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Development of a Scalable Synthesis of GSK183390A, a PPAR α/γ Agonist

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Abstract:

A scalable synthesis of GSK183390A, a PPAR α/γ agonist, is described. This synthesis is highlighted by (1) a regioselective formal 1,3-dipolar cycloaddition reaction between an enamine and a nitrile imine dipole to form a 1,3,5-trisubstituted pyrazole and (2) a regioselective amidomethylation of an *o*-cresol derivative using 2-chloro-*N*-hydroxymethylacetamide.

Introduction

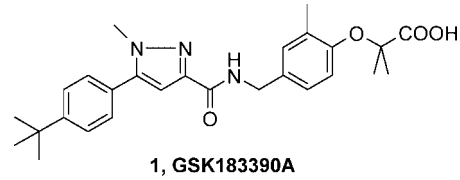
Peroxisome proliferator-activated receptors (PPARs) are a group of ligand-activated transcription factors of the nuclear receptor family, including three distinct subtypes commonly designated as PPARα, PPARγ and PPARδ. These PPARs bind to DNA sequences and regulate gene expression, thus influencing cellular functions such as lipid metabolism, cell proliferation and differentiation. Consequently, the activation of PPARs provides promising therapeutic opportunities for the management of diseases related to these cellular activities. GSK183390A (**1**, Figure 1) has recently emerged as a potent dual agonist of PPARα/γ and a candidate for treatment of dyslipidemia.[1] Its progression into clinical studies has necessitated a synthetic route amenable to large-scale synthesis.

Shown in Scheme 1 is the original synthetic route to **1** via the coupling of benzylamine **10** and pyrazole **11**. Two main drawbacks exist for this route: (1) The condensation between methylhydrazine and diketone **4** produced a mixture of the desired 1,3,5-trisubstituted pyrazole **5** and the undesired isomer **6** in a 1:2 ratio, with the desired isomer **5** as the minor product. Not only did the poor regioselectivity render the yield of this step unacceptably low, but it also entailed chromatographic purification of the product. (2) The synthesis of benzylamine **10** required six linear steps, which seemed lengthy for a molecule of its size and relative simplicity.

Our search for a new route, therefore, focused on a regioselective method for the pyrazole formation to deliver isomer **5** exclusively, as well as a more efficient synthesis of benzylamine **10**. This report discloses a new and scalable route to **1**, which was employed in a pilot plant campaign to produce 40 kg of active pharmaceutical ingredient (API).

Results and Discussion

Synthesis of Pyrazole 11. In order to address the serious regiochemical issue in the pyrazole formation step, we proposed an alternative route employing a formal 1,3-dipolar cycloaddition reaction between a nitrile imine



1, GSK183390A

Figure 1. **GSK183390.**

dipole **13**, generated by base-promoted dehydrohalogenation of hydrazonoyl halides **12**,[2] and alkyne **14** or its equivalent (Scheme 2). Since the appropriate pairing of the reacting partners would be crucial for ensuring both regioselectivity and reactivity,[3] we started our investigation by screening different dipole precursors and dipolarophiles.

1,3-Dipolar Cycloaddition Reaction. The preparation of the coupling partners is outlined in Scheme 3. Hydrazonoyl halides **18** and **19** were prepared by condensation of methylhydrazine with ethyl glyoxylate, followed by treatment of the resulting hydrazone **17** with NBS or NCS. Four electron-rich olefins were synthesized[5] for use as potential alkyne equivalents to be screened in the cycloaddition reaction.

With the coupling partners in hand, the cycloaddition reaction was evaluated to identify the ideal pairing. The results are summarized in Table 1.

Chloride **19** proved to be an unreactive partner with all the dipolarophiles screened, providing minor conversion to the desired product even after extended reaction times. The reactions of bromide **18** with 4-*tert*-butylphenylacetylene **14**,TMS enol ether **20** or enol phosphate **21** were sluggish and gave complex mixtures. Among several unidentified components, the major product proved to be tetrazine **25**, the head-to-tail dimer of the dipole. However, the pairing of hydrazonoyl bromide **18** and the more electron-rich morpholine enamines (**22**, **23**) provided good reactivity and readily gave clean pyrazole formation.

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(1) Faucher, N. E.; Martres, P. PCT Int. Appl. WO 2005049578 A1, 2005.

(2) (a) Oh, L. M. *Tetrahedron Lett.* **2006**, *47*, 7943. (b) Tanaka, K.; Maeno, S.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1985**, *22*, 565. (c) Tanaka, K.; Maeno, S.; Mitsuhashi, K. *Chem. Lett.* **1982**, *4*, 543. (d) Shawali, A. S.; Párkányi, C. *J. Heterocycl. Chem.* **1980**, *17*, 833.

(3) For general reviews, see: (a) Bianchi, G.; DeMicheli, C.; Gandolfi, R. 1,3-Dipolar Cycloadditions involving X=Y Groups. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Interscience: London, 1977: pp 369–532. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press, 1990, New York.

(4) It is known that electron-rich olefins promote reactivity since this is a LUMO-dipole, HOMO-dipolarophile controlled reaction.[3b]

(5) (a) TMS enol ether **20**: Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.-B.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965. (b) Enol phosphate **21**: Whitehead, A.; Moore, J. D.; Hanson, P. R. *Tetrahedron Lett.* **2003**, *44*, 4275. (c) Enamine **22**: Modified procedure of Carlson, R.; Nilsson, A.; Stromquist, M. *Acta Chem. Scand.* **1983**, *B37*, 7. Hünig's base was added to ensure complete reaction. (d) Enamine **23**: Schiehser, G. A.; White, J. D. *J. Org. Chem.* **1980**, *45*, 1864.

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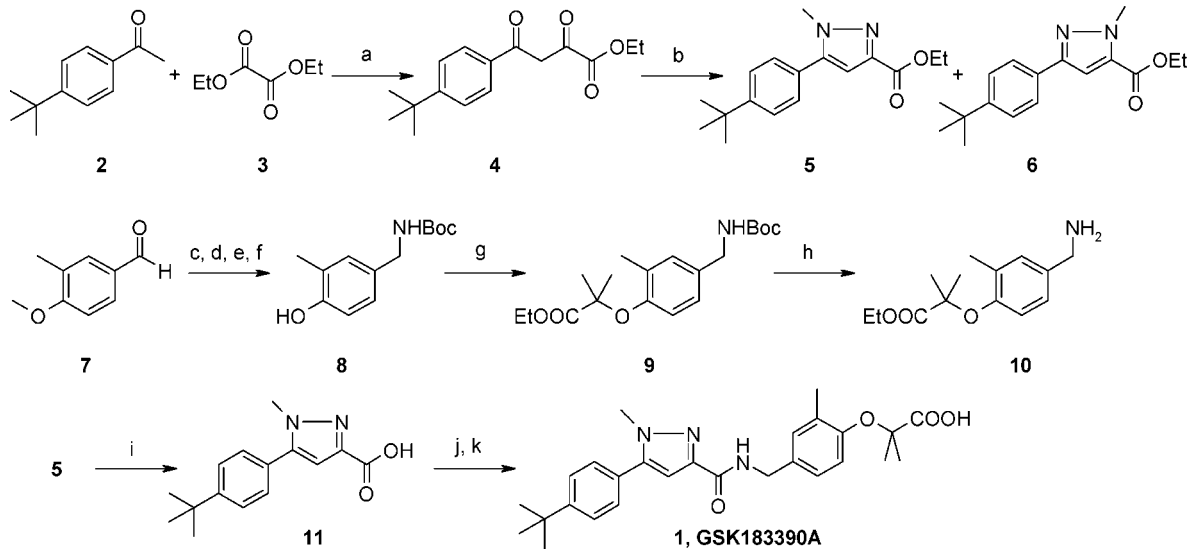
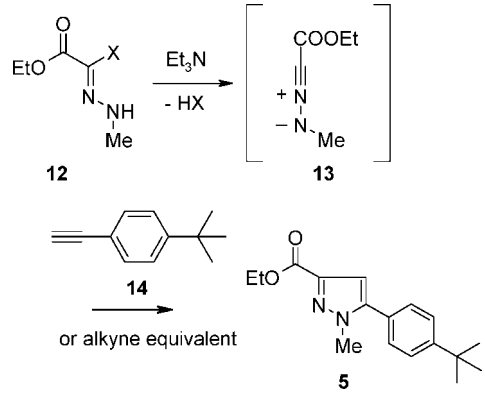
Scheme 1. **Original synthesis of GSK183390**[a]



[a] (a) NaOEt, 0 to 80 °C, 99%; (b) CH_3NHNH_2, EtOH, 90 °C, **5**, 22%, **6**, 45%; (c) $NH_2OH \cdot HCl$, NaOAc, EtOH, rt, 93%; (d) ammonium formate, Pd/C, reflux MeOH, 50%; (e) aq HBr, 97%; (f) Boc_2O, CH_2Cl_2, Et_3N, 96%; (g) K_2CO_3, DMF, ethyl bromoisobutyrate, 69%; (h) TFA, CH_2Cl_2, 82%; (i) NaOH, rt, 98%; (j) $SOCl_2$, toluene, 80 °C, then Et_3N, **10**, rt, 96%; (k) NaOH, 80 °C, 73%.

