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 b-ketoester with N,N,N-dimethylformamide dimethyl acetal in N,N-dimethylformamide (DMF) gave a 95% yield of the 2-dimethylaminomethylene derivative. Subsequent reaction of this b-enaminone with primary amines in DMF at 120°C for 24 h then afforded the target compounds in 47–82% yields by a tandem SNAr-addition-elimination reaction. Synthetic and procedural details as well as a mechanistic rationale are presented.
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 SNAr...
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 mononitroarene substrates [1] suggests that 2-chloropyridones are significantly more reactive in SN₂Ar 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 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, ‘H- 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-butyl-lithium (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-butyl-lithium (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 (s, 1.5H), 1.35 (t, 1.5H, 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,
Ethyl 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates by a Tandem $\text{Sr}$Ar-Addition-Elimination Reaction

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, 1.6), 8.74 (dd, 1H, J = 4.4, 1.4), 8.64 (s, 1H), 7.42 (dd, 1H, J = 7.7, 4.4), 6.07 (ddt, 1H, J = 16.5, 10.4, 5.5), 5.32 (d, 1H, J = 10.4), 5.25 (d, 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, 60.9, 52.5, 14.3; ms: m/z 258 (M⁺). Anal. Calcld. for $\text{C}_7\text{H}_7\text{N}_2\text{O}_2$: C, 65.12; H, 5.43; N, 10.85. Found: C, 65.16; H, 5.42; N, 10.81.

Ethyl 1,4-dihydro-1-phenylethyl-1,8-naphthyridine-3-carboxylate (7f) and the corresponding acid. This compound (106 mg, 70%) 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, 1634, 1613, 1601 cm⁻¹; 1HNMR: δ 8.78 (dd, 1H, J = 7.7, 1.6), 8.74 (dd, 1H, J = 4.4, 1.4), 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. Calcld. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_3$: C, 67.55; H, 7.28; N, 9.27. Found: C, 67.51; H, 7.25; 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, 121.0, 121.5, 109.6, 52.6, 31.2, 29.8, 26.2, 22.4, 13.9; ms: m/z 274 (M⁺). Anal. Calcld. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$: C, 65.69; H, 5.67; N, 10.22. Found: C, 65.73; 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 = 4.4, 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. Calcld. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3$: C, 65.69; 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
17.46, 164.9, 152.3, 149.5, 149.0, 137.1, 136.9, 128.8 (2C), 127.0, 123.6, 120.9, 111.5, 60.8, 53.1, 35.6, 14.3; ms: m/z 231 (M–C2H5–H). Anal. Calcld. for C19H18N2O3: C, 69.41; H, 5.80; N, 9.04.

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 182–184°C. IR: 1725, 1691, 1625, 1600 cm–1; 1HNMR: δ 8.78 (dd, 1H, J = 7.7, 1.6), 8.75 (dd, 1H, J = 4.4, 1.6), 8.72 (s, 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); 13CNMR: δ 174.6, 165.3, 159.6, 152.3, 149.3, 149.1, 136.9, 129.4, 127.3, 123.7, 121.1, 60.5, 53.6, 14.4; ms: m/z 308 (M+). Anal. Calcld. for C19H18N2O4: C, 66.76; H, 4.70; N, 9.52.

Ethyl 1-(4-chlorobenzyl)-1,4-dihydro-4-oxo-1-(2-methylphenyl)-1,8-naphthyridine-3-carboxylate (7i). This compound (132 mg, 75%) was prepared from 142 mg (0.50 mmoles) of 6 and 64 mg (0.045 mL, 0.50 mmoles) of 4-chloroaniline. The product was isolated as a tan solid following workup and trituration with ether, mp 193–194°C. IR: 1731, 1692, 1638, 1597 cm–1; 1HNMR: δ 8.81 (dd, 1H, J = 7.7, 1.6), 8.67 (s, 1H), 8.64 (dd, 1H, J = 4.4, 1.6), 7.57 (dd, 2H, J = 8.8), 7.42 (obsured dd, 1H, J = 7.7, 4.4), 7.41 (d, 2H, J = 8.8), 4.40 (q, 2H, J = 7.1), 1.40 (t, 3H, J = 7.1); 13CNMR: δ 174.6, 164.8, 165.2, 150.0, 149.2, 138.7, 137.0, 135.4, 129.8, 128.3, 123.2, 121.4, 61.1, 55.6, 14.4; ms: m/z 324 (M+). Anal. Calcld. for C19H16ClN2O4: C, 66.67; H, 4.94; N, 8.64. Found: C, 66.73; H, 4.98; N, 8.55.

Ethyl 1,4-dihydro-4-oxo-1-(2-methylphenyl)-4-oxo-1,8-naphthyridine-3-carboxylate (7j). This compound (123 mg, 75%) was prepared from 142 mg (0.50 mmoles) of 6 and 64 mg (0.045 mL, 0.50 mmoles) of 4-chloroaniline. The product was isolated as a tan solid following workup and trituration with ether, mp 201–212°C. IR: 1732, 1694, 1643, 1604 cm–1; 1HNMR: δ 8.81 (dd, 1H, J = 7.7, 1.6), 8.70 (s, 1H), 8.64 (dd, 1H, J = 4.4, 1.6), 7.38 (m, 5H), 4.39 (q, 2H, J = 7.1), 2.48 (s, 3H), 1.40 (t, 3H, J = 7.1); 13CNMR: δ 174.6, 164.8, 152.5, 150.2, 149.7, 139.5, 137.7, 136.7, 130.2, 127.0, 123.2, 121.1, 60.9, 21.1, 14.2; ms: m/z 308

Ethyl 1,4-dihydro-4-oxo-1-(2-fluorobenzyl)-1,8-naphthyridine-3-carboxylate (7k). This compound (151 mg, 80%) was prepared from 142 mg (0.50 mmoles) of 6 and 88 mg (0.071 mL, 0.50 mmoles) of 4-(trifluoromethyl)benzylamine. The product was isolated as a white solid following workup and trituration with ether, mp 202–204°C. IR: 1678, 1651, 1610, 1334 cm–1; 1HNMR: δ 8.80 (dd, 1H, J = 7.7, 1.6), 8.72 (s, 1H), 8.71 (obsured dd, 1H, J = 4.9, 1.6), 7.61 (dd, 1H, J = 8.2), 7.42 (dd, 1H, J = 7.7, 4.9), 7.41 (d, 2H, J = 8.2), 5.69 (s, 2H), 4.40 (q, 2H, J = 7.1), 1.41 (t, 3H, J = 7.1); 13CNMR: δ 174.5, 165.0, 152.4, 149.2, 149.1, 139.6, 137.0, 130.5 (q, J = 32.4), 127.7, 125.9 (q, J = 3.7), 123.8 (q, J = 27.1), 123.7, 121.3, 112.8, 61.1, 53.3, 14.3; ms: m/z 376 (M+). Anal. Calcld. for C19H16F3N2O4: C, 60.64; H, 3.99; N, 7.45. Found: C, 60.71; H, 4.04; N, 7.39.
Analytical. Calcd. for CH18H16NO3: C, 70.13; H, 5.19; N, 9.09. Found: C, 70.22; H, 5.21; N, 9.06.

Acknowledgments. B.N. thanks Oklahoma State University for a research assistantship and the Department of Chemistry for an O. C. Dermer Scholarship. Funding for the 300 MHz NMR spectrometer of the Oklahoma Statewide Shared NMR Facility was provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Finally, the authors wish to thank the OSU College of Arts and Sciences for funds to upgrade our departmental FT-IR and GC-MS instruments.

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.


学霸图书馆

www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具