A series of N-substituted 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate esters has been prepared in two steps from ethyl 2-(2-chloronicotinoyl)acetate. Treatment of the \(\beta\)-ketoester with \(N, N\)-dimethylformamide dimethyl acetal in \(N, N\)-dimethylformamide (DMF) gave a 95% yield of the 2-dimethylaminomethylene derivative. Subsequent reaction of this \(\beta\)-enaminone with primary amines in DMF at 120\(^\circ\)C for 24 h then afforded the target compounds in 47–82% yields by a tandem S_NAr-addition-elimination reaction. Synthetic and procedural details as well as a mechanistic rationale are presented.

**INTRODUCTION**

We recently reported a two-step synthesis of 1-alkyl- and 1-aryl-1,4-dihydro-4-oxo-3-quinolinecarboxylate esters from ethyl 2-(2-fluorobenzoyl)acetate involving conversion to a \(\beta\)-enaminone followed by reaction with a primary amine (e.g., \(RNH_2\)) [1]. This strategy avoided the intermediacy of an alkoxymethylene derivative and afforded the final products in higher yields (by 5–15%) over previous preparations. The current project sought to extend this method to the synthesis of 1-alkyl- and 1-aryl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates, which would feature a tandem S_NAr-addition-elimination reaction with a 2-chloropyridine moiety as the acceptor in the S_NAr step. Like the dihydroquinolines described previously [1], the target dihyronaphthyridines have high potential as antibiotics [2] as well as anti-HIV [3] and anti-inflammatory drugs [4,5]. Thus, improved access to these structures is highly desirable.

Earlier syntheses of these ring systems followed three basic strategies and focused on the preparation of 1-aryl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates. The first method began with a substituted 2-(2-chloronicotinoyl)acetate substrate and involved generation of the alkoxymethylene derivative, conversion to an intermediate alkylaminomethylene congener and finally ring closure. Although similar to our procedure, this protocol incorporated an extra step, and gave the dihyronaphthyridines in only 45–60% yields [2a,2f,3]. The second preparation entailed addition of a 2-aminopyridine to diethyl ethoxymethylene malonate, followed by thermal ring closure. While requiring only two steps, this approach furnished the desired heterocycles in moderate yields of 60–65% [2b]. Finally, acylation to the ester group of ethyl 3-(dimethylamino)acrylate with 2-chloronicotinoyl chloride and subsequent reaction with a functionalized aniline also afforded the target ring system [5b], but the overall yields were variable and generally modest (45–78%).

**RESULTS AND DISCUSSION**

The synthesis of the required cyclization substrate is outlined in Scheme 1. Conversion of ethyl hydrogen malonate (1) [6] to its dianion 2 with excess \(n\)-butyllithium and reaction with 2-chloronicotinoyl chloride (4) derived from acid 3 afforded ethyl 2-(2-chloronicotinoyl)acetate (5) in 83% yield [7]. Condensation of 5 with \(N, N\)-dimethylformamide dimethyl acetal in DMF at 100\(^\circ\)C for 30 min then afforded \(\beta\)-enaminone 6 in 95% yield [8]. Although enaminone 6 (a vinylogous amide) appeared to be a single isomer, the E-Z stereochemistry was unknown.

The results of our cyclization study are summarized in Figure 1. Since two bonds must be formed to close the ring, primary amines were required for the cyclizations. Treatment of enaminone 6 with an equimolar quantity of each amine in DMF under argon at 120\(^\circ\)C generally afforded the target ethyl 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates 7 in 70–82% yields. One notable exception was the cyclization using tert-butylamine (Fig. 1, entry g), which gave the heterocycle in only 47% yield, presumably due to steric hindrance around the nucleophilic...
amine nitrogen. Reactions were conveniently run in a Pyrex pressure vessel, though this was only necessary for amines with boiling points less than 100°C (Fig. 1, entries a, c, e, and g). The dihydronaphthyridine products were all solids and, thus, easily purified by trituration in ether or by preparative thin layer chromatography followed by trituration in ether.

