Synthesis of an Azabicyclo[3.1.0]hexanone-Containing Inhibitor of NF-κB Inducing Kinase via Catalytic C–H Activation

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Abstract The synthesis of an azabicyclo[3.1.0]hexanone-containing inhibitor of the nuclear factor-κB inducing kinase (NIK) is reported. The initial route to this compound was streamlined from 13 to 7 linear steps through the use of a catalytic, enantioselective C–H activation step. A procedure for lactam oxidation was identified that avoided use of peroxides on scale. These synthetic improvements allowed for the synthesis of multigram quantities of the desired NIK inhibitor for in vivo profiling.

Key words C–H activation, NIK inhibitor, enantioselective, azabicyclo[3.1.0]hexanone, nuclear factor-κB, medicinal chemistry

The nuclear factor-κB (NF-κB) family of transcription factors are regulated via a pair of signaling pathways – referred to as the canonical and non-canonical pathways – that differ in both their components and biological function.1 The non-canonical NF-κB pathway plays a number of key roles in regulating immune functions. Pathway dysregulation has been linked to the pathogenesis of autoimmune and inflammatory diseases such as systemic lupus erythematosus (SLE), while defective signaling is associated with severe immune deficiencies.2,3 Non-canonical NF-κB signaling is dependent on NF-κB inducing kinase (NIK, or MAP3K14), which is continuously degraded through its association with the TNF receptor-associated factors 2/3-ubiquitin ligase complex.4 Pathway activation leads to dissociation of NIK from this complex, allowing it to accumulate and phosphorylate IKKα. This results in phosphorylation of p100, and the release and heterodimerization with RelB of the mature transcription factor p52 (NF-κB2).5 Ultimately, the p52-RelB complex translocates to the nucleus and triggers transcription of pathway target genes.5,6

Pharmacological intervention via NIK inhibition has been of significant interest in the pharmaceutical industry,7,8 and a selective NIK inhibitor has been shown to be efficacious in an NZB/W F1 model of SLE.1 As a part of our medicinal chemistry program, we have previously reported the discovery of pyrazolopyridine 1 as a potent and selective inhibitor of NIK (Figure 1).9-11 Cyclopropyl lactam 2 was subsequently identified as a promising lead compound.12 In order to facilitate in vitro and in vivo profiling, multigram quantities of cyclopropane 2 were required.

As a route to the pyrazolopyridine core of 1 was already developed,9-11 we focused our efforts on developing a synthetic strategy for the densely-functionalized lactam of 2 (Figure 1, highlighted portion). This fragment contains three contiguous stereocenters, one of which is a tertiary alcohol. Anticipating that the alkynylated lactam could be installed via a late-stage Sonogashira coupling, the synthesis of terminal alkyne 14 was targeted (Scheme 1).

Our initial route to alkyne 14 commenced from commercially available pyrrolidine 7 (Scheme 1). Boc-protection of pyrrolidine 7 followed by ruthenium-mediated oxidation of protected pyrrolidine 8 provided pyrrolidinone 9. Subsequent acidic deprotection afforded cyclopropyl lactam 10, which was methylated to provide tertiary lactam 11. After an exhaustive screen of oxidation reagents, α-oxidation of lactam 11 to alcohol 12 was effected with bis(trimethylsilyl)peroxide.13 Oxidation of alcohol 12 with Dess–Martin periodinane to dione 13 followed by chemoselective Grignard addition completed the synthesis of alkyne 14.

Figure 1 Previously-reported NIK inhibitor 1 and cyclopropane-containing compound 2

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Our original synthesis of alkyne 14 provided a fit-for-purpose solution for early-stage medicinal chemistry efforts, but a number of issues became evident in attempting to scale this route. Although pyrrolidine 7 was a convenient starting point for medicinal chemistry, its sourcing and price on scale made its continued use untenable. As an initial approach, pyrrolidine 7 was synthesized in-house through four steps following a known procedure (Scheme 1, top).14 Suarez-type decarboxylation of proline derivative 3 yielded N,O-acetal 4 which, after loss of methanol, cyclopropanation, and deprotection, provided desired pyrrolidine 7. Attempting to scale this 4-step sequence to meet our initial materials needs (15 g of 14) revealed that 120 liters of pyrophoric ZnEt₂ (1 M) would be required for the synthesis. Advancing intermediate 7 to lactam 14 brought to light additional issues of this synthetic approach: (1) the use of gram-quantities of potentially explosive bis(trimethylsilyl)peroxide,15 (2) challenges in isolating water-soluble 12 on scale, and (3) the inefficiency associated with a low-yielding 11-step sequence.

