



One-pot synthesis of highly functionalized 1,2-dihydropyridines from primary alkylamines, alkyl isocyanides, and acetylenic esters

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ABSTRACT

A novel one-pot isocyanide-based cascade four-component reaction between primary alkylamines, acetylenic esters, and alkyl isocyanides led to tetraalkyl 1-alkyl(aryl)-4-alkylamino-1,2-dihydropyridine-2,3,5,6-tetracarboxylates in good yields.

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1. Introduction

Dihydropyridines have long been recognized as versatile synthetic intermediates¹ that provide ready access to a variety of substituted *N*-heterocycles, such as piperidines² and pyridines.³ Historically, 1,4-dihydropyridines have been the most studied, whereas 1,2-dihydropyridines have received relatively little attention. The majority of synthetic approaches to 1,2-dihydropyridines has relied on nucleophilic addition to *N*-alkyl or *N*-acylpyridinium salts.^{4,5} However, regioisomeric mixtures of addition products are often obtained if unsymmetrically substituted pyridinium salts are employed.⁶ More recently, other strategies for the synthesis of 1,2-dihydropyridines have emerged that address some of these limitations.⁷ Because of the lack of general methods for the regioselective synthesis of highly functionalized 1,2-dihydropyridines, their synthetic and biological potential remains largely unexplored.

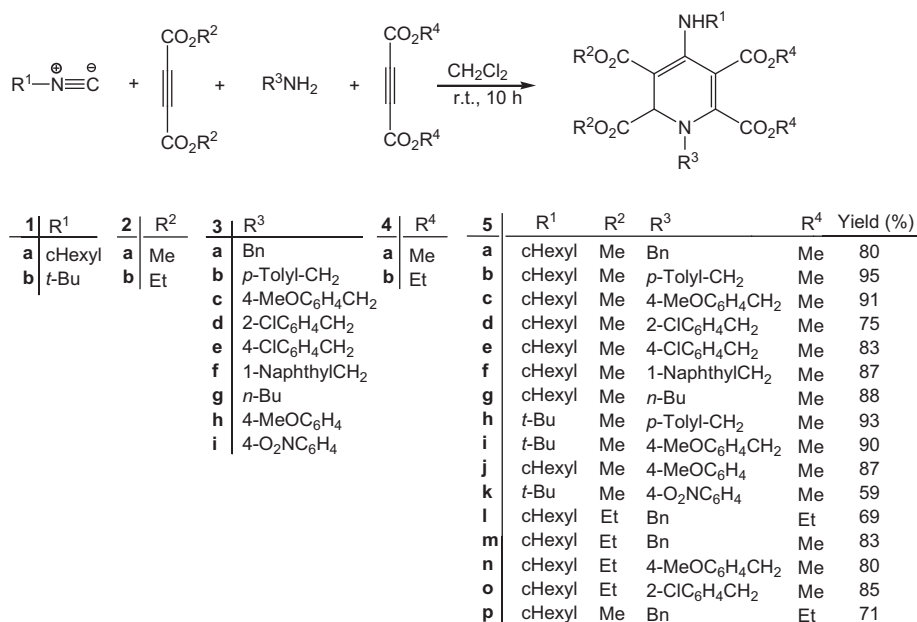
One-pot, multi-component reactions continue to be of interest in the synthesis of various compounds containing particularly nitrogen atoms^{8,9} owing to the fast assembly of poly-substituted systems without isolation of unstable intermediates. The importance of these one-pot reactions in such syntheses has been demonstrated in the Mannich, Ugi,⁸ Biginelli,⁹ and aza-Baylis–Hillman¹⁰ reactions, and in Hantzsch dihydropyridine synthesis.¹¹

2. Results and discussion

As a part of our current studies on the development of new routes in heterocyclic synthesis,^{12–15} we report the results of our studies involving the reaction of the zwitterionic intermediates derived from alkyl isocyanides **1** and acetylenic esters **2** with dialkyl 2-(alkyl(aryl)amino)but-2-enedioates [generated in situ from primary alkyl(aryl)amines and acetylenic esters **4**], which constitutes a synthesis of highly functionalized 1,2-dihydropyridines (**5**) in good yields (Scheme 1).

The reaction of alkyl isocyanides **1**, dimethyl acetylenedicarboxylate (**2a**), and primary amines **3**, proceeded smoothly in CH₂Cl₂ at rt and produced tetramethyl 4-(alkylamino)-1-alkyl(aryl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylates **5a–k**, in good yields after purification (Scheme 1). A wide range of structurally varied primary amines were employed in this cyclocondensation reaction. Addition of a solution of equimolar amounts of primary amine **3** and **2a** to a 1:1 mixture of cyclohexyl isocyanide (**1a**), and diethyl acetylenedicarboxylate (**2b**) in CH₂Cl₂ at rt, produced 5,6-diethyl 2,3-dimethyl 4-(cyclohexylamino)-1-(arylmethyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylates **5m–p**, which contain two different ester groups (Scheme 1). The formation of a single product when two different acetylenic esters are used (Scheme 1, compounds **5m–p**), is presumably controlled by the sequence in which the reaction is carried out. When the ethyl and methyl substituents of the alkynes are reversed, two different products (**5m** and **5p**) were obtained. Although compounds **5** are well set up to undergo a [1,5]-

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Scheme 1. The four-component one-pot synthesis of functionalized 1,2-dihydropyridines **5**.

sigmatropic shift, we conclude that no [1,5]-sigmatropic shift is taking place under the reaction conditions employed.