The reaction was successful for primary amines incorporating cyclic (Fig. 1, entries a-b), minimally branched straight chain (entries c-f), benzylic (entries h-k), and aromatic (entries l-o) R groups. In fact, the target heterocycles were produced in similar yields from all amines when the R group was primary, secondary or aromatic. Our previous work [1] indicated that primary amines incorporating a tertiary R group reacted poorly, and this was borne out in this study where tert-butylamine (entry g) gave the lowest yield. Nevertheless, hindered aromatic amines, such as 2-methylaniline (o-toluidine, entry o), afforded dihydro-naphthyridine 7o in a respectable 78% yield, despite the steric congestion created by the ortho methyl group. Thus, the current method appears to be a general route to these compounds except when R is tertiary.

Although most of our reactions proceeded cleanly, early reactions using hexylamine and 2-phenylethylamine (Fig. 1, entries d and f) gave the carboxylic acids rather than the ester products. This anomaly was not encountered in our previous work to prepare 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate esters [1], or from any other amine in this study. Attempts to suppress this process by running the reaction at lower temperature (90–100°C) were unsuccessful and gave ester-acid mixtures. Initially, we believed that these acids resulted from SN2 dealkylation of the esters [9] by chloride ion produced in the reaction. Chloride is a potent nucleophile in polar aprotic solvents and could easily displace the carboxylate anion from an unhindered primary carbon [10]. In support of this hypothesis, the esters were isolated in 50–60% yields from these same reactions under more dilute ([substrate]/2) conditions where the chloride concentration remained low, though 12–24% of residual ester cleavage was still observed. More importantly, however, experiments designed to favor acid formation using excess chloride (up to five equivalents) in several of the other reactions proceeded normally to give esters under our standard conditions. This last result led us to rule out the SN2 dealkylation process as the source of the acid products.

A second plausible explanation relates to the source of the amines. While most of our amines were from freshly opened bottles, the hexylamine and 2-phenylethylamine came from previously opened containers. Thus, it was possible that water absorbed by these older reagents was promoting hydrolysis of the ester products [10]. This rationale would be consistent with the results of our dilution experiments, since additional dry solvent in the reaction would lower the water concentration and decrease, but not completely suppress, ester cleavage. Validation of this proposal came when repetition of these two runs using anhydrous amines gave the ester products without significant acid formation.

The proposed mechanism for the process is summarized in Scheme 2. Though the reaction chronology is somewhat speculative, the sequence likely involves an initial S_N_Ar
reaction with the activated aromatic ring to give 8 [11]. At 120°C, intermediate 8 would then rapidly undergo ring closure by an addition-elimination reaction with the side chain enamino to give 7. Since resonance reduces the double bond character of the α,β bond in 8, the E and Z forms of this intermediate should readily equilibrate to allow for cyclization, presumably via the Z isomer (NMe₂ trans to the ketone). The observation that the current reaction occurs at lower temperature and in shorter reaction time than for ketone). The observation that the current reaction occurs at lower temperature and in shorter reaction time than for monoanilinouren substrates [1] suggests that 2-chloropyridines are significantly more reactive in SNAr reactions [12]. This would be expected based on the greater electron deficiency of the pyridine ring and the more polarized nature of the aromatic C=N bond [13].

**CONCLUSION**

We have developed an alternative synthesis of N-substituted ethyl 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates, thus providing access to new derivatives of these valuable pharmaceutical building blocks. The synthesis is operationally simple and gives the target heterocycles in ≥70% overall yields, which represents a 5–15% improvement over previous methods. The synthesis appears to be general for all primary amines (e.g., RNH₂), though yields are reduced when the R of the primary amine is a tertiary alkyl group.

**EXPERIMENTAL**

All reactions were run under dry nitrogen in oven-dried glassware. Commercial anhydrous N,N-dimethylformamide (DMF) was stored under nitrogen and transferred by syringe into reactions where it was used. Tetrahydrofuran (THF) was dried over potassium hydroxide pellets and distilled from lithium aluminium hydride prior to use. Other commercial reagents and solvents were used as received. Note: Unless the amines are used from freshly opened bottles, they should be dried over calcium hydride (12 h, 60°C) and distilled prior to use. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No. 21521). Preparative separations were performed using flash chromatography [14] on silica gel (Grade 62, 60–200 mesh) mixed with UV-active phosphor (Sorbent Technologies No. UV-5) or preparative thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech No. 02015); band elution for both methods was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on sodium chloride disks. Unless otherwise indicated, ¹H- and ¹³CNMR spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (J) are reported in Hz. Low resolution mass spectra (electron impact/direct probe) were run at 30 eV.