Seeking to ameliorate the aforementioned issues, a more efficient and scalable route to alkyne 14 was developed (Scheme 2). This route relied on use of recently published research from the Cramer laboratory describing the

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**Scheme 1** Initial synthetic route to alkyne 14. Top, grey box: literature procedure for the synthesis of intermediate 7. Middle, cyan box: commercially-available starting point for medicinal chemistry efforts. Reagents and conditions: (a) 4 M Boc₂O in THF (1.1 equiv), 1 M Na₂CO₃ in H₂O (2.1 equiv), 1:1 THF/H₂O (0.4 M), r.t.; (b) RuO₂-xH₂O (0.4 equiv), NaIO₄ (5.0 equiv), 1:3.1 EtOH: H₂O (0.03 M), r.t.; (c) 4 M HCl in 1,4-dioxane (8 equiv), DCM (0.25 M), r.t.; (d) MeI (1.5 equiv), Cs₂CO₃ (1.7 equiv), MeCN (0.23 M), 75 °C; (e) 1 M LiHMDS in THF (1.5 equiv), (TMSO)₂ (3.0 equiv), THF (0.3 M), –78 to –30 °C; (f) Dess–Martin periodinane (1.2 equiv), DCM (0.16 M), r.t.; (g) 0.5 M ethynylmagnesium bromide (2.0 equiv), THF (0.3 M), –78 °C. The yields of 9, 11 and 12 are based on crude products obtained without column purification. All other yields are from isolation after purification.

**Scheme 2** Streamlined route for the synthesis of dione 13 on scale. Reagents and conditions: (a) Et₃N (3.5 equiv), 16 (1.1 equiv), DCM (0.28 M), –20 °C to r.t.; (b) Pd(dba)₂ (0.03 equiv), 18 (0.06 equiv), adamantane-1-carboxylic acid (0.03 equiv), Cs₂CO₃ (1.5 equiv), 4 Å molecular sieves (0.15 g/mol), toluene (0.1 M), 70 °C; (c) 2 M LiNH₂·Pr₃ in THF (1.5 equiv), MeSO₂Me (1.5 equiv), THF (0.20 M), –30 °C to r.t.; (d) PIFA (2.0 equiv), 10:1 MeCN/H₂O (0.05 M), 0 °C; (e) Screening was conducted on 5 mmol scale and yields were assessed by LC/MS by relative peak area integration. Standard screening conditions: Pd(dba)₂ (0.05 equiv), 18 (0.10 equiv), adamantane-1-carboxylic acid (0.05 equiv), Cs₂CO₃ (1.5 equiv), toluene (0.1 M), 70 °C. Molecular sieves (M.S.) were used at a loading of 0.15 g/mol.

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C–H functionalization of cyclopropanes to form cyclopropyl lactams. Indeed, use of C–H activation in drug discovery has become a popular means to streamline synthetic routes. Our modified route commenced with the acylation of commercially available and inexpensive cyclopropylmethylamine (15) with acyl chloride 16 to yield alky chloride 17. Alkyl chloride 17 served as the starting material for the key C–H activation step; it is proposed that this process occurs through oxidative addition to the carbon–chlorine bond by TADDOL phosphinite-ligated Pd(0), subsequent intramolecular C–H activation of the proximal cyclopropane mediated by a Pd-carboxylate, and Csp3–Csp3 reductive elimination to form the product. Use of a chiral phosphinite ligand renders this transformation enantioselective, although the viability of N-methylamides as substrates was not demonstrated in the original report.