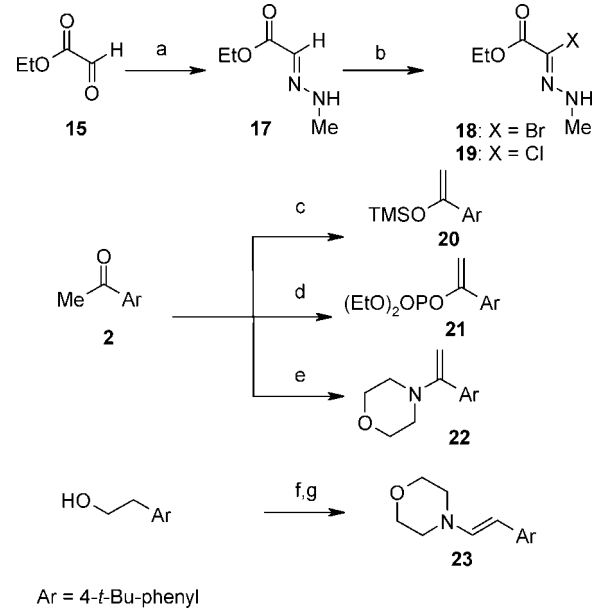
Scheme 2. **Proposed 1,3-dipolar cycloaddition for regioselective pyrazole formation.**



Furthermore, the regioselectivity of the cycloaddition was completely controlled by the substitution pattern of the enamine: when 1,1-disubstituted morpholine enamine **22** was used, only the desired 1,3,5-pyrazole isomer **5** was produced, whereas the 1,2-disubstituted morpholine enamine **23** led exclusively to the 1,3,4-pyrazole isomer **24**.[6] Since the pairing of 1,1-disubstituted enamine **22** and hydrazonoyl bromide **18** in the 1,3-dipolar cycloaddition fulfilled both requirements of reactivity and regioselectivity, scale-up and optimization activities on each were initiated.[7]

*Scale-Up Studies of Hydrazonoyl Bromide **18** Synthesis.* The laboratory preparation of hydrazone **17** called for the addition of ethyl glyoxylate (purchased and used as a solution in toluene)

Scheme 3. **Preparation of hydrazonoyl halides and alkyne equivalents**[a]



[a] (a) $MeNHNH_2$ (**16**), THF; (b) NBS or NCS, THF; (c) LiHMDS, TMSCl, THF, –25 °C; (d) LDA, $ClPO(OEt)_2$, THF, –25 °C; (e) $TiCl_4$, morpholine, toluene, 80 °C; (f) $SO_2 \cdot$pyridine, DMSO, CH_2Cl_2; (g) morpholine.

to a THF solution of methylhydrazine at 0 °C and subsequent heating to 50 °C. Examination of this procedure revealed a number of serious process safety problems.

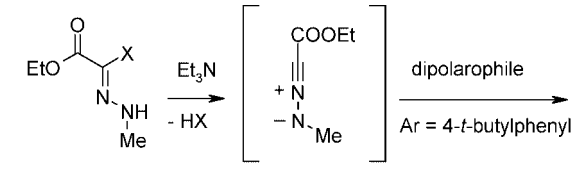
First, the product showed limited thermal stability. The adiabatic calorimetry on hydrazone **17** detected decomposition initiating at 75 °C, and such early decomposition put significant constraints on the permissible operating temperature of the process. There was also significant sample-to-sample variability in the onset of decomposition depending on the purity, especially in highly colored samples.

Second, calorimetry on the original procedure showed that the addition of ethyl glyoxylate resulted in a large but addition

(6) The reaction involving the 1,2-disubstituted enamine **23** also appeared to be more sluggish than the corresponding 1,1-disubstituted enamine **22**. For studies on the relative reactivity of olefins as dipolarophiles, including the effects of 1,1- versus 1,2-substitution, see: Jäger, V.; Colinas, P. A. Nitrile Oxides. In *1,3-Dipolar Cycloadditions*; Padwa, A., Pearson,W. H., Eds.; Interscience: New York, 2002; pp 376–378.

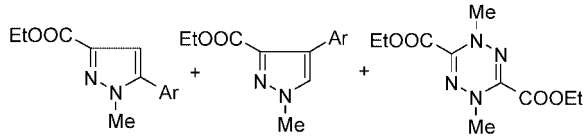
(7) A brief base screen revealed that triethylamine was the best base, whereas Hünig's base and *N*-methylmorpholine gave incomplete conversions for the cycloaddition reaction. A solvent screen also indicated that a number of solvents could be employed, including EtOAc, toluene, THF and CH_2Cl_2.

Table 1. **Preliminary screen of the 1,3-dipolar cycloaddition[a]**

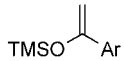
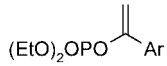
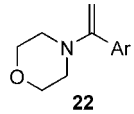
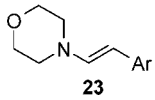


18, X=Br
19, X=Cl

13



5 **24** **25**

Dipolarophile	Dipole precursor[a]	Product Yield (%) 5	24	25
 **14**	**18**	<5	ND	20-30
 **20**	**18**	<5	ND	20-30
 **21**	**18**	<5	ND	20-30
 **22**	**18**	85	ND	ND
 **23**	**18**	ND	60	ND

[a] Chloride **19** was unreactive with all dipolarophiles screened.

rate-controlled exotherm (−63 kJ/mol of methylhydrazine). However, the heat-up to 50 °C was accompanied by additional heat output (−28 kJ/mol; patr[8] 25 °C) which started from 23 °C, increased at ∼35 °C, reached a maximum rate at 50 °C, and then continued for another 15 min (Figure 2). The significant heat accumulation, combined with the low thermal stability of the product hydrazone **17**, raised serious problems of possible runaway decomposition.

A third issue also arose during the safety test run. It was observed that uncontrolled precipitation of hydrazone **17** occurred during the heat-up stage, resulting in fouling on the ReactIR probe and disabling the process monitoring. Considering the batch variation in the thermal stability profile of **17**, it was speculated that a better controlled crystallization might yield product of more consistent quality.

It became clear that the key to an inherently safer process was the temperature control, with a higher starting temperature in order to accelerate the reaction and minimize the thermal accumulation. On the other hand, an upper boundary should also be placed on the system temperature so as not to exceed the thermally stable range of hydrazone **17**. Therefore, a revised process was developed in which the toluene solution of ethyl glyoxylate was added to a methanol solution of methylhydrazine at 40–50 °C. The heat output (−75 kJ/mol of methylhydrazine; patr 53 °C, Figure 3) was now addition rate-limited, while the boiling point of the MeOH cosolvent introduced an upper temperature barrier that eliminated the possibility of runaway decomposition of hydrazone **17**.

The revised procedure also produced a reaction mixture that was homogeneous throughout and allowed for online spectroscopic monitoring by ReactIR. Figure 4 illustrates the ReactIR monitoring of the pilot plant run. The toluene solution of ethyl glyoxylate was added over 2.25 h.[9] The addition of ethyl glyoxylate (approximated by the growth of toluene at 773 cm^{-1}), the consumption of methylhydrazine (1621 cm^{-1}) and the formation of hydrazone **17** (1710 cm^{-1}) all occurred at a steady rate[10] and reached a plateau upon the completion of addition. A process sample taken approximately 45 min after the end of addition confirmed that the reaction was complete. The success of ReactIR monitoring not only cut the cycle time by over 2 h but also reduced the plant personnel's exposure to toxic methylhydrazine by requiring a single sample.

This new procedure was executed successfully in our pilot plant, producing 39.4 kg of hydrazone **17** (59–64% yield). Moreover, hydrazone **17** produced by the revised procedure was only slightly colored and showed a markedly improved thermal stability profile, with the onset of decomposition at 124 °C shown by adiabatic calorimetry.