**Ethyl 2-(2-chloronicotinoyl)acetate (5).** The procedure of Domagala and coworkers was modified [7]. A 100-mL, single-necked, round-bottomed flask, equipped with a reflux condenser and a magnetic stirrer, was charged with 5.00 g (31.7 mmoles) of 2-chloronicotinic acid (2) and 25 mL of thionyl chloride. A drop of DMF was added and the reaction was heated at reflux (oil bath) for 3 h. At the end of this period, 25 mL of benzene was added and the excess thionyl chloride was removed by distillation. This process was repeated three times before final concentration under vacuum gave 2-chloronicotinoyl chloride (3) as a tan solid. The isolated material was used without further purification.

In a 500-mL, three-necked, round-bottomed flask, equipped with an efficient magnetic stirrer, 6.70 g (50.7 mmoles) of ethyl hydrogen malonate (1) [6] was dissolved in 200 mL of THF and 10 mg of bipyridyl was added as an internal indicator. The mixture was cooled to –30°C and 22.5 mL of 2.27M n-butyllithium (51.0 mmoles) was added dropwise over 20 min. The reaction mixture was warmed to –5°C and another portion of 22.5 mL of 2.27M n-butyllithium (51.0 mmoles) was added until a red color persisted for 5–10 min. The resulting solution of 2 was cooled to –78°C and a solution of 5.58 g (31.7 mmoles) of 2-chloronicotinoyl chloride (4) in 25 mL of THF was added dropwise over 25 min. The reaction was kept at –78°C for 30 min and then slowly warmed to –30°C and stirred for 30 min. The crude mixture was poured into ice containing 250 mL of 1M hydrochloric acid and extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with water (1 × 200 mL), 5% aqueous sodium bicarbonate (1 × 200 mL) and 1M hydrochloric acid (1 × 200 mL). The dichloromethane layer was finally washed with saturated aqueous sodium chloride (1 × 200 mL), dried (magnesium sulfate) and concentrated under vacuum to give a dark yellow oil. The product was purified by flash chromatography on a 50 cm × 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes to give 5.98 g (83%) of 5 as a colorless oil consisting of a 1:1 keto/enol mixture. IR: 1743, 1707, 1633 cm⁻¹; ¹HNMR (keto-enol mixture): δ 12.5 (s, 0.5H), 8.53 (dd, 0.5H, J = 4.8, 2.0), 8.45 (dd, 0.5H, J = 4.8, 2.0), 7.99 (dd, 0.5H, J = 7.5, 2.0), 7.95 (dd, 0.5H, J = 7.5, 2.0), 7.39 (dd, 0.5H, J = 7.5, 4.8), 5.70 (s, 0.5H), 4.29 (q, 1H, J = 7.1), 4.19 (q, 1H, J = 7.1), 4.10 (t, 1H, J = 7.1), 1.25 (t, 1.5H, J = 7.1); ¹³CNMR (keto-enol mixture): δ 193.5, 172.3, 168.0, 166.5, 151.8, 150.4, 148.5, 147.5, 139.1, 138.7, 134.0, 130.1, 122.6, 122.2, 94.0, 61.5, 60.7, 48.6, 42.0, 13CNMR spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (J) are reported in Hz.
Ethyl 1-allyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (7e). This compound (101 mg, 78%) was prepared from 142 mg (0.50 mmoles) of 6 and 29 mg (0.038 mL, 0.50 mmoles) of allylamine. The product was isolated as a white solid following preparative thin layer chromatography eluted with ethyl acetate and trituration with ether, mp 97–98°C. IR: 1725, 1692, 1631, 1601 cm⁻¹; ¹HNMR: δ 8.78 (dd, 1H, J = 7.7, 1.1), 8.74 (dd, 1H, J = 4.4, 1.1), 8.64 (s, 1H), 7.42 (dd, 1H, J = 7.7, 4.4), 6.07 (dd, 1H, J = 16.7, 10.4), 5.5, 5.32 (1H, J = 10.4), 5.25 (dd, 1H, J = 16.5), 5.07 (d, 2H, J = 5.5), 4.41 (q, 2H, J = 7.1), 1.41 (t, 3H, J = 7.1); ¹³CNMR: δ 174.7, 165.3, 152.3, 149.1 (2C), 136.9, 131.7, 123.6, 121.0, 119.3, 121.0, 52.5, 14.3; ms: m/z 258 (M⁺). Anal. Calcd. for C₁₅H₁₄N₂O₂: C 65.6; H, 5.4; N, 10.82. Found: C, 65.6; H, 5.4; N, 10.82.