The structures of compounds **5a–p** were deduced from their elemental analyses and their IR, ¹H NMR, ¹³C NMR, and single-crystal X-ray analyses. The mass spectra of compounds **5a–p** displayed in each case, the molecular ion peak at the appropriate *m/z* values. The ¹H and ¹³C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. For example, the ¹H NMR spectrum of **5a** in CDCl₃ showed six singlets for the methoxy (δ =3.49, 3.65, 3.73, 3.94), methine (δ =5.13), and amino (δ =8.37) protons, along with a characteristic AB system for the diastereotopic benzylic methylene protons. The cyclohexyl and phenyl groups exhibited characteristic multiplets in the appropriate regions of the ¹H NMR spectrum. The ¹H-decoupled ¹³C NMR

spectrum of **5a** exhibited 24 signals in agreement with the proposed structure. The IR spectrum of **5a** displayed characteristic ester carbonyl bands. The ¹H NMR and ¹³C NMR spectra of **5b–p** are similar to those for **5a**, except for the alkyl and aryl groups.

Unambiguous evidence for the structure and stereochemistry of **5c** was obtained from a single-crystal X-ray analysis. An ORTEP¹⁶ diagram of **5c** is shown in the Figure 1. There are two molecules of **5c** together with two molecules of CH₂Cl₂ in the unit cell. The structure deduced from the crystallographic experiment, by analogy can be applied to the other products on account of their NMR-spectroscopic similarities. For details of the structure-determination and refinement, see the Experimental section.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product

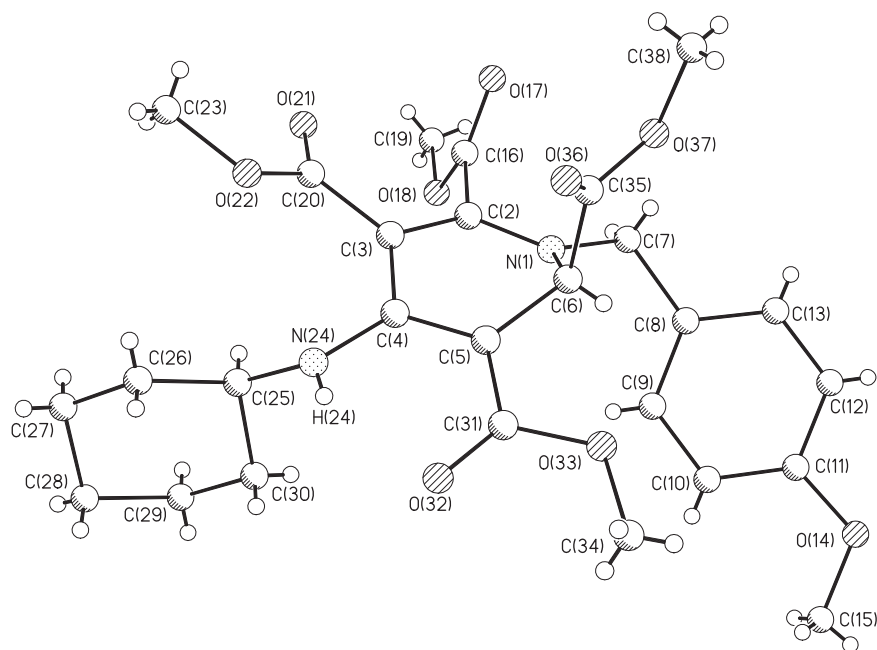
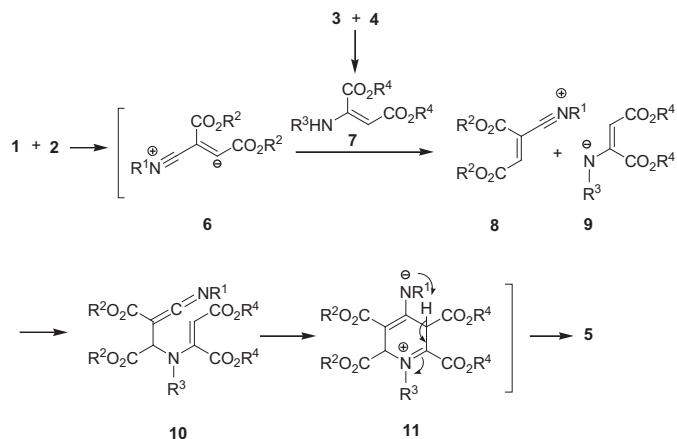


Figure 1. X-ray crystal structure of **5c**. ORTEP-III Plot,¹⁶ arbitrary atom numbering.

formation. Presumably, the zwitterionic intermediate **6**, formed from isocyanide **1** and acetylenic ester **2**, is protonated by the enaminoester **7**, generated in situ from primary amine **3** and acetylenic ester, to produce intermediates **8** and **9** (Scheme 2). Ketenimine **10**, produced from addition of **8** to **9**, undergoes a cyclization reaction to afford **11**, which is converted to **5** by proton transfer.