The bromination of hydrazone **17** was then achieved by slow addition of a methylene chloride (CH_2Cl_2) solution of hydrazone **17** to a slurry of *N*-bromosuccinimide (NBS) in ethyl acetate (EtOAc).[11] After the reaction was over, the slurry was filtered to remove succinimide, and the product was stored as a cold solution in EtOAc/CH_2Cl_2. Bromide **18** had only limited thermal stability when isolated as an oil, exhibiting early and severe decomposition with a large exotherm (−722 J/g) during differential scanning calorimetry (94–131 °C). Adiabatic calorimetry also indicated the onset of decomposition at a relatively low temperature (∼69 °C), prompting us to closely monitor its behavior during the 1,3-dipolar cycloaddition step (vide infra).

*Scale-Up Studies of Enamine **22** Synthesis.* Enamine **22** was prepared from commercially available 4-*tert*-butylacetophenone and morpholine with $TiCl_4$ as a water scavenger, Hünig's base as an HCl scavenger and toluene as the solvent. One difficulty encountered during scale-up was that the preformed $TiCl_4$–morpholine complex and side products (TiO_2 and the HCl salt of Hünig's base) formed sticky agglomerates that resulted in a very slow

(8) Predicted adiabatic temperature rise.

(9) A Dynochem model was built to predict the addition time needed to maintain reactor temperature at or below the 50 °C threshold. The actual addition time in the plant correlated very well to the recommended addition time of 2.5 h.

(10) The species at 1745 cm^{-1} is presumably the tetrahedral intermediate (addition of methylhydrazine to ethyl glyoxylate) prior to the loss of water. It initiated upon the addition of ethyl glyoxylate and reached maximum at approximately 50% addition.

(11) This procedure resulted in an addition rate-controlled heat output. Dynochem model predictions of the heat curve over the addition time correlated well with plant data.

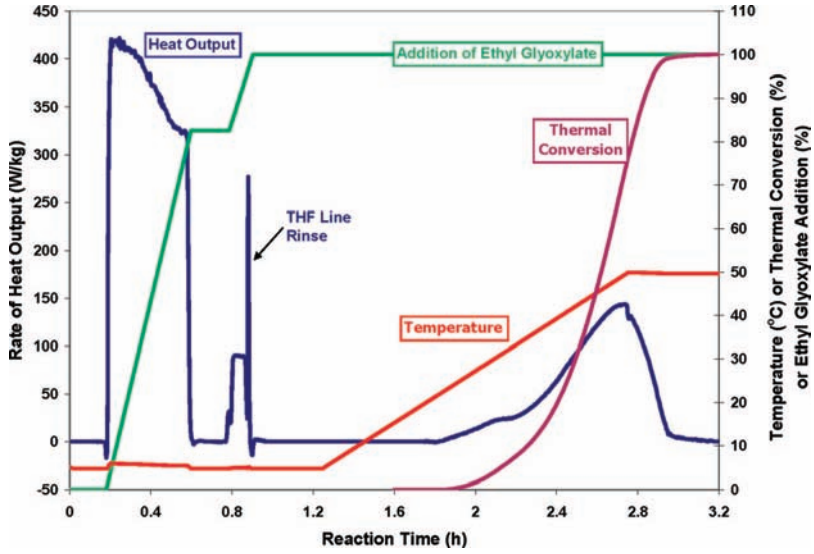


Figure 2. **Heat output during hydrazone formation using the original procedure.**

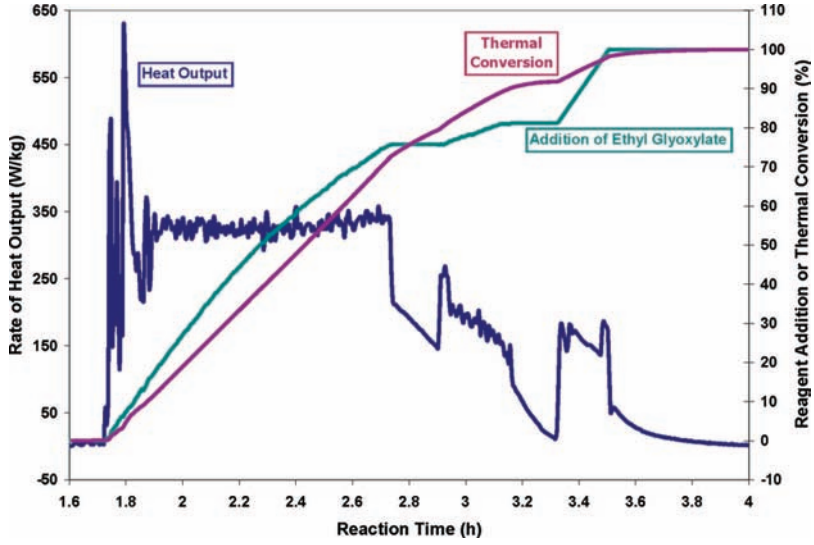


Figure 3. **Heat output during hydrazone formation using the revised procedure.**

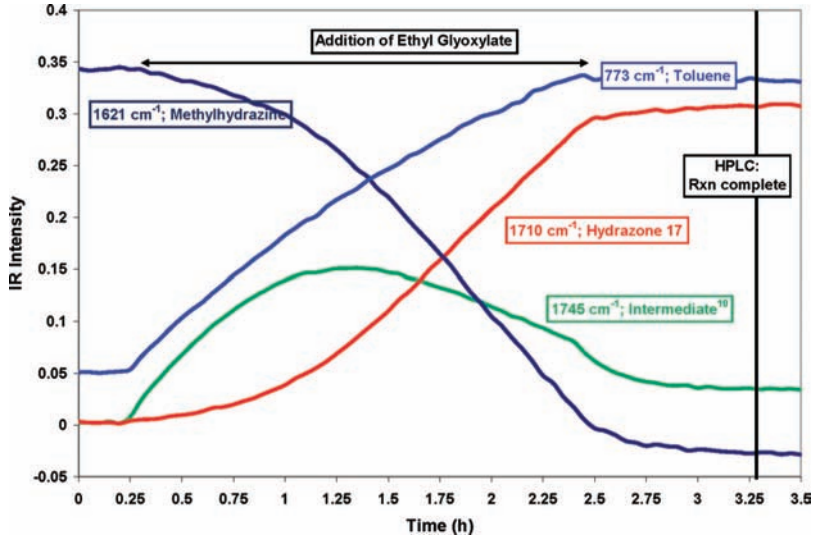


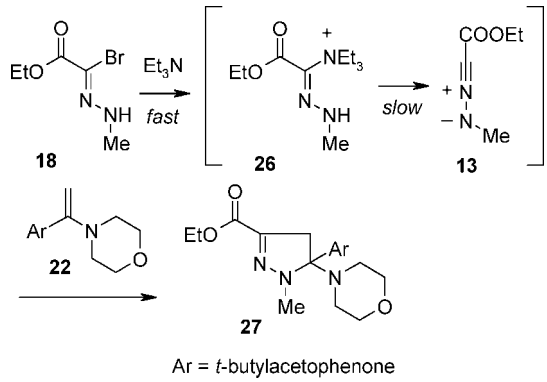
Figure 4. **ReactIR monitoring of hydrazone 17 formation in the pilot plant.**

filtration. This was circumvented by adding solid sodium sulfate at the beginning of the reaction (before the formation of the $TiCl_4$–morpholine complex) to give a suspendable slurry of the reaction mixture which was

easily filtered.[12] The resulting filtrate, containing enamine **22**, was distilled to remove excess morpholine and excess Hünig's base and stored with triethylamine (base for the cycloaddition step).

Scale-Up Studies of the 1,3-Dipolar Cycloaddition. During our initial investigation, it was revealed by LC/MS that, upon addition of triethylamine, bromide **18** was transformed immediately into triethylamine adduct **26**. Therefore, we reasoned that this adduct was the immediate precursor to nitrile imine dipole **13**, which participated in the regioselective 1,3-dipolar cycloaddition.