Initial application of the reported C–H activation conditions provided 20% starting material 17 along with 40% of hydrolysis product 20 (Scheme 2, insert, entry 1). To minimize hydrolysis, the reaction was next conducted in the presence of 4Å molecular sieves. To our nearly unspeakable jouissance, these anhydrous conditions provided the desired product 11 in 85% yield while abating formation of alcohol 20 (entry 2). These conditions were accompanied by the formation of a small amount of proto-dehalogenated 19. Concentrating the reaction to 0.3 M decreased formation of desired 11 while increasing the observed amount of dehalogenated 19 (entry 3). It was found that reducing the catalyst loading to 3 mol% Pd(dba)2 and 6 mol% 18 had a minimal effect on product yield (entry 4). These optimized conditions were used to run three >20 g scale reactions, which were combined and purified by distillation as a single batch to provide >50 g of desired 11 in 76% yield. Notably, lactam 11 was now accessible on scale in only 2 steps, compared to our previously used 8-step route.

Prior structure-activity relationships had revealed (1R,4R,5S)-14 to be the desired stereoisomer for NIK inhibition (Scheme 3). In order to bias C–H activation towards the formation of this stereoisomer, (R,R)-18 was used in analogy to the stereochemical outcomes reported by the Cramer laboratory. The enantiomeric enrichment of product lactam 11, however, was not quantified at this stage since the retention time of the desired absolute enantiomer was unknown. Previous efforts demonstrated that stereoisomers of advanced intermediates could be separated by chiral chromatography and hence, lactam 11 was advanced as a presumed scemilc mixure.

With decagram quantities of lactam 11 in hand, our focus turned to establishing a scalable means for lactam α-oxidation. Due to the hazards of working with peroxides on scale, issues sourcing bis(trimethylsilyl) peroxide, and local regulations, our previously developed conditions were no longer viable. An alternative 2-step procedure for α-oxidation was identified that avoided the use of peroxides.

Oxidation of lactam 11 with S-methyl methanethiosulfonate provided thioketal 21, which was converted to previously-made dione 13 through the action of phenyldine bis(trifluoroacetate) (PIFA) in aqueous conditions. Dione 13 intercepted our former synthetic route, and was converted to alkyn 14 by Grignard addition.

Scheme 3 Separation of the stereoisomers of lactam 14 by chiral-phase SFC

Stereochemically pure (1R,4R,5S)-14 was accessed through preparative supercritical fluid chromatography (SFC) (Scheme 3). Analysis of the initial mixture revealed the presence of four stereoisomers: both enantiomers of lactam 14 were produced in the C–H activation of cyclopropylamine 17, and Grignard addition to dione 13 produced alkyn 14 as a mixture of diastereomers. Identification of appropriate conditions allowed for 17 g of alkyn 14 to be separated into its components with 90% recovery. The desired isomer (1R,4R,5S)-14 was isolated in 70% yield (11.9 g) and 99.5% ee, and the structures of diastereomeric (1R,4S,5S)-14 and (1R,4R,5S)-14 were confirmed by X-ray crystallography (see Supporting Information). Although an imperfect measure of stereoselectivity, the isolated yields of each stereoisomer suggests that C–H activation occurred with ~84% ee and Grignard addition proceeded in ~6:1 dr for the desired cyclopropyl enantiomer.

The synthesis of NIK inhibitor 2 was completed in analogy to our previously disclosed route. Chan–Lam coupling of azaindazole 22 and aryboronic acid 23 provided N-aryl iodide 24. Sonogashira coupling of 24 with alkyn (1R,4R,5S)-14 yielded ester 25, which was subjected to aminolysis producing the desired amide 2 on multigram scale (Scheme 4). The structure of NIK inhibitor 2 was unambiguously confirmed by X-ray crystallography (see Supporting Information).