Scheme 2. Plausible mechanism for the formation of functionalized 1,2-dihydropyridines **5**.

In conclusion, the zwitterionic 1:1 intermediates generated by addition of alkyl isocyanides to acetylenic esters is trapped by enaminoesters generated in situ from primary amines and dialkyl acetylenedicarboxylates, to yield tetraalkyl 1-alkyl(aryl)-4-alkylamino-1,2-dihydropyridine-2,3,5,6-tetracarboxylates in good yields. The present method may be considered as a practical route for the synthesis of functionalized 1,2-dihydropyridine-ring systems.

3. Experimental

3.1. General

Primary amines **3**, isocyanides **1**, and the dialkyl acetylenedicarboxylates **2** were obtained from Merck and used without further purification. Mp: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer; in cm^{-1} . ^1H and ^{13}C NMR Spectra: Bruker DRX-500 AVANCE instrument; in CDCl_3 at 500.1 and 125.7 MHz, respectively; δ in parts per million, J in hertz. EIMS: Finnigan-MAT-8430 mass spectrometer, at 70 eV; in m/z . Elemental analyses: Heraeus CHN–O–Rapid analyzer.

3.2. Compounds **5a–l**: general procedure

To a stirred solution of amine **3** (2 mmol) and acetylenic ester **2** (4 mmol) in CH_2Cl_2 (10 mL), was added the isocyanide **1** (2 mmol) at -5°C . The mixture was allowed to reach rt. After completion of the reaction (6–12 h; TLC (AcOEt/hexane 1:4) monitoring), the solvent was evaporated, and the residue was purified by column chromatography (silica gel (230–400 mesh; Merck), hexane/AcOEt 5:1): pure product.

3.2.1. Tetramethyl 1-benzyl-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5a). Yellow powder; mp: 99–101 $^\circ\text{C}$; yield: 0.80 g (80%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3460, 2940, 1743, 1694, 1647, 1597, 1523, 1432, 1357, 1281, 1231, 1110, 1081, 809, 772, 693. ^1H NMR (500.1 MHz, CDCl_3): δ =1.50–1.59 (4H, m, 2CH₂), 1.65–1.73 (4H, m, 2CH₂), 1.76–1.82 (2H, m, CH₂), 3.24–3.26 (1H, m, CH), 3.49 (3H, s, MeO), 3.65 (3H, s, MeO), 3.73 (3H, s, MeO), 3.94 (3H, s, MeO), 4.52 (1H, d, 2J =15.3 Hz, CH_AH_B), 4.60 (1H, d, 2J =15.3 Hz, CH_AH_B), 5.13 (1H, s, CH), 7.25 (2H, d, 3J =8.2 Hz, CH), 7.34–7.36 (3H, m, CH), 8.35

(1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =24.6 (CH₂), 24.9 (CH₂), 25.5 (CH₂), 33.2 (CH₂), 34.4 (CH₂), 50.5, 51.4, 52.5, 53.2, 55.4, 56.4, 58.4 (4MeO, CH₂N, 2CHN), 96.1 (C), 125.7 (C), 127.8 (2 CH), 128.3 (CH), 128.7 (2CH), 134.6 (C), 153.5 (C), 154.5 (C), 164.3 (COO), 165.7 (COO), 167.0 (COO), 171.0 (COO) ppm. MS: m/z (%)=501 (M^+ +1, 9), 500 (M^+ , 3), 469 (30), 441 (70), 236 (20), 166 (10), 177 (15), 91 (85). Anal. Calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_8$ (500.54): C, 62.39; H, 6.44; N, 5.60. Found: C, 62.8; H, 6.5; N, 5.7.