Ethyl 1-cyclohexyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (7d). This compound (106 mg, 76%) was prepared from 142 mg (0.50 mmoles) of 6 and 51 mg (0.066 mL, 0.50 mmoles) of dried n-hexylamine. The product was isolated as a white solid following preparative thin layer chromatography eluted with ethyl acetate and trituration with ether, mp 68–69°C. IR: 1728, 1694, 1641, 1634 cm⁻¹; ¹HNMR: δ 8.78 (dd, 1H, J = 7.7, 1.6), 8.74 (dd, 1H, J = 4.4, 1.6), 8.65 (s, 1H), 7.41 (dd, 1H, J = 7.7, 4.4), 4.43 (t, 2H, J = 7.1), 4.41 (q, 2H, J = 7.1), 1.88 (quintet, 2H, J = 6.6), 1.42 (t, 3H, J = 7.1), 1.42-1.22 (complex, 6H), 0.89 (distorted t, 3H, J = 6.6); ¹³CNMR: δ 174.6, 165.3, 152.2, 149.4, 149.2, 136.7, 120.8, 120.7, 111.8, 60.9, 51.6, 31.2, 29.5, 26.1, 22.4, 14.3, 13.8; ms: m/z 302 (M⁺). Anal. Calcd. for C₁₅H₁₄N₂O₂: C 67.5; H, 7.28; N, 9.27. Found: C, 67.5; H, 7.21; N, 9.18.

The corresponding acid was produced when an older, undried sample of the amine was used. The acid was isolated as a white solid following preparative thin layer chromatography eluted with ethyl acetate and trituration with ether, mp 124–125°C. IR: 3490-2405, 1720, 1630 cm⁻¹; ¹HNMR: δ 14.5 (s, 1H), 8.93 (s, 1H), 8.91 (dd, 1H, J = 4.4, 2.0), 8.83 (dd, 1H, J = 7.8, 2.0), 7.57 (dd, 1H, J = 7.8, 4.4), 4.56 (t, 2H, J = 7.3), 1.92 (m, 2H), 1.38 (m, 6H), 0.89 (distorted t, 3H, J = 6.4); ¹³CNMR: δ 178.8, 166.3, 153.9, 149.0, 149.5, 136.3, 121.9, 121.5, 109.6, 52.6, 31.2, 29.8, 26.2, 22.4, 13.9; ms: m/z 274 (M⁺). Anal. Calcd. for C₁₅H₁₄N₂O₂: C 65.6; H, 6.57; N, 10.22. Found: C, 65.7; H, 6.53; N, 10.13.