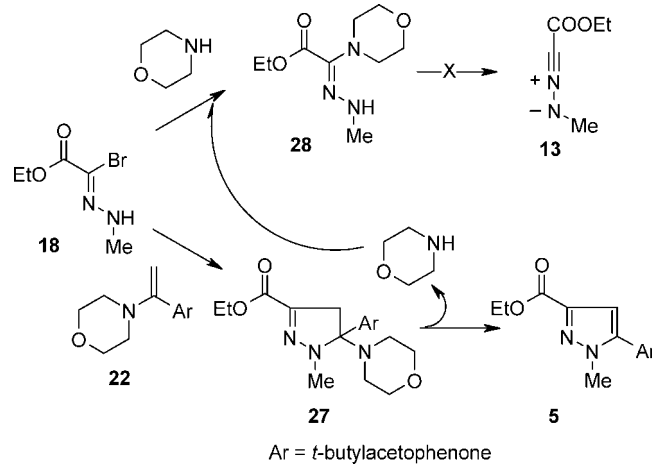
Scheme 4. **Formation of triethylamine adduct 26**



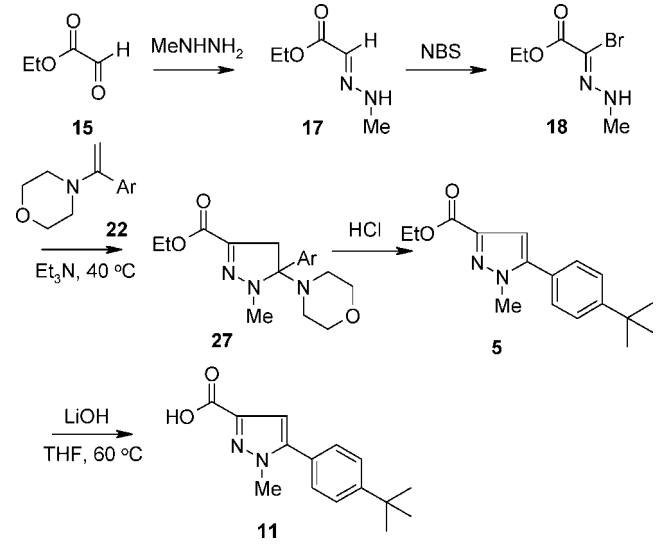
This speculation was supported by calorimetry data obtained for the reaction. The cycloaddition reaction was carried out in a step-wise fashion where an EtOAc solution of bromide **18** was treated with triethylamine at 40 °C. After holding the reaction mixture overnight, a solution of enamine **22** was added as a bolus, and the reaction mixture was held at 40 °C for another 3 h. The reaction between triethylamine and bromide **18** produced an addition rate-limited exotherm (−76 kJ/mol of enamine **22**) with a patr of 10 °C, indicating a fast, moderately exothermic transformation of bromide **18** to triethylamine adduct **26**. The bolus addition of enamine **22** produced a heat spike, with heat output (−96 kJ/mol of enamine **22**; patr 12 °C) continuing at a low rate for ∼1.5 h post-addition. The overall enthalpy for the two processes, −172 kJ/mol of enamine **22**, compared reasonably well to the results obtained from a typical procedure (−211 kJ/mol of enamine **22**; patr 27 °C).[13]

Although the fast consumption of bromide **18** alleviated our concerns with its thermal instability (vide supra), its chemical instability in the presence of nucleophilic organic bases caused a different issue. It was found that the displacement of bromide also occurred with morpholine.[14] Unlike the triethylamine adduct **26**, the morpholine adduct **28** does not re-eliminate to generate the dipole. In order to control its formation, the residual morpholine from the enamine formation has to be removed by thorough distillation. However, since morpholine is also generated in situ during the spontaneous elimination of pyrazoline **27** to pyrazole **5** (Scheme 5), the reaction conditions need to be carefully controlled to minimize the formation of morpholine adduct **28**.

Scheme 5. **Formation of morpholine adduct 28**



Scheme 6. **New route to pyrazole 11**



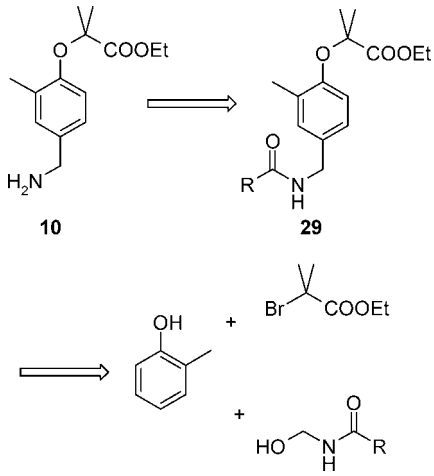
It was found that temperature control was again critical in this process. The rate of the in situ elimination of morpholine from **27** is faster at 70 °C, generating as much as 10–20% of **28**. On the other hand, when the reaction was conducted at 40 °C, the formation of morpholine adduct **28** was minimized (3–5%) while an acceptable rate of the cycloaddition reaction was still maintained. Therefore, a solution of bromide **18** in $EtOAc/CH_2Cl_2$ was added to a solution of enamine **22** and triethylamine in toluene at 40 °C. After the reaction was complete, hydrochloric acid was added to ensure complete elimination of morpholine from pyrazoline **27** to form pyrazole **5** (Scheme 6). Morpholine adduct **28** was removed in the aqueous layer during the workup. The organic layer containing pyrazole **5** was then concentrated and diluted with THF, and the hydrolysis to pyrazole acid **11** was effected by aqueous lithium hydroxide. This procedure was scaled up in the pilot plant to deliver a total of 28.1 kg of pyrazole acid **11** (53–56% yield based on enamine **22**).

(12) Glass coupon abrasion tests in the laboratory showed that the addition of solid sodium sulfate would not damage glass-lined vessels, which was confirmed by visual inspection after the run in the plant.

(13) The typical procedure consisted of adding a solution of bromide **18** to a solution of enamine **22** and triethylamine at 40 °C. The yield in the step-wise calorimetry experiment was ∼10% lower, and the HPLC profile was also messier than the typical runs.

(14) It is interesting to note that the displacement of bromide was not observed with Hünig's base, presumably due to its greater steric bulk.

Scheme 7. **Proposed synthesis of benzylamine 10**



Synthesis of Benzylamine 10. It was envisioned that a more efficient synthesis of benzylamine **10** could start from inexpensive *o*-cresol, as shown in Scheme 7. Three chemical transformations would be needed to install the functionalities of **10**: (1) amidomethylation of the arene, (2) alkylation of the phenoxide, and (3) deprotection of the amide, in order to deliver amine **10** for coupling with the pyrazole fragment.

Amidomethylation of o-Cresol Derivatives. It was identified at the outset that the feasibility of this new route hinged on the *para*/*ortho* selectivity of the amidomethylation reaction.[15] Therefore, a brief study was conducted with *o*-cresol derivatives **30–32** to investigate the regioselectivity of the amidomethylation reaction (Table 2).

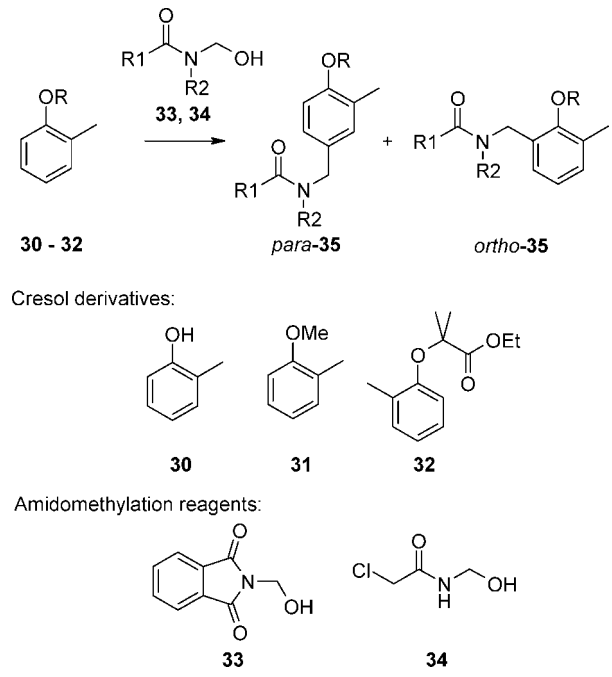
Initial amidomethylation of *o*-cresol with phthalimide **33** in toluene with catalytic amount of *p*TSA gave a ~1:1 mixture of *p*-**35** and *o*-**35** at elevated temperatures (entry 1). However, strongly acidic conditions (H_2SO_4/HOAc) allowed the reaction to proceed at a lower temperature and improved the *para*:*ortho* ratio for *o*-cresol to ~3:1 (entry 3). Anisole **31** gave a higher *para*:*ortho* ratio (14:1) than *o*-cresol (entry 4), whereas reaction with less electron-rich **32** required a higher temperature which resulted in a lower selectivity (entry 5). Switching to the more reactive chloroacetamide **34**, however, successfully installed the amide functionality on **32** with virtually complete selectivity for the desired *para*-product (entry 7).

Not only did this study establish 2-chloro-*N*-hydroxymethylacetamide **34** as a suitable amidomethylation reagent, it is also worth noting that alkylated derivatives **31** and **32** gave higher *para* selectivity than the parent *o*-cresol. This finding led to the conclusion that the alkylation of *o*-cresol should precede amidomethylation in the synthetic sequence.