3.2.2. Tetramethyl 4-(cyclohexylamino)-1-(4-methylbenzyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5b). Yellow powder; mp: 105–107 $^\circ\text{C}$; yield: 0.97 g (95%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3410, 2935, 1741, 1693, 1647, 1597, 1433, 1354, 1282, 1153, 1015, 798, 762, 590. ^1H NMR (500.1 MHz, CDCl_3): δ =1.50–1.58 (4H, m, 2CH₂), 1.63–1.70 (4H, m, 2CH₂), 1.76–1.80 (2H, m, CH₂), 2.32 (3H, s, Me), 3.08–3.15 (1H, m, CH), 3.52 (3H, s, MeO), 3.63 (3H, s, MeO), 3.73 (3H, s, MeO), 3.93 (3H, s, MeO), 4.47 (1H, d, 2J =15.2 Hz, CH_AH_B), 4.55 (1H, d, 2J =15.2 Hz, CH_AH_B), 5.13 (1H, s, CH), 7.12 (4H, s, 4 CH), 8.32 (1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =20.8 (Me), 24.3 (CH₂), 24.6 (CH₂), 25.3 (CH₂), 33.9 (CH₂), 34.2 (CH₂), 50.2, 51.1, 52.2, 52.9, 55.2, 55.9, 58.0 (4MeO, CH₂N, 2CHN), 95.6 (C), 125.2 (C), 127.6 (2CH), 129.1 (2CH), 131.3 (C), 137.8 (C), 153.3 (C), 154.2 (C), 164.1 (COO), 165.5 (COO), 167.4 (COO), 170.7 (COO) ppm. MS: m/z (%)=515 (M^+ +1, 13), 514 (M^+ , 5), 455 (20), 483 (90), 236 (5), 183 (20), 177 (15), 105 (85). Anal. Calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_8$ (514.57): C, 63.02; H, 6.66; N, 5.44. Found: C, 63.2; H, 6.6; N, 5.4%.

3.2.3. Tetramethyl 4-(cyclohexylamino)-1-(4-methoxybenzyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5c). Yellow powder; mp: 96–98 $^\circ\text{C}$; yield: 0.96 g (91%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3380, 2955, 1741, 1699, 1581, 1533, 1433, 1410, 1290, 1213, 1140, 1082, 1028, 991, 622, 739. ^1H NMR (500.1 MHz, CDCl_3): δ =1.53–1.60 (4H, m, CH₂), 1.62–1.71 (4H, m, CH₂), 1.90–1.95 (2H, m, CH₂), 3.05–3.15 (1H, m, CH), 3.45 (3H, s, MeO), 3.55 (3H, s, MeO), 3.63 (3H, s, MeO), 3.70 (3H, s, MeO), 3.86 (3H, s, MeO), 4.39 (1H, d, 2J =14.9 Hz, CH_AH_B), 4.45 (1H, d, 2J =14.9 Hz, CH_AH_B), 5.07 (1H, s, CH), 6.78 (2H, d, 3J =8.5 Hz, CH), 7.10 (2H, d, 3J =8.5 Hz, CH), 8.26 (1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =24.3 (CH₂), 24.6 (CH₂), 25.3 (CH₂), 32.9 (CH₂), 34.1 (CH₂), 50.1, 51.0, 52.0, 52.9, 54.9, 55.0, 55.5, 57.8 (5MeO, CH₂N, 2CHN), 95.4 (C), 113.7 (2CH), 126.2 (C), 129.1 (2CH), 131.7 (C), 153.3 (C), 154.1 (C), 159.4 (C), 164.0 (COO), 165.5 (COO), 166.6 (COO), 170.6 (COO) ppm. MS: m/z (%)=531 (M^+ +1, 11), 530 (M^+ , 4), 499 (20), 471 (80), 236 (10), 199 (20), 177 (10), 121 (90). Anal. Calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_9$ (530.57): C, 61.12; H, 6.46; N, 5.28. Found: C, 61.4; H, 6.4; N, 5.3%.

3.2.3.1. X-ray crystal-structure determination of 5c·CH₂Cl₂. Structure-determination and refinement data: formula, $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_9\cdot\text{CH}_2\text{Cl}_2$; M_r 615.49; crystal size, $0.14\times0.11\times0.08\text{ mm}^3$; crystal system, Triclinic, $a=8.4612(9)$, $b=11.2718(12)$, $c=16.3865(17)\text{ \AA}$, $\alpha=73.625(2)^\circ$, $\beta=83.472(2)^\circ$, $\gamma=88.267(2)^\circ$; space group $P-1$; $Z=2$, $V=1489.7(3)\text{ \AA}^3$, $D_{\text{calcd}}=1.372\text{ Mg/m}^3$; $R=0.0349$ (for 7900 reflections), $R_w=0.0539$; $-11\leq h\leq 11$; $-15\leq k\leq 15$; $-22\leq l\leq 22$; Mo $K\alpha$ radiation ($0.71073\text{ \AA}$); $T=120(2)\text{ K}$. The crystallographic data of **5c·CH₂Cl₂** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-737929. Copies of the data can be obtained, free of charge, via the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44 1223 336033).

3.2.4. Tetramethyl 1-(2-chlorobenzyl)-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5d). Yellow powder; mp: 104–106 $^\circ\text{C}$; yield: 0.80 g (75%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3375, 2935, 1742, 1696, 1648, 1596, 1523, 1434, 1282, 1231, 1140, 1013, 794, 753. ^1H NMR (500.1 MHz, CDCl_3): δ =1.51–1.60 (4H, m, CH₂), 1.63–1.69 (4H, m, CH₂), 1.71–1.81 (2H, m, CH₂), 3.13–3.15 (1H, m, CH), 3.55 (3H, s, MeO), 3.69 (3H, s, MeO), 3.73 (3H, s, MeO), 3.93 (3H, s, MeO),