Ethyl 1,4-dihydro-1-isobutyl-4-oxo-1,8-naphthyridine-3-carboxylate (7e). This compound (105 mg, 76%) was prepared from 142 mg (0.50 mmoles) of 6 and 37 mg (0.051 mL, 0.50 mmoles) of isobutylamine. The product was isolated as a white solid following workup and trituration with ether, mp 73–75°C. IR: 1727, 1694, 1628, 1611 cm⁻¹; ¹HNMR: δ 8.75 (dd, 1H, J = 7.7, 1.6), 8.73 (dd, 1H, J = 1.4, 1.6), 8.60 (s, 1H), 7.40 (dd, 1H, J = 7.7, 4.4), 4.42 (q, 2H, J = 7.1), 4.24 (d, 2H, J = 7.1), 2.32 (nonet, 1H, J = 7.1), 1.43 (t, 3H, J = 7.1), 0.98 (d, 6H, J = 7.1); ¹³CNMR: δ 174.6, 165.4, 152.2, 149.8, 149.4, 136.8, 123.7, 120.9, 111.5, 60.9, 58.5, 28.3, 19.8, 14.3; ms: m/z 274 (M⁺). Anal. Calcd. for C₁₅H₁₄N₂O₂: C 65.6; H, 6.57; N, 10.22. Found: C, 65.66; H, 6.55; N, 10.19.

Ethyl 1,4-dihydro-4-oxo-1-(2-phenylethyl)-1,8-naphthyridine-3-carboxylate (7f) and the corresponding acid. This compound (116 mg, 72%) was prepared from 142 mg (0.50 mmoles) of 6 and 61 mg (0.063 mL, 0.50 mmoles) of dried 2-phenylethylamine. The product was isolated as a white solid following preparative thin layer chromatography eluted with ethyl acetate and trituration with ether, mp 97–98°C. IR: 1725, 1692, 1631, 1601 cm⁻¹; ¹HNMR: δ 8.78 (m, 2H), 8.30 (s, 1H), 7.43 (dd, 1H, J = 8.2, 4.9), 7.27 (m, 3H), 7.12 (d, 2H, J = 6.6), 4.64 (t, 2H, J = 7.1), 4.31 (q, 2H, J = 7.1), 3.17 (t, 2H, J = 7.1), 1.37 (t, 3H, J = 7.1); ¹³CNMR: δ...
Ethyl 1-tert-butyl-1,4-dihydropyrolo-4-oxo-1,8-naphthyridine-3-carboxylate (7g). This compound (64 mg, 47%) was prepared from 142 mg (0.50 mmoles) of 6 and 37 mg (0.053 mL, 0.50 mmoles) of tert-butylamine. The product was isolated as a white solid following workup and trituration with ether, mp 154–155°C. IR: 3700, 2960, 1690 cm⁻¹; ¹H NMR: δ 8.79 (dd, 1H, J = 7.7, 1.6), 8.73 (dd, 1H, J = 4.4, 1.6), 8.72 (s, 1H, 7.41 (dd, 1H, J = 7.7, 4.4), 7.32 (m, 5H), 5.65 (s, 2H), 4.39 (q, 2H, J = 7.1), 1.40 (t, 3H, J = 7.1); ¹³C NMR: δ 174.7, 165.2, 152.4, 149.3 (2C), 136.9, 135.5, 129.0, 128.4, 127.6, 127.3, 121.1, 112.5, 60.1, 53.6, 14.4; ms: m/z 308 (M⁺). Anal. Calcld. for C₁₇H₁₈N₂O₄: C, 65.7; H, 5.7; N, 9.09. Found: C, 65.68; H, 5.67; N, 9.70.

Ethyl 1-benzyl-1,4-dihydropyrolo-4-oxo-1,8-naphthyridine-3-carboxylate (7h). This compound (113 mg, 73%) was prepared from 142 mg (0.50 mmoles) of 6 and 54 mg (0.054 mL, 0.50 mmoles) of benzylamine. The product was isolated as a white solid following workup and trituration with ether, mp 154–155°C. IR: 3700, 2960, 1690 cm⁻¹; ¹H NMR: δ 8.79 (dd, 1H, J = 7.7, 1.6), 8.73 (dd, 1H, J = 4.4, 1.6), 8.72 (s, 1H, 7.41 (dd, 1H, J = 7.7, 4.4), 7.32 (m, 5H), 5.65 (s, 2H), 4.39 (q, 2H, J = 7.1), 1.40 (t, 3H, J = 7.1); ¹³C NMR: δ 174.7, 165.2, 152.4, 149.3 (2C), 136.9, 135.5, 129.0, 128.4, 127.6, 127.3, 121.1, 112.5, 60.1, 53.6, 14.4; ms: m/z 308 (M⁺). Anal. Calcld. for C₁₇H₁₈N₂O₄: C, 65.7; H, 5.7; N, 9.09. Found: C, 65.68; H, 5.67; N, 9.70.