In conclusion, scalable access to NIK inhibitor 2 was enabled through use of a catalytic, enantioselective C–H activation step. This methodology was incorporated at an early stage in the synthesis and provided access to the densely functionalized chiral 2-azabicyclo[3.1.0]hexane motif of this inhibitor in decagram quantities. Such tactical applica-
Reagents were purchased from the following vendors and used without further purification: Shanghai Chiral Chemicals Inc., Sinopharm Chemical Reagent Beijing Co., Ltd, Shanghai Huiquan Chemical Technology Co., Ltd, ZN Biochemical Company Ltd, Shanghai Hangui Hualun Chemical Co., Ltd, Shaanxi Rock New Materials Co. Ltd, Suzhou High fine Biotech Co., Ltd, and Guan Jingqiu Huagong Chanpin Co., Ltd. Li-gand 18 was obtained by a previously reported method.22 1H NMR spectra were recorded on Bruker Avance 300, 400, or 500 spectrometer. Chemical shifts are expressed in δ ppm referred to an internal standard, tetramethylsilane (δ = 0). Standard abbreviations were used in describing peak signals. All final compounds were purified by flash chromatography using silica (100–200 mesh) provided by Rushanshi Shuangbang Xincailiao Co., Ltd. The purity was assessed by reverse phase HPLC with a gradient of 5–95% MeCN in H2O (with either acid or base modifier) and monitored by absorption at 190 nm. LCMS (ESI) analysis was performed using Agilent Instruments. The LC was monitored by absorption at 220 nm and 254 nm. MS full scan with 10 000 resolution was applied to all experiments. Preparative SFC was conducted using a SFC Jasco PREP 150 (Jasco 150 SFC) instrument on a Chiralpak IC (250 × 30 mm, 5 μm) column.

tert-Butyl 2-Azabicyclo[3.1.0]hexan-2-carboxylate (8)12
CAS Number: 154874-95-0
A 1 M solution of Na2CO3 in H2O (79 mL, 79 mmol) and a solution of di-tert-butyl dicarbonate (9.06 g, 42 mmol) in THF (10 mL) were added dropwise to a stirred solution of tert-butyl 2-azabicyclo[3.1.0]hexane-2-carboxylate (810 mg, 4.5 mmol), Cs2CO3 (73.5 g, 225 mmol), and toluene (1500 mL). The reaction was sealed and stirred for 5.56 g (83%) of the title compound as a white solid.

2-Azabicyclo[3.1.0]hexan-3-one (10)12
CAS Number: 2193098-04-1
A 4 M solution of HCl in 1,4-dioxane (20 mL, 80 mmol) was added dropwise to a stirred solution of tert-butyl 3-oxo-2-azabicyclo[3.1.0]hexane-2-carboxylate (8; 1.97 g, 10 mmol) in DCM (40 mL). Evolution of CO2 ceased after 2 h, at which point the reaction mixture was concentrated under reduced pressure thrice to give 946 mg (97%) of the title compound.

2-Methyl-2-azabicyclo[3.1.0]hexan-3-one (11)12
CAS Number: 2193098-05-2
Via Methylation of 10: A mixture of 2-azabicyclo[3.1.0]hexan-3-one (10; 946 mg, 9 mmol) and Cs2CO3 (5.12 g, 16 mmol) in MeCN (40 mL) was stirred for 15 min and then MeI (0.87 mL, 14 mmol) was added dropwise to the suspension. The mixture was heated at 75 °C in a sealed vial for 12 h. The resulting mixture was cooled to r.t. and filtered. The filtrate was concentrated in vacuum to give 873 mg (85%; 82% from 9) of the title compound as a light yellow oil.

C-H Activation Procedure: To a 3000 mL 4-necked round-bottom flask purged with and maintained under an inert atmosphere of argon was placed 2-chloro-N-cyclopropyl-N-methylacetamide (17; 22.2 g, 150 mmol). Pd(dbaz)2 (2.6 g, 4.5 mmol), (3Ar=8Ar)-4,4,8,8-tetraakis(3,5-di-tert-butylphenyl)-2,2-dimethyl-6-phenyltetrahydro[1,3]dioxolo[4,5-e][1,3]dioxophosphine (18; 9.2 g, 9 mmol), admantane-1-carboxylic acid (810 mg, 4.5 mmol), Cs2CO3 (73.5 g, 225 mmol), 4A molecular sieves (22.2 g), and toluene (1500 mL). The resulting mixture was stirred overnight at 70 °C in an oil bath. This process was repeated identically 3 times and the crude reaction mixtures were combined. The combined reaction mixtures were cooled to r.t., filtered, and washed with EtOAc (2 L). The filtrate was concentrated under reduced pressure. The crude product was purified by distilla-
tion under reduced pressure (10 mm Hg) and the fraction that distilled at 80 °C was collected to afford 51 g (76%) of the title compound as a light yellow oil.