Alkylation of o-Cresol. The original alkylation of *o*-cresol in the synthesis of **10** employed α-bromoisobutyrate **36**. This procedure produced a mixture of desired ester product **32** and

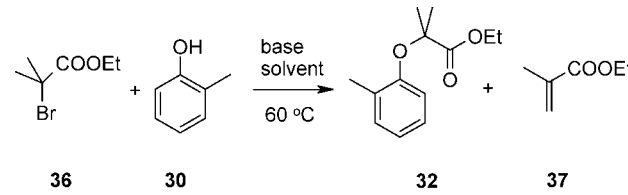
(15) For general reviews on amidomethylation, see: (a) Zaugg, H.; Martin, W. *Org. React.* **1965**, *14*, 52. (b) Zaugg, H. E. *Synthesis* **1970**, 49. (c) Zaugg, H. E. *Synthesis* **1984**, 85. (d) Zaugg, H. E. *Synthesis* **1984**, 181.

Table 2. **Regioselectivity in the amidomethylation of *o*-cresol derivatives**



entry	reagent	arene	conditions	regioselectivity *p*-**35**:*o*-**35**
1	**33**	**30**	*p*TSA (cat.), tol, 70–90 °C	0.8:1
2	**33**	**31**	*p*TSA (cat.), tol, 70–90 °C	4:1
3	**33**	**30**	H_2SO_4/HOAc (1/10), rt	3:1
4	**33**	**31**	H_2SO_4/HOAc (1/10), rt	14:1
5	**33**	**32**	H_2SO_4/HOAc (1/10), 60 °C	7:1
6	**34**	**31**	H_2SO_4/HOAc (1/10), rt	60:1
7	**34**	**32**	H_2SO_4/HOAc (1/10), rt	*para* only

Scheme 8. **Alkylation of *o*-cresol with α-bromoisobutyrate**



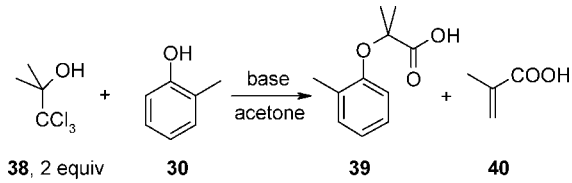
Conditions	Rxn time / h	Conv. / %	**32** / **37** (by HPLC area)
KO*t*Bu/THF	2	74	5.4
KO*t*Bu/DMF	0.5	52	0.8
NaO*t*Bu/DMF	0.5	58	1.2
K_2CO_3/DMF	25	53	0.7
K_2CO_3/acetone	25	42	0.7

methacrylate **37**. A quick screen of base/solvent combinations revealed that this reaction was sluggish and often stalled (Scheme 8).

As an alternative, the more reactive chloretone (**38**) was investigated as the alkylator in this reaction.[16] The reaction

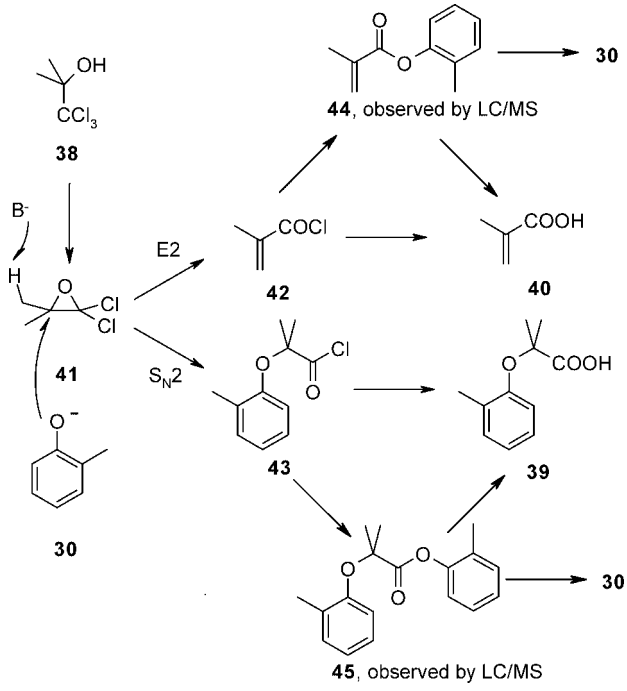
(16) Corey, E. J.; Barcza, S.; Klotmann, G. *J. Am. Chem. Soc.* **1969**, *91*, 4782.

Scheme 9. **Alkylation of *o*-cresol with chloretone**



Conditions	Conv / %	**39** / **40** (by HPLC area)
LiOH, 60 °C	44	2.8
NaOH, rt	90	5.7
KOH, rt	70	3.8

Scheme 10. **Mechanism of chloretone alkylation**



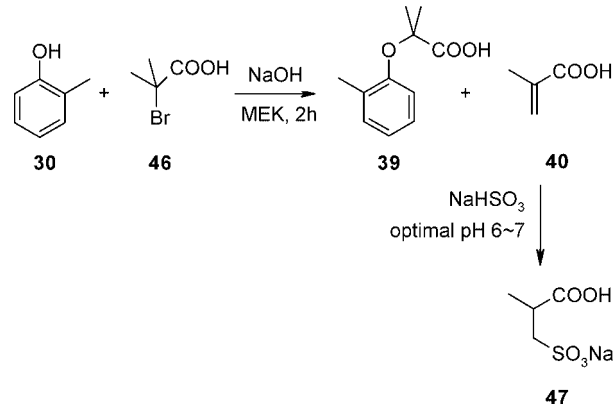
between *o*-cresol and chloretone proceeded much faster than that with bromoester **36**, producing the desired product **39**, as well as methacrylic acid (**40**) as the main side product (Scheme 9).

However, *o*-cresol could not be completely consumed in this reaction (Scheme 10). Upon treatment with base, chloretone is converted into epoxide **41**, which opens to give acid chlorides **42** and **43**. Each acid chloride then either hydrolyzes to give the corresponding acid (**40**, **39**) directly or reacts with *o*-cresol to give an ester (**44** or **45**), which then hydrolyzes slowly to regenerate *o*-cresol. The intermediacy of esters **44** and **45** was established by LC/MS analysis.

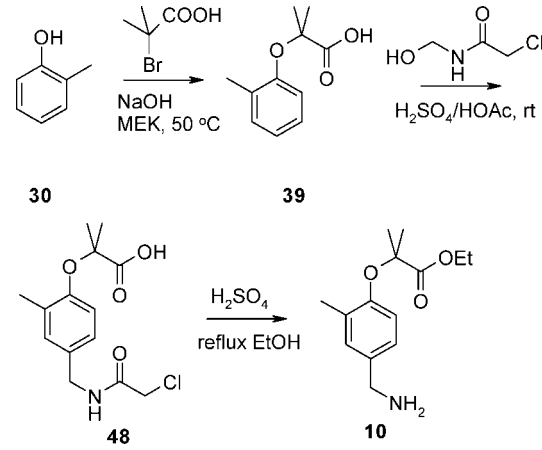
Although *o*-cresol was inexpensive, its presence in the product mixture complicated purification of the product. Furthermore, the isolated yield obtained from this reaction was only 65%. Therefore, focus was shifted to finding another alkylator that would consume the starting material and provide a higher yield.

Fortunately, it was found that α-bromoisobutyric acid alkylated *o*-cresol smoothly in the presence of NaOH. The phenol was consumed in 2 h at 50 °C in MEK, and the yield

Scheme 11. **Alkylation of *o*-cresol with α-bromobutyric acid**



Scheme 12. **New route to benzylamine 10**



was near quantitative. The major side product was methacrylic acid (**40**), which was difficult to separate from the desired product **39** by simple extraction methods due to the similarity in their pK_a's. However, it was found that methacrylic acid could be removed by the addition of $NaHSO_3$, presumably in a Michael fashion to form water-soluble adduct **47**, which allowed the extraction of pure **39** into an organic solvent. The addition of HSO_3^- to methacrylic acid was found to be very pH-sensitive, with the optimal pH value between 6 and 7 (Scheme 11).

Deprotection of the Amide. With amide-acid **48** in hand from the alkylation/amidomethylation sequence, the deprotection of the amide functionality was accomplished in refluxing ethanol using H_2SO_4.[17] The free acid was concomitantly esterified to give the desired free amine **10** in >90% yield (Scheme 12). This new route provided a much more efficient synthesis of the benzylamine fragment, and scale-up was conducted.