Ethyl 1,4-dihydropyrolo-4-(4-methoxybenzyl)-4-oxo-1,8-naphthyridine-3-carboxylate (7i). This compound (133 mg, 82%) was prepared from 142 mg (0.50 mmoles) of 6 and 62 mg (0.057 mL, 0.50 mmoles) of 4-methoxyaniline. The product was isolated as a pale yellow solid following workup and trituration with ether, mp 203–205°C. IR: 3700, 2960, 1690, 1600 cm⁻¹; ¹H NMR: δ 8.82 (dd, 1H, J = 7.7, 1.6), 8.73 (dd, 1H, J = 4.4, 1.6), 8.72 (s, 1H, 7.41 (dd, 1H, J = 7.7, 4.4), 7.29 (d, 2H, J = 8.4), 6.87 (d, 2H, J = 8.4), 5.51 (s, 2H, 4.39 (q, 2H, J = 7.1), 3.78 (s, 3H), 1.40 (t, 3H, J = 7.1); ¹³C NMR: δ 174.6, 165.3, 159.6, 152.3, 149.3, 149.1, 136.9, 129.4, 127.4, 123.7, 121.0, 114.3, 124.2, 61.0, 55.3, 51.3, 14.6; ms: m/z 338 (M⁺). Anal. Calcld. for C₁₉H₁₈N₂O₄: C, 67.67; H, 5.35; N, 8.26. Found: C, 67.69; H, 5.35; N, 8.21.

Ethyl 1-(4-chlorobenzyl)-1,4-dihydropyrolo-4-oxo-1,8-naphthyridine-3-carboxylate (7j). This compound (130 mg, 75%) was prepared from 142 mg (0.50 mmoles) of 6 and 71 mg (0.061 mL, 0.50 mmoles) of 4-chlorobenzylamine. The product was isolated as a tan solid following workup and trituration with ether, mp 155–156°C. IR: 3700, 2960, 1690, 1629, 1611 cm⁻¹; ¹H NMR: δ 8.78 (dd, 1H, J = 7.7, 1.6), 8.75 (dd, 1H, J = 4.4, 1.6), 8.71 (s, 1H, 7.41 (dd, 1H, J = 7.7, 4.4), 7.29 (d, 2H, J = 8.4), 6.87 (d, 2H, J = 8.4), 5.51 (s, 2H, 4.39 (q, 2H, J = 7.1), 3.78 (s, 3H), 1.40 (t, 3H, J = 7.1); ¹³C NMR: δ 174.5, 165.1, 152.4, 149.1 (2C), 137.0, 134.3, 134.0, 129.1, 129.0, 123.7, 121.2, 116.0, 53.1, 14.3; ms: m/z 342, 344 (ca. 3:1, M⁺). Anal. Calcld. for C₁₉H₁₇ClN₂O₄: C, 63.07; H, 4.38; N, 8.18. Found: C, 63.10; H, 4.41; N, 8.12.
(M\(^+\)). Anal. Calcd. for C\(_{18}\)H\(_{16}\)NO\(_3\): C, 70.13; H, 5.19; N, 9.09.
Found: C, 70.22; H, 5.21; N, 9.06.

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REFERENCES AND NOTES

[10] We wish to thank one of the referees for suggesting the presence of water in these amines as a possible cause for the observed ester hydrolysis. We did not initially suspect this problem, since acids were not produced in earlier work with related materials.
[11] Although reaction at the side chain could also occur as the first step, the fact that no dimethylamine addition was observed suggests that the sequence is initiated by addition to the aromatic ring. On the other hand, dimethylamine is highly volatile (bp 7°C) and would not be expected to build up significant concentrations in the reaction at 120°C. Additionally, intramolecular ring closure is most likely faster than intermolecular addition of dimethylamine to the activated aromatic ring. Thus, initial attack at the side chain is also possible.
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