9 Inhibitor. *Org. Process Res. Dev.* **2017**, *21*, 1990. (g) Bader, S. J.; Herr, M.; Aspnes, G. E.; Cabral, S.; Li, Q.; Bian, J.; Coffey, S. B.; Dowling, M. S.; Fernando, D. P.; Jiao, W.; Lavergne, S. Y.; Kung, D. W. Route Selection and Optimization in the Synthesis of Two Imidazopyridine Inhibitors of DGAT-2. *Org. Process Res. Dev.* **2018**, *22*, 360. (h) Karlsson, S.; Bergman, R.; Broddefalk, J.; Löfberg, C.; Moore, P. R.; Stark, A.; Emtenäs, H. A Practical Telescoped Three-Step Sequence for the Preparation of (1*R*,2*R*)-2-(4-Bromobenzoyl)-cyclohexanecarboxylic Acid: A Key Building Block Used in One of Our Drug Development Projects. *Org. Process Res. Dev.* **2018**, *22*, 618. (i) Li, B.; Barnhart, R. W.; Hoffman, J. E.; Nematalla, A.; Raggon, J.; Richardson, R.; Sach, N.; Weaver, J. Exploratory Process Development of Lorlatinib. *Org. Process Res. Dev.* **2018**, *22*, 1289. (j) Fox, R. J.; Schmidt, M. A.; Eastgate, M. D. Strategy to Prepare 3-Bromo- and 3-Chloropyrazoles. *J. Org. Chem.* **2018**, *83*, 2830.

(3) (a) Buysse, A. M.; Niyaz, N. M.; Zhang, Y.; Walsh, M. J.; Kubota, A.; Hunter, R.; Trullinger, T. K.; Lowe, C. T.; Knueppel, D.; Demeter, D. A.; Patny, A.; Garizi, N.; LePlae, P. R.; Wessels, F. Preparation of pyridinylpyrazolamine derivatives as pesticides and their pesticidal compositions. WO 2013162715, 2013. (b) Buysse, A. M.; Niyaz, N. M.; Demeter, D. A.; Zhang, Y.; Walsh, M. J.; Kubota, A.; Hunter, R.; Trullinger, T. K.; Lowe, C. T.; Knueppel, D.; Patny, A.; Garizi, N.; LePlae, P. R.; Wessels, F.; Ross, R.; Deamicis, C.; Borromeo, P. WO 2013162716, 2013.

DOI: 10.1021/acs.oprd.9b00129
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(4) (a) Yang, Q.; Li, X.; Lorsbach, B. A.; Roth, G.; Podhorez, D. E.; Ross, R., Jr.; Niyaz, N.; Buysse, A.; Knueppel, D.; Nissen, J. Development of a Scalable Process for the Insecticidal Candidate Tyclopyrazoflor. Part 1. Evaluation of [3 + 2] Cyclization Strategies to 3-(3-Chloro-1*H*-pyrazol-1-yl)pyridine. *Org. Process Res. Dev.* **2019**, DOI: 10.1021/acs.oprd.9b00127. (b) Yang, Q.; Li, X.; Lorsbach, B. A.; Muhuhi, J. M.; Roth, G. A.; Gray, K.; Podhorez, D. E. Development of a Scalable Process for the Insecticidal Candidate Tyclopyrazoflor. Part 2. Fit-for-Purpose Optimization of the Route to Tyclopyrazoflor Featuring [3 + 2] Cyclization of 3-Hydrazinopyridine·2HCl and Methyl Acrylate. *Org. Process Res. Dev.* **2019**, DOI: 10.1021/acs.oprd.9b00128.

(5) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.

(6) Leng, R. B.; Emonds, M. V. M.; Hamilton, C. T.; Ringer, J. W. Holistic Route Selection. *Org. Process Res. Dev.* **2012**, *16*, 415.

(7) (a) Nair, D. P.; Podgórski, M.; Chatani, S.; Gong, T.; Xi, W.; Fenoli, C. R.; Bowman, C. N. The Thiol-Michael Addition Click Reaction: A Powerful and Widely Used Tool in Materials Chemistry. *Chem. Mater.* **2014**, *26*, 724. (b) Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. Thiol-click chemistry: a multifaceted toolbox for small molecule and polymer synthesis. *Chem. Soc. Rev.* **2010**, *39*, 1355.

(8) Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. Thiyl Radicals in Organic Synthesis. *Chem. Rev.* **2014**, *114*, 2587.

(9) Methyl ester **4** has a vapor pressure of 10 mmHg at 94.8 °C.

(10) The branched isomer **14** has a boiling point of 90 °C at 10 mmHg, and the branched/linear binary system has a measured relative volatility of 1.5 from 10−25 mmHg across the composition range, which is indicative of a separation that is expected to be difficult and require a large number of equilibrium stages to significantly purify the linear isomer. At a 27 kg linear isomer scale (combined batches for distillation), this multistage distillation removed toluene and unreacted methyl ester as lights with relative ease and also afforded easy separation from the double addition and other heavier impurities, but it required a significant number of stages (10−20 theoretical stages from a 60″ vertical packed column) and a high reflux ratio (10:1) with a top-of-column pressure of 5 mmHg in order to separate the linear and branched isomers with reasonable efficiency. With this distillation system and starting with 85.6% pure linear isomer with toluene prestripped, 94.3% distillation recovery of 95.0% pure linear isomer was achieved, but the recovery drops to only 67% when 98.0% pure linear isomer is needed.

(11) In this batch-mode reaction, all of the reagents, including the catalyst, were loaded, and then the reaction contents were heated until the radical reaction initiated, which occurred at around 65 °C. Upon initiation, the vessel jacket was switched to full cooling, but the reaction still proceeded quickly, with the exotherm rising within 5 to 7 min to the maximum observed temperature before the system could be cooled back to the desired aging temperature of 80 °C. These 5 kg-scale reactions occurred in a well-stirred 10 gal stainless steel reactor with external jacket services. Upon scale-up of this process to larger scales with lower heat transfer area-to-volume ratios in stirred tank reactors, this approach would be expected to produce larger observed exotherms. Reducing the temperature of initiation and/or determining a way to run this reaction in semibatch mode to extend the exotherm were both identified as project goals following these scale-up batches.

(12) (a) Kottari, N.; Chabre, Y. M.; Shiao, T. C.; Rej, R.; Roy, R. Efficient and accelerated growth of multifunctional dendrimers using orthogonal thiol-ene and S_N2 reactions. *Chem. Commun.* **2014**, *50*, 1983. (b) Choudhary, U.; Northrop, B. H. Allyl-functionalized dioxynaphthalene[38]crown-10 macrocycles: Synthesis, self-assembly, and thiol-ene functionalization. *Chem. - Eur. J.* **2014**, *20*, 999.

(13) Hirota, M.; Miyazaki, H.; Itoh, T. Process for producing (fluoroalkylthio)acetic acid ester. US20120101294A1, 2012.

(14) Sideridou, I. D.; Achilias, D. S.; Karava, O. Reactivity of Benzoyl Peroxide/Amine System as an Initiator for the Free Radical Polymerization of Dental and OrthopaedicDimethacrylate Monomers: Effect of the Amine and Monomer Chemical Structure. *Macromolecules* **2006**, *39*, 2072.

(15) The autoclave reactor tests were all run at elevated pressure (>75 psig) in order to pump **3** as a liquid through an Isco pump.

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