*Scale-Up Studies of Benzylamine **10** Synthesis.* Most of the investigation during the scale-up focused on the *o*-cresol alkylation stage and the subsequent workup. It was observed during the calorimetry evaluation that the addition of α-bromoisobutyric acid caused a large (−300 kJ/mol), addition rate-moderated exotherm. The reaction mixture was very thick, which occasionally led to loss of agitation and, consequently,

(17) It is important to use chloroacetamide as the protecting group for ease of removal: alcoholysis of the corresponding acetamide was ~5 times slower than that of **48**.

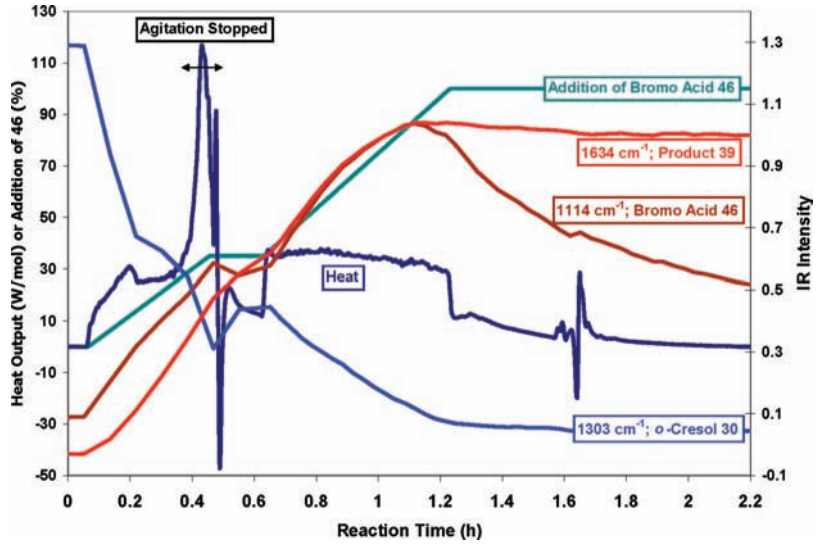


Figure 5. **Heat output of the *o*-cresol alkylation reaction.**

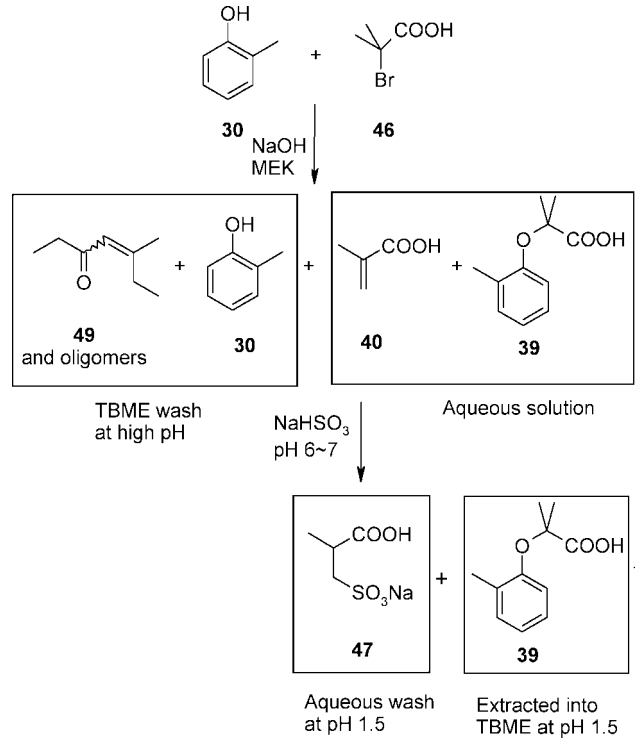
large heat spikes. The degradation of α-bromoisobutyric acid to methacrylic acid was also observed post-addition and could be monitored spectroscopically (Figure 5).

To avoid agglomeration and loss of agitation, alkylation of *o*-cresol was carried out by slowly adding α-bromoisobutyric acid to the sodium salt of *o*-cresol. The addition was completed over 8 h in the plant. After the reaction was complete, the reaction mixture was held at 50 °C to consume the excess α-bromoisobutyric acid.

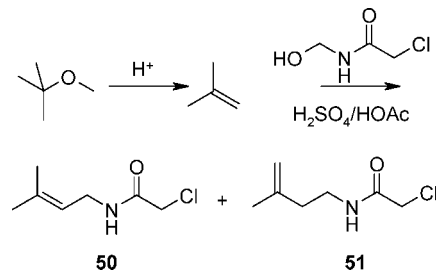
The resultant reaction mixture contained several components besides the desired product: aldol condensation products from methyl ethyl ketone, methacrylic acid, and occasionally excess *o*-cresol. It was found that accurate control of the pH was crucial for the separation of these components. After the reaction was complete, water was added to the mixture and methyl ethyl ketone was removed by distillation, resulting in an aqueous solution of pH = 14. A TBME wash was performed to remove the MEK self-aldol condensation products. The pH was then lowered from 14 to 6.5,[18] $NaHSO_3$ was added, and the mixture was stirred at room temperature overnight. After the complete consumption of methacrylic acid, the pH of the mixture was adjusted further to 1.5 to fully protonate acid **39**. Extraction with TBME separated it from the methacrylic acid adduct, which was left in the aqueous layer (Scheme 13).

In transitioning from the alkylation step to the amidomethylation step, concerns arose with the potential interaction between residual TBME, the extraction solvent in the alkylation stage, and sulfuric acid, the cosolvent in the amidomethylation stage. It was observed in the laboratory that the amidomethylation was sluggish when **39** was contaminated with residual TBME. Moreover, two side products were observed and assigned structures **50** and **51** based on LC/MS information (Scheme 14). The apparent presence of isobutylene raised concerns about possible uncontrolled decomposition of TBME under strongly acidic conditions. Therefore, after TBME extraction of the alkylation product, we elected to switch solvent from TBME to HOAc, allowing for complete removal of TBME before the addition of sulphuric acid and 2-chloro-*N*-hydroxymethylacetamide.

Scheme 13. **Removal of side products from the *o*-cresol alkylation**

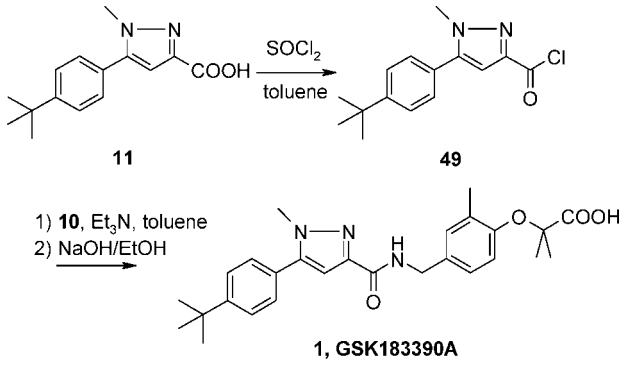


Scheme 14. **TBME participation in the amidomethylation reaction**



(18) In the case of excess *o*-cresol being present in the reaction mixture, the pH could first be lowered to 8.5 and the aqueous layer washed with TBME to remove *o*-cresol. However, *o*-cresol was usually consumed during our plant runs.

Scheme 15. **Formation of GSK183390A**



With residual TBME completely removed, the amidomethylation proceeded smoothly to give exclusively the *para* product **48**, which was crystallized from toluene to produce a total of 47.9 kg of acid-amide **48** (77–79% yield over two steps, based on *o*-cresol). The deprotection of the amide was accomplished in refluxing EtOH with H_2SO_4, and extraction with toluene provided free amine **10** as a toluene solution.

Coupling and Final Particle Formation. The coupling of benzylamine **10** and pyrazole **11** was achieved by converting pyrazole acid **11** to its acid chloride using $SOCl_2$, followed by exposure to benzylamine **10** in the presence of triethylamine (Scheme 15). The reaction proceeded smoothly in toluene at 0 °C to room temperature. The ester functionality was saponified using NaOH in aqueous ethanol to afford the desired product **1**. The wet crude API, obtained after acidification and filtration, was dissolved in *n*-propyl acetate and washed with 0.5 N HCl at 65 °C. Subsequent distillation followed by a cooled, seeded crystallization produced API grade GSK183390A. The yield of the process was determined to be 86% on a 40-kg scale (based on pyrazole acid **11**).

Conclusion

A scalable synthesis of GSK183390A, a PPAR α/γ agonist, was developed. This synthesis is highlighted by (1) a regioselective, formal 1,3-dipolar cycloaddition reaction to form 1,3,5-trisubstituted pyrazole **5** and (2) a regioselective amidomethylation of *o*-cresol derivatives to allow for an efficient synthesis of benzylamine **10**. This route has been scaled up to produce 40 kg of API in the pilot plant.