1H NMR (CDCl₃, 400 MHz): δ = 3.00–2.95 (m, 1 H), 2.75 (dd, J = 17.9, 7.2 Hz, 1 H), 2.34 (d, J = 17.9 Hz, 1 H), 1.53–1.42 (m, 1 H), 0.88–0.81 (m, 1 H), 0.31–0.26 (m, 1 H).

MS [ESI]: m/z [M + H]+ calculated for C₁₂H₁₉N₂O₄: 255.13; found: 255.

4-Hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one (12) CAS Number: 2193098-07-4

A 1 M solution of LiHMDS in THF (7.5 mL, 7.5 mmol) was added dropwise to a mixture of 2-methyl-2-azabicyclo[3.1.0]hexan-3-one (11: 55.6 mg, 0.50 mmol) and bis(trimethylsilyl)peroxide (3.3 mL, 15 mmol) in THF (15 mL) at –78 °C. The mixture was stirred at this temperature for 1 h, allowed to warm to –30 °C, and left at this temperature for 1 h.

The mixture was quenched with 1 M aq HCl and stirred for 30 min. The resulting mixture was extracted with pentane (3 ×). The aqueous layer was neutralized to pH 7 by the addition of sat. aq NaHCO₃ and concentrated in vacuum. The dry residue was extracted with DCM, filtered, and the filtrate was concentrated to give 498 mg (78%) of the title compound as a yellow oil, which solidified upon standing.

1H NMR (CDCl₃, 600 MHz): δ = 5.69 (d, J = 4.3 Hz, 1 H), 4.16 (dd, J = 4.3, 1.6 Hz, 1 H), 3.12–3.01 (m, 1 H), 2.91 (s, 3 H), 1.90–1.84 (m, 1 H), 0.81–0.74 (m, 1 H), 0.56–0.51 (m, 1 H).

MS [ESI]: m/z [M + H]+ calculated for C₁₂H₁₉N₂O₄: 255.13; found: 255.

4-Hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one (12) CAS Number: 2193098-06-3

A 1 M solution of LiHMDS in THF (7.5 mL, 7.5 mmol) was added dropwise to a mixture of 2-methyl-2-azabicyclo[3.1.0]hexan-3-one (11: 55.6 mg, 0.50 mmol) and bis(trimethylsilyl)peroxide (3.3 mL, 15 mmol) in THF (15 mL) at –78 °C. The mixture was stirred at this temperature for 1 h, allowed to warm to –30 °C, and left at this temperature for 1 h.

The mixture was quenched with 1 M aq HCl and stirred for 30 min. The resulting mixture was extracted with pentane (3 ×). The aqueous layer was neutralized to pH 7 by the addition of sat. aq NaHCO₃ and concentrated in vacuum. The dry residue was extracted with DCM, filtered, and the filtrate was concentrated to give 498 mg (78%) of the title compound as a yellow oil, which solidified upon standing.

1H NMR (CDCl₃, 400 MHz): δ = 4.86 (d, J = 4.3 Hz, 1 H), 4.17 (dd, J = 4.3, 1.6 Hz, 1 H), 3.12–3.01 (m, 1 H), 2.91 (s, 3 H), 1.72–1.63 (m, 1 H), 1.02–0.92 (m, 1 H), 0.39–0.31 (m, 1 H).

MS [ESI]: m/z [M + H]+ calculated for C₁₂H₁₉N₂O₄: 255.13; found: 255.