4.70 (2H, s, CH₂), 5.11 (1H, s, CH), 7.25–7.28 (3H, m, CH), 7.37–7.39 (1H, m, CH), 8.30 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=24.5 (CH₂), 24.9 (CH₂), 25.5 (CH₂), 33.5 (CH₂), 34.5 (CH₂), 50.5, 51.4, 52.6, 53.2, 53.9, 55.4, 58.8 (4MeO, CH₂N, 2CHN), 96.7 (C), 126.2 (C), 127.7 (CH), 129.1 (CH), 129.4 (CH), 129.7 (CH), 132.5 (C), 133.4 (C), 153.3 (C), 154.5 (C), 164.1 (COO), 165.6 (COO), 167.0 (COO), 171.0 (COO). MS: *m/z* (%)=535 (M⁺+1, 12), 534 (M⁺, 6), 529 (30), 475 (85), 236 (50), 200 (15), 177 (10), 125 (90). Anal. Calcd for C₂₆H₃₁ClN₂O₈ (534.98): C, 58.37; H, 5.84, N, 5.24. Found: C, 58.7; H, 5.9; N, 5.3%.

3.2.5. Tetramethyl 1-(4-chlorobenzyl)-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5e). Yellow oil; yield: 0.88 g (83%). IR (KBr) (*ν*_{max}/cm⁻¹): 3490, 2940, 1741, 1694, 1649, 1597, 1525, 1432, 1278, 1231, 1157, 1087, 1013, 773, 730. ¹H NMR (500.1 MHz, CDCl₃): δ=1.53–1.59 (4H, m, CH₂), 1.63–1.70 (4H, m, CH₂), 1.71–1.80 (2H, m, CH₂), 3.08–3.11 (1H, m, CH), 3.58 (3H, s, MeO), 3.67 (3H, s, MeO), 3.74 (3H, s, MeO), 3.95 (3H, s, MeO), 4.49 (1H, d, ²J=15.0 Hz, CH_AH_B), 4.57 (1H, d, ²J=15.0 Hz, CH_AH_B), 5.09 (1H, s, CH), 7.21 (2H, d, ³J=8.4 Hz, CH), 7.33 (2H, d, ³J=8.4 Hz, CH), 8.36 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=24.3 (CH₂), 24.7 (CH₂), 25.3 (CH₂), 32.9 (CH₂), 34.2 (CH₂), 50.4, 51.2, 52.3, 53.0, 55.2, 55.4, 58.2, (4MeO, CH₂N, 2CHN), 96.4 (C), 127.1 (C), 128.7 (2CH), 128.9 (2CH), 133.1 (C), 134.0 (C), 153.0 (C), 153.9 (C), 164.0 (COO), 165.5 (COO), 167.3 (COO), 170.6 (COO). MS: *m/z* (%)=535 (M⁺+1, 8), 534 (M⁺, 2), 529 (30), 475 (80), 236 (50), 200 (25), 177 (10), 125 (90). Anal. Calcd for C₂₆H₃₁ClN₂O₈ (534.98): C, 58.37; H, 5.84, N, 5.24. Found: C, 58.7; H, 5.9; N, 5.3%.

3.2.6. Tetramethyl 4-(cyclohexylamino)-1-(1-naphthylmethyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5f). Yellow powder; mp: 106–108 °C; yield: 0.96 g (87%). IR (KBr) (*ν*_{max}/cm⁻¹): 3475, 3280, 2935, 1744, 1689, 1651, 1597, 1521, 1432, 1359, 1277, 1243, 1196, 1083, 1011, 906, 791, 730. ¹H NMR (500.1 MHz, CDCl₃): δ=1.50–1.58 (4H, m, CH₂), 1.61–1.69 (4H, m, CH₂), 1.72–1.78 (2H, m, CH₂), 3.07–3.09 (1H, m, CH), 3.20 (3H, s, MeO), 3.63 (3H, s, MeO), 3.72 (3H, s, MeO), 3.95 (3H, s, MeO), 4.05 (1H, d, ²J=14.8 Hz, CH_AH_B), 4.14 (1H, d, ²J=14.8 Hz, CH_AH_B), 5.00 (1H, s, CH), 7.37–7.48 (5H, m, CH), 7.81–7.85 (2H, m, CH), 8.22 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=24.5 (CH₂), 24.8 (CH₂), 25.5 (CH₂), 33.1 (CH₂), 34.4 (CH₂), 50.1, 51.3, 52.4, 53.3, 54.1, 57.5, 65.7 (4MeO, CH₂N, 2CHN), 96.6 (C), 122.0 (C), 122.7 (CH), 125.0 (CH), 125.9 (CH), 126.4 (CH), 126.5 (CH), 128.6 (CH), 129.3 (CH), 129.7 (C), 131.2 (C), 133.8 (C), 153.2 (C), 154.3 (C), 164.5 (COO), 165.7 (COO), 166.8 (COO), 171.2 (COO). MS: *m/z* (%)=551 (M⁺+1, 10), 550 (M⁺, 3), 500 (25), 441 (70), 314 (20), 236 (10), 177 (10), 141 (80). Anal. Calcd for C₃₀H₃₄N₂O₈ (550.60): C, 65.44; H, 6.22; N, 5.09. Found: C, 65.7; H, 6.1; N, 5.1%.