Experimental Section

General. Unless otherwise indicated, all reactions were conducted in glass-lined reactors under a nitrogen atmosphere. Solvents and reagents were obtained from commercial sources and used without further purification.

General Procedure for 1,3-Dipolar Cycloaddition Screening Study in Table 1. In a reaction vial, hydrazonoyl bromide **18** or chloride **19** (500–700 mg, 1.0 equiv) and dipolarophile (0.8 equiv) were dissolved in toluene (5 mL). Triethylamine (3.0 equiv) was added, and the reaction mixture was heated from 25 to 70 °C for 2–3 h. After the reaction was over, the mixture was cooled to 5–10 °C, 4 N HCl (5 mL) was added, and the mixture was stirred for approximately 1 h. The acidic aqueous layer was separated to waste, and the organic layer was washed with water (5 mL). After concentration via rotary evaporation, the crude mixtures were subjected to column chromatogaphy using ethyl acetate/heptane as eluent to provide the following. 1-Methyl-5-(4-tert-butylphenyl)-2*H*-pyrazole-3-(carboxylic acid ethyl ester) (**5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, J = 8.0 Hz), 7.28 (2H, d, J = 8.0 Hz), 6.79 (1H, s), 4.36 (2H, q, J = 7.2 Hz), 4.06 (s, 3H), 1.36 (3H, t, J = 7.2 Hz), 1.29 (9H, s). 1-Methyl-4-(4-tert-butylphenyl)-2*H*-pyrazole-3-(carboxylic acid ethyl ester) (**24**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (5H, m), 4.31 (2H, q, J = 7.2 Hz), 3.94 (3H, s), 1.29 (12H, m). Diethyl 1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (**25**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (4H, q, J = 7.2 Hz), 3.18 (6H, s), 1.30 (6H, t, J = 7.2 Hz).

[Methylhydrazono] Acetic Acid Ethyl Ester (17). Methylhydrazine (12.5 kg, 271 mol, 1.0 equiv) was dissolved in MeOH (90.7 L) and heated to 40–43 °C. Ethyl glyoxylate (50.4 kg, 45–50% solution in toluene, 247 mol, 0.93 equiv) was added while maintaining the temperature below 50 °C. MeOH (3.3 L) was added to the reaction mixture through the addition line. The mixture was heated to 50 °C for 3 h. Volatiles (MeOH, methylhydrazine and toluene) were distilled off, and TBME (20.2 L)/heptane (20.2 L) was added to the reaction mixture. The mixture was cooled to −5–0 °C during which time solids began to precipitate out. After a 1-h hold at 0 °C, the slurry was filtered, and the cake was washed with TBME (20.2 L)/heptane (20.2 L). Yield = 20.6 kg (64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (1H, s), 6.5 (1H, s), 4.11 (2H, q, J = 7.2 Hz), 2.79 (3H, d, J = 4.0 Hz), 1.21 (3H, t, J = 7.2 Hz).

Bromo[methylhydrazono] Acetic Acid Ethyl Ester (18). A slurry of NBS (28.2 kg, 158 mol, 1.0 equiv) in EtOAc (82.4 L) was cooled to 0–5 °C. In another vessel, hydrazone **17** (20.6 kg, 158 mol, 1.0 equiv) was dissolved in methylene chloride (82.4 L) and added to the NBS/EtOAc slurry while maintaining the temperature below 25 °C. The mixture was stirred at 5–10 °C for 1 h. Once the reaction was complete, the mixture was filtered, and the unwanted cake was washed with EtOAc (41.2 L). The combined filtrate and wash were stored at 5–10 °C for use in the next step.[19] Quantitative yield was assumed. An analytically pure sample can be obtained by removing the solvent: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (1H, s), 4.35 (2H, q, J = 7.2 Hz), 3.31 (3h, d, J = 2.7 Hz), 1.36 (3H, t, J = 7.2 Hz).

4-[1-(4-*tert*-Butyl-phenyl)-vinyl]-morpholine (22). Morpholine (52.0 kg, 597 mol, 6.0 equiv) was added to a slurry of toluene (175.0 L) and sodium sulfate (87.5 kg) at 5–8 °C. Titanium tetrachloride (18.8 kg, 99 mol, 1.0 equiv) was added while maintaining the reaction temperature below 15 °C. A light green slurry (titanium tetrachloride–morpholine complex) formed, and Hünig's base (64.2 kg, 497 mol, 5.1 equiv) was added followed by *tert*-butylacetophenone (17.5 kg, 99 mol, 1.0 equiv). The reaction mixture was heated to 70–73 °C for 3 h. Once the reaction was complete, the mixture was cooled to 20–23 °C and centrifuged. The cake was washed with toluene (35.0 L), and the wash was added to the filtrate. The filtrate, containing enamine **22**, was subjected to vacuum distillation until morpholine was <10% and Hünig's base was <10% by

(19) Hydrazonyl bromide **18** is a skin sensitizer, and extra precautions were taken in the plant during its handling.

GC analysis. Ethyl acetate (73.5 L) and triethylamine (58.3 kg, 576 mol) were added in preparation for the next step. Quantitative yield was assumed. An analytically pure sample can be obtained by removing the solvent: ^{1}H NMR (400 MHz, pyridine-d_5) δ 7.56 (2H, d, J = 8.0 Hz), 7.44 (2H, d, J = 8.0 Hz), 4.46 (1H, s), 4.25 (1H, s), 3.71 (2H, t, J = 4.8 Hz), 2.79 (2H, t, J = 4.8 Hz), 1.33 (9h, s).

1-Methyl-5-(4-*tert*-butylphenyl)-2*H*-pyrazole-3-(carboxylic acid ethyl ester) (5). The mixture of enamine **22** (24.4 kg, 99 mol, 1.0 equiv), triethylamine (58.3 kg, 576 mol, 5.8 equiv) and EtOAc (73.5 L) from the previous step was heated to 40–43 °C, at which time an EtOAc (116.5 L)/CH_2Cl_2 (77.5 L) solution of bromide **18** (31.2 kg, 149 mol, 1.5 equiv) was added over 30–45 min while maintaining the temperature between 40 and 50 °C. The reaction mixture was held at 40–43 °C for an additional 3.5 h. After the reaction was complete, the mixture was cooled to 0–5 °C, and 4 N HCl (213.2 kg, 8.0 equiv) was added while maintaining the temperature below 30 °C. After acidification was complete, the mixture was stirred for an additional 1 h at 20–23 °C. The phases were allowed to separate, and the aqueous layer was discarded. The organic layer was sequentially washed with deionized water (104.9 L) and aqueous lithium hydroxide solution (8.4 kg, 200 mol) in deionized water (83.2 L) to ensure that the pH was basic. The organic layer was distilled under reduced pressure to remove ethyl acetate (approximately 373 L) in preparation for the hydrolysis step.[20]

1-Methyl-5-(4-*tert*-butylphenyl)-2*H*-pyrazole-3-(carboxylic acid) (11). To the remaining solution of pyrazole ester in EtOAc/toluene (~63 L) was added THF (122.0 L) followed by aqueous solution of lithium hydroxide (29.2 kg, 696 mol) in deionized water (300 L). The mixture was heated to 60–63 °C for 4–6 h. After the reaction was complete, THF/toluene (~170 L) was distilled off under vacuum while maintaining the temperature below 60 °C. TBME (87.8 L) was added, and the reactor contents stirred and allowed to settle. The organic layer was removed, and the aqueous layer (containing the lithium salt of acid **11**) was washed with TBME (87.8 L). The aqueous layer was heated to 35 °C, and isopropanol (104.9 L) was added. The pH was adjusted to 4 by addition of 4 N HCl (156.3 kg) while maintaining the process temperature at 40–45 °C. Seeds of acid **11** (200 g, 0.77 mol) were added, and the mixture stirred at pH = 4 for approximately 1 h, during which time a light precipitate was observed. The acidification was continued with 4 N HCl (37.0 kg) until pH = 0 was achieved. The mixture was cooled to 0 °C over 1 h and filtered via centrifuge. After filtration, the cake was washed with water (70.8 L) followed by TBME/heptane (7.1 L/63.7 L). Yield = 14.4 kg (56% from enamine **22**). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.69 (1H, s), 7.52 (4H, m, A_2B_2), 6.80 (1H, s), 3.91 (3H, s), 1.32 (9H, s).