2-Methyl-2-azabicyclo[3.1.0]hexane-3,4-dione (13) CAS Number: 2193098-08-5

Via Oxidation of 12: Dess–Martin periodinane (1.99 g, 4.7 mmol) was added dropwise to a solution of 2-methyl-2-azabicyclo[3.1.0]hexane-3,4-dione (13: 498 mg, 3.92 mmol) in DCM (25 mL). The mixture was stirred at r.t. for 1 h. The resulting mixture was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (24 g) eluting with a 0–100% gradient of EtOAc in petroleum ether to afford 44 g (55%) of the title compound as a light yellow solid.

X-ray structure in Supporting Information.

2-Chloro-N-cyclopropyl-N-methylacetamide (17) CAS Number: 722538-31-0

To a 500 mL 4-necked round-bottomed flask purged with and maintained under an inert atmosphere of N₂ was placed a solution of N-methylcyclopropanamine hydrochloride (15: 90 g, 837 mmol) in DCM (3000 mL) followed by the addition of Et₃N (296 g, 2.92 mol) dropwise with stirring in an ice/salt bath. To this was added 2-chloroacetyl chloride (16: 103 g, 914 mmol) dropwise with stirring at –20 °C. The resulting solution was allowed to slowly warm to r.t. and stirred overnight.

The reaction mixture was cooled to –30 °C and 2 M LDA in THF (200 mL) over 1 h. This process was repeated identically once and the crude reactions were combined and warmed to 0 °C. After 4 h, the reaction mixture was cooled to –30 °C, quenched with sat. aq NH₄Cl (400 mL), and extracted with EtOAc (3 × 500 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in petroleum ether and then crystallized from EtOAc to afford 17 g (88%) of the title compound as a light yellow solid.

Procedure for SFC Separation

To a 500 mL 4-necked round-bottomed flask purged with and maintained under an inert atmosphere of N₂ was placed a solution of 2-methyl-2-azabicyclo[3.1.0]hexane-3,4-dione (13: 498 mg, 3.92 mmol) in DCM (25 mL) over 1 h. This process was repeated identically once and the crude reactions were combined and warmed to 0 °C. After 4 h, the reaction mixture was cooled to –30 °C, quenched with sat. aq NH₄Cl (400 mL), and extracted with EtOAc (3 × 500 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in petroleum ether and then crystallized from EtOAc to afford 17 g (88%) of the title compound as a light yellow solid.
Methyl 1-((3-iodophenyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (24)\(^2\)

A 1000 mL round-bottomed flask was charged with methyl 1H-pyrazolo[3,4-b]pyridine-3-carboxylate (24: 10.0 g, 56.5 mmol), (3-iodophenyl)boronic acid (23: 15.4 g, 62.2 mmol), Cu(OAc)\(_2\) (5.6 g, 31.8 mmol), pyridine (9.8 g, 124 mmol), and THF (400 mL). The reaction mixture was sparged with O\(_2\) and was stirred at 50 °C under an atmospheric pressure of O\(_2\) overnight. The mixture was quenched by the addition of H\(_2\)O (30 mL). The quenched reaction mixture was filtered and the filtrate was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with brine (2 × 100 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in hexanes to provide 4.0 g (65%) of the title compound as a white solid.

Methyl 1-3((1R,4R,5S)-4-Hydroxy-2-methyl-3-oxo-2-azabicyclo[3.1.0]hexan-4-yl)ethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate (25)\(^3\)

A 500 mL round-bottomed flask was charged with methyl 1H-pyrazolo[3,4-b]pyridine-3-carboxylate (24: 5.83 g, 15.4 mmol), 4-ethyl-4-hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one (1R,4R,5S)-14: 3.02 g, 20.0 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (2.16 g, 3.1 mmol), Et\(_3\)N (30 mL, 215 mmol), and DMSO (60 mL). The reaction mixture was stirred at 95 °C overnight, quenched with H\(_2\)O (30 mL), and the filtrate was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (2 × 100 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in hexanes to provide 5.14 g (44%) of the title compound as a white solid; [\(\text{M} + \text{H}\)]\(^+\) calcd for C\(_{21}\)H\(_{19}\)N\(_4\)O\(_4\): 403.13; found: 403.13.

**References**