3.2.7. Tetramethyl 1-butyl-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5g). Yellow oil; yield: 0.82 g (88%). IR (KBr) (*ν*_{max}/cm⁻¹): 3385, 2940, 1741, 1704, 1649, 1596, 1537, 1433, 1359, 1249, 1144, 1094, 1042, 907, 808, 733, 688. ¹H NMR (500.1 MHz, CDCl₃): δ=0.92 (3H, t, ³J=6.9 Hz, Me), 1.15–1.43 (8H, m, 4CH₂), 1.54–1.74 (4H, m, 2CH₂), 1.76–1.83 (2H, m, CH₂), 3.33–3.39 (1H, m, CH), 3.67 (3H, s, MeO), 3.70 (3H, s, MeO), 3.75 (3H, s, MeO), 3.76–3.90 (2H, m, CH₂N), 3.95 (3H, s, MeO), 5.11 (1H, s, CH), 8.31 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=13.2 (Me), 19.2 (CH₂), 24.4 (CH₂), 24.9 (CH₂), 25.4 (CH₂), 30.5 (CH₂), 33.1 (CH₂), 34.6 (CH₂), 49.1, 50.4, 51.0, 52.3, 52.8, 55.3, 59.1 (4MeO, CH₂N, 2CHN), 95.5 (C), 125.0 (C), 153.6 (C), 154.4 (C), 163.6 (COO), 164.0 (COO), 165.5 (COO), 170.7 (COO). MS: *m/z* (%)=467 (M⁺+1, 9), 452 (20), 452 (80), 236 (10), 133 (20), 177 (10), 55 (90). Anal. Calcd for C₂₃H₃₄N₂O₈ (466.52): C, 59.21; H, 7.35; N, 6.00. Found: C, 59.2; H, 7.3; N, 6.1%.

3.2.8. Tetramethyl 4-(tert-butylamino)-1-(4-methylbenzyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5h). Yellow powder; mp: 102–104 °C; yield: 0.90 g (93%). IR (KBr) (*ν*_{max}/cm⁻¹): 3410, 2935,

1741, 1693, 1647, 1597, 1520, 1432, 1282, 1230, 1140, 1083, 1014, 888, 777. ¹H NMR (500.1 MHz, CDCl₃): δ=1.39 (9H, s, 3 Me), 2.31 (3H, s, Me), 3.58 (3H, s, MeO), 3.65 (3H, s, MeO), 3.71 (3H, s, MeO), 3.91 (3H, s, MeO), 4.49 (1H, d, ²J=15.1 Hz, CH_AH_B), 4.55 (1H, d, ²J=15.1 Hz, CH_AH_B), 4.71 (1H, s, CH), 7.09 (4H, s, CH), 8.35 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=20.97 (Me), 30.1 (3Me), 50.7, 51.2, 51.7, 52.5, 52.8, 60.3, 62.5 (4MeO, CH₂N, CHN, C–N), 88.9 (C), 126.4 (2CH), 127.7 (C), 128.9 (2CH), 132.9 (C), 136.5 (C), 153.5 (C), 163.7 (C), 165.5 (COO), 167.5 (COO), 168.9 (COO), 169.4 (COO) ppm. MS: *m/z* (%)=489 (M⁺+1, 11), 488 (M⁺, 4), 473 (20), 429 (85), 236 (10), 180 (15), 177 (20), 105 (85), 72 (5). Anal. Calcd for C₂₅H₃₂N₂O₈ (488.53): C, 61.46; H, 6.60; N, 5.73. Found: C, 61.7; H, 6.5; N, 5.8%.

3.2.9. Tetramethyl 4-(tert-butylamino)-1-(4-methoxybenzyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5i). Yellow powder; mp: 98–100 °C; yield: 0.90 g (90%). IR (KBr) (*ν*_{max}/cm⁻¹): 3390, 2955, 1740, 1698, 1579, 1510, 1433, 1365, 1250, 1171, 1107, 1031, 972, 813, 780, 731. ¹H NMR (500.1 MHz, CDCl₃): δ=1.39 (9H, s, 3Me), 3.58 (3H, s, MeO), 3.65 (3H, s, MeO), 3.70 (3H, s, MeO), 3.78 (3H, s, MeO), 3.91 (3H, s, MeO), 4.35 (1H, d, ²J=14.5 Hz, CH_AH_B), 4.43 (1H, d, ²J=14.5 Hz, CH_AH_B), 4.71 (1H, s, CH), 6.82 (2H, d, ³J=8.3 Hz, CH), 7.15 (2H, d, ³J=8.3 Hz, CH), 8.35 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=30.1 (3Me), 50.7, 51.0, 51.7, 52.5, 52.8, 55.1, 60.2, 62.5 (5MeO, CH₂N, CHN, C–N), 88.9 (C), 113.7 (2CH), 114.5 (C), 127.7 (2CH), 127.9 (C), 153.6 (C), 158.7 (C), 163.6 (C), 165.5 (COO), 167.5 (COO), 168.9 (COO), 169.4 (COO). MS: *m/z* (%)=505 (M⁺+1, 8), 504 (M⁺, 5), 473 (20), 445 (80), 236 (20), 196 (10), 177 (10), 121 (90), 72 (5). Anal. Calcd for C₂₅H₃₂N₂O₉ (504.53): C, 59.52; H, 6.39; N, 5.55. Found: C, 59.5; H, 6.3; N, 5.6%.