2-Methyl-2-[(2-methylphenyl)oxy]propanoic acid (39). *o*-Cresol (14.5 kg, 134 mol) was dissolved in methyl ethyl ketone (290 L), and NaOH pellets (26.8 kg, 670 mol, 5 equiv) were added. The mixture was heated to 50 °C and stirred at 50 °C for 2 h. A solution of α-bromoisobutyric acid (40.3 kg, 241 mol, 1.8 equiv) in methyl ethyl ketone (87 L) was added to the resultant suspension over ~8 h. The reaction mixture was stirred at 50 °C for an additional 3 h. Water (145 L) was added, and the reaction mixture was held at room temperature overnight. MEK was removed by vacuum distillation. The resultant solution was washed with TBME (145 L). The pH of the aqueous phase was adjusted to 6.5 with 3 N HCl (59.9 kg) before $NaHSO_3$ (27.9 kg, 268 mol) was added to the reaction mixture. The resultant mixture was stirred at room temperature overnight. The mixture was acidified with 3 N HCl (124 kg) to pH 1.6 and extracted with TBME (290 L × 2). The product was isolated as a TBME solution (quantitative yield assumed). An analytically pure sample can be obtained by removing TBME: ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.20 (d, 1H, J = 7.3 Hz), 7.13 (t, 1H, J = 8.3 Hz), 6.97 (t, 1H, J = 7.5 Hz), 6.84 (d, 1H, J = 8.2 Hz), 2.29 (s, 3H), 1.67 (s, 6H); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 16.70, 25.17, 78.93, 117.43, 122.26, 126.29, 129.82, 131.09, 153.16, 180.32.

2-[(4-{[(Chloroacetyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic Acid (48). The TBME solution of **39** from the previous stage (19.7 kg assuming 100% yield, 101 mol) was distilled to minimum stir volume and HOAc (49.4 L) was charged. Vacuum distillation was continued until the content of residual TBME was 0.5%. Additional HOAc (18.2 kg) and a premixed solution of HOAc and H_2SO_4 (49.4 L/9.9 L) were added to achieve a 10:1 ratio of HOAc and H_2SO_4. 2-Chloro-*N*-(hydroxymethyl)acetamide (13.8 kg, 112 mol, 1.1 equiv) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with aqueous NaOAc (18.4 kg, 224 mol, in 197.5 L of water) and extracted with TBME (99 L × 2). The combined organic layer was washed with water (99 L) and then distilled to minimum stir volume. Toluene (198 L) was added, and the reactor contents were distilled to minimum stir volume. The toluene charge-distillation process was repeated a second time to ensure complete azeotropic removal of residual water and HOAc. Toluene (198 L) was added, and GC analysis showed HOAc content in the reaction mixture to be 1.7%.[21] Additional toluene (40 L) was added, the mixture was heated to 90 °C, and complete dissolution was achieved. The reactor content was cooled to 50 °C over 30 min. Crystallization of the product was observed. The mixture was held at 50 °C for 1 h, cooled to room temperature over 20 min, and held at room temperature for 1 h. The product was collected by centrifuge filtration, rinsed with cyclohexane (40 L × 2), and tray-dried under vacuum at 45 °C: 24.1 kg, 79% from *o*-cresol. LC purity: 99.8%. ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.11 (d, 1H, J = 2 Hz), 7.00 (dd, 1H, J = 8.0, 2.0 Hz), 6.87 (br s, 1H), 6.78 (d, 1H, J = 8.0 Hz), 4.40 (d, 2H, J = 5.6 Hz), 4.13 (s, 2H), 2.26 (s, 3H), 1.65 (s, 6H); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 16.72, 25.22, 42.48, 43.40, 78.95, 116.91, 125.86, 130.06, 130.23, 130.75, 153.02, 166.39, 178.40.

Ethyl 2-{[4-(Aminomethyl)-2-methylphenyl]oxy}-2-methylpropanoate (10). Amide **48** (23.6 kg, 78.7 mol) was dissolved in EtOH/H_2SO_4 (94.4 L/11.8 L), and the resultant solution was heated to reflux for 19 h. The reaction mixture was distilled to minimum stir volume, toluene (118 L) was

(20) It is important to remove EtOAc completely before charging LiOH. Residual EtOAc is hydrolyzed by LiOH to acetate which buffers the reaction at a lower pH, leading to slow or incomplete hydrolysis.

(21) The crystallization of the product is inhibited by large amounts of residual HOAc.

added, and the mixture was concentrated to minimum stir volume. The azeotropic distillation was repeated a second time with a fresh portion of toluene (118 L), and the product was extracted into water (118 L). The aqueous layer was diluted with a fresh portion of toluene (118 L) and basified with NaOH (18.9 kg, in 112 L of water) at 0 °C. The free amine was extracted into toluene and used as a solution in the next stage (quantitative yield assumed). An analytically pure sample of the amine could be isolated as the oxalate: ^{1}H NMR δ (DMSO-d_6, 400 MHz) 7.28 (d, 1H, J = 2.2 Hz), 7.17 (dd, 1H, J = 8.4, 2.2 Hz), 6.61 (d, 1H, J = 8.4 Hz), 4.18 (q, 2H, J = 7.1 Hz), 3.91 (s, 2H), 2.17 (s, 3H), 1.54 (s, 6H), 1.18 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ (DMSO-d_6, 100 MHz) 14.36, 16.82, 25.51, 42.21, 61.56, 79.11, 116.39, 127.45, 127.64, 129.04, 132.14, 153.87, 164.84, 173.78.

2-[(4-{[({5-[4-(1,1-Dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic Acid (1, GSK183390). A toluene solution of $SOCl_2$ (9.3 kg, 78 mol, 1.3 equiv, in 6.8 L of toluene) was added to acid **5** (15.5 kg, 60 mol) in toluene (155 L) at 90 °C over 27 min. The resultant mixture was heated at 90 °C for 1 h, and the conversion to the acid chloride was complete. The reaction mixture was distilled to minimum stir volume to remove excess $SOCl_2$, and the residue was diluted with toluene (77.5 L). The acid chloride solution was added to a mixture of benzylamine **10** (121.9 kg of toluene solution, containing 19.7 kg of benzylamine **10**, 78 mol, 1.3 equiv) and Et_3N (23.6 kg, 234 mol) at 0 °C over 30 min. The reaction mixture was then stirred at 20 °C for 30 min. The reaction mixture was washed with HCl (2 N, 160 kg) and NaOH (1 N, 159 kg). Water (109 L) was added to the resultant toluene solution, and toluene was removed by azeotrope. EtOH (201 L) and NaOH (1 N, 143 kg) were added to the resultant suspension, and the mixture was heated at 60 °C for 2 h to effect hydrolysis of the ester. EtOH was removed from the mixture by vacuum distillation. The aqueous solution was cooled to room temperature and acidified with 1 N HCl (158 kg). The product acid GSK183990A precipitated and was collected by centrifuge filtration.

GSK183390A (1). Crude GSK183390 (137.4 kg wet crude cake containing 47.0 kg of GSK183390, 101 mol) was slurried in water-saturated *n*-propyl acetate (376 L) and heated to 45–50 °C followed by the addition of 0.5 N HCl solution (141 L) to guarantee dissolution of crude **1**. The reactor contents were then stirred and settled, and the aqueous acidic layer was removed to waste. Deionized water (141 L) was added, the mixture was stirred and settled, and the aqueous layer was removed to waste. The organic phase was heated to 65–70 °C, and a clarification filtration was performed. The organic phase was distilled down to 5–6 vol under reduced pressure while maintaining temperature below 60 °C and ensuring the KF specification was met (<5000 ppm for maximum recovery). The temperature was heated up to 70 °C to ensure complete dissolution. The contents of the reactor were cooled to between 58 and 62 °C, and seeds of **1** (470 g, 1.0 mol, 0.001 equiv) were added as a slurry in *n*-propyl acetate (800 mL). The contents of the reactor were held at 60 °C for approximately 30 min, then cooled down to 0 °C over 2 h and held at 0 °C for 1 h before filtration through a centrifuge. The cake was washed with heptane (188.0 L) and dried in the oven at 60–65 °C under vacuum. Yield = 43.6 kg (86% based on acid **11**). NMR (300 MHz, DMSO-d_6) δ 8.59 (1H, t, J = 6.3 Hz), 7.51 (4H, m, A_2B_2), 7.10 (s, 1H), 7.01 (1H, d, J = 9.0 Hz), 6.74 (s, 1H), 6.65 (1H, d, J = 9.0 Hz), 4.31 (2H, d, J = 6.0 Hz), 3.90 (3H, s), 2.13 (3H, s), 1.48 (6H, s), 1.32 (9H, s).

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