3.2.10. Tetramethyl 4-(cyclohexylamino)-1-(4-methoxyphenyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5j). Yellow powder; mp: 107–109 °C; yield: 0.87 g (84%). IR (KBr) (*ν*_{max}/cm⁻¹): 3381, 2950, 1735, 1690, 1575, 1540, 1430, 1409, 1293, 1215, 1146, 1080, 1010, 980, 610, 725. ¹H NMR (500.1 MHz, CDCl₃): δ=1.12–1.32 (4H, m, CH₂), 1.53–1.57 (4H, m, CH₂), 1.63–1.67 (2H, m, CH₂), 3.18–3.22 (1H, m, CH), 3.60 (3H, s, MeO), 3.62 (3H, s, MeO), 3.63 (3H, s, MeO), 3.65 (3H, s, MeO), 3.81 (3H, s, MeO), 5.46 (1H, s, CH), 6.84 (2H, d, ³J=8.5 Hz, CH), 7.26 (2H, d, ³J=8.5 Hz, CH), 8.37 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=24.6 (CH₂), 24.9 (CH₂), 25.6 (CH₂), 33.2 (CH₂), 34.5 (CH₂), 50.8, 51.5, 52.7, 52.8, 55.4, 55.7, 63.6 (5MeO, 2CHN), 99.0 (C), 114.3 (2CH), 115.1 (C), 127.1 (2CH), 135.6 (C), 152.6 (C), 152.8 (C), 159.1 (C), 163.7 (COO), 165.5 (COO), 167.1 (COO), 171.4 (COO). MS: *m/z* (%)=517 (M⁺+1, 9), 516 (M⁺, 4), 485 (20), 457 (60), 177 (10). Anal. Calcd for C₂₆H₃₂N₂O₉ (516.54): C, 60.46; H, 6.24; N, 5.42. Found: C, 61.2; H, 6.4; N, 5.3%.

3.2.11. Tetramethyl 4-(tert-butylamino)-1-(4-nitrophenyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5k). Yellow powder; mp: 110–112 °C; yield: 0.62 g (59%). IR (KBr) (*ν*_{max}/cm⁻¹): 3395, 2935, 1755, 1699, 1580, 1554, 1433, 1415, 1297, 1225, 1154, 1075, 1011, 984, 613, 737. ¹H NMR (500.1 MHz, CDCl₃): δ=1.49 (9H, s, 3Me), 3.69 (3H, s, MeO), 3.75 (3H, s, MeO), 3.81 (3H, s, MeO), 3.86 (3H, s, MeO), 5.92 (1H, s, CH), 6.78 (2H, d, ³J=8.9 Hz, CH), 6.85 (2H, d, ³J=8.9 Hz, CH), 8.38 (1H, br s, NH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ=28.3 (3Me), 52.2, 51.4, 52.7, 52.9, 53.1, 53.2 (4MeO, 2CHN), 95.0 (C), 121.7 (CH), 122.3 (CH), 124.5 (CH), 124.8 (CH), 127.6 (C), 142.5 (C), 148.1 (C), 156.1 (C), 157.3 (C), 163.5 (COO), 163.9 (COO), 164.1 (COO), 165.5 (COO). MS: *m/z* (%)=532 (M⁺+1, 10), 531 (M⁺, 8), 500 (20), 472 (65), 231 (10). Anal. Calcd for C₂₅H₂₉N₃O₁₀ (531.51): C, 56.49; H, 5.50; N, 7.91. Found: C, 56.7; H, 5.4; N, 7.8%.

3.2.12. 2,3,5,6-Tetraethyl 1-benzyl-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5l). Yellow powder; mp: 112–114 °C; yield: 0.76 g (69%). IR (KBr) (*ν*_{max}/cm⁻¹): 3445, 2930, 1745, 1688, 1648, 1581, 1525, 1427, 1354, 1288, 1233, 1119, 1079, 801, 789, 699.

^1H NMR (500.1 MHz, CDCl_3): δ =1.04 (3H, t, 3J =7.1 Hz, Me), 1.17 (3H, t, 3J =7.0 Hz, Me), 1.26 (3H, t, 3J =7.1 Hz, Me), 1.32 (3H, t, 3J =7.0 Hz, Me), 1.53–1.59 (4H, m, 2CH_2), 1.63–1.70 (4H, m, 2CH_2), 1.75–1.83 (2H, m, CH_2), 3.17–3.22 (1H, m, CH), 4.05 (2H, q, 3J =7.1 Hz, CH_2O), 4.17 (2H, q, 3J =7.0 Hz, CH_2O), 4.23 (2H, q, 3J =7.1 Hz, CH_2O), 4.33 (2H, q, 3J =7.0 Hz, CH_2O), 4.56 (1H, d, 2J =15.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.63 (1H, d, 2J =15.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 5.41 (1H, s, CH), 6.88 (2H, d, 3J =7.5 Hz, CH), 7.23–32 (3H, m, CH), 8.29 (1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =13.8 (Me), 14.0 (Me), 14.2 (Me), 14.4 (Me), 24.6 (CH_2), 24.9 (CH_2), 25.1 (CH_2), 33.1 (CH_2), 34.3 (CH_2), 48.6, 55.1, 56.2, 58.9, 60.3, 61.4, 62.4 (4OCH_2 , CH_2N , 2CHN), 96.7 (C), 125.8 (C), 127.9 (2CH), 128.2 (CH), 128.7 (2CH), 134.9 (C), 153.7 (C), 154.2 (C), 161.8 (COO), 163.9 (COO), 165.4 (COO), 170.7 (COO) ppm. MS: m/z (%)=557 (M^++1 , 10), 556 (M^+ , 7), 513 (37), 483 (16), 91 (52). Anal. Calcd for $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_8$ (556.65): C, 64.73; H, 7.24; N, 5.03. Found: C, 64.6; H, 7.4; N, 5.5.

3.3. Compounds 5m–p: general procedure

To a stirred solution of amine **3** (2 mmol) and the first acetylenic ester (2 mmol) in CH_2Cl_2 (10 mL), was added the isocyanide **1** (2 mmol) and the second acetylenic ester (2 mmol) at -5°C . The mixture was allowed to reach rt. After completion of the reaction (6–12 h; TLC (AcOEt/hexane 1:4) monitoring), the solvent was evaporated, and the residue was purified by column chromatography (silica gel (230–400 mesh; Merck), hexane/AcOEt 5:1): pure product.

3.3.1. 2,3-Diethyl 5,6-dimethyl 1-benzyl-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5m). Yellow powder; mp: 103–105 $^\circ\text{C}$; yield: 0.88 g (83%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3455, 2925, 1751, 1692, 1659, 1585, 1515, 1426, 1363, 1281, 1231, 1110, 1081, 809, 772, 691. ^1H NMR (500.1 MHz, CDCl_3): δ =1.04 (3H, t, 3J =7.1 Hz, Me), 1.18 (3H, t, 3J =7.1 Hz, Me), 1.52–1.57 (4H, m, 2CH_2), 1.65–1.71 (4H, m, 2CH_2), 1.75–1.81 (2H, m, CH_2), 3.17–3.19 (1H, m, CH), 3.72 (3H, s, MeO), 3.94 (3H, s, MeO), 4.07 (2H, q, 3J =7.1 Hz, CH_2O), 4.48 (2H, q, 3J =7.1 Hz, CH_2O), 4.46 (1H, d, 2J =15.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.64 (1H, d, 2J =15.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 5.44 (1H, s, CH), 7.26–7.29 (3H, m, CH), 7.35 (2H, d, 3J =7.0 Hz, CH), 8.34 (1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =13.9 (Me), 14.1 (Me), 24.6 (CH_2), 24.9 (CH_2), 25.6 (CH_2), 33.1 (CH_2), 34.4 (CH_2), 51.3, 53.1, 55.4, 56.3, 58.3, 58.9, 61.6 (2OCH_2 , 2MeO , CH_2N , 2CHN), 96.2 (C), 125.8 (C), 127.9 (2CH), 128.4 (CH), 128.7 (2CH), 134.8 (C), 153.3 (C), 154.4 (C), 164.4 (COO), 165.8 (COO), 167.1 (COO), 170.5 (COO) ppm. MS: m/z (%)=529 (M^++1 , 25), 528 (M^+ , 4), 497 (65), 469 (15), 437 (80), 264 (20), 91 (40). Anal. Calcd for $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_8$ (528.59): C, 63.62; H, 6.86; N, 5.30. Found: C, 63.4; H, 6.9; N, 5.4.

3.3.2. 2,3-Diethyl 5,6-dimethyl 4-(cyclohexylamino)-1-(4-methoxybenzyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5n). Yellow powder; mp: 108–110 $^\circ\text{C}$; yield: 0.89 g (80%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3450, 2941, 1741, 1690, 1645, 1589, 1521, 1430, 1359, 1279, 1240, 1081, 811, 765, 690. ^1H NMR (500.1 MHz, CDCl_3): δ =1.31 (3H, t, 3J =7.1 Hz, Me), 1.38 (3H, t, 3J =7.1 Hz, Me), 1.53–1.57 (4H, m, CH_2), 1.62–1.70 (4H, m, CH_2), 1.76–1.83 (2H, m, CH_2), 3.33–3.39 (1H, m, CH), 3.54 (3H, s, MeO), 3.65 (3H, s, MeO), 3.81 (3H, s, MeO), 4.18 (2H, q, 3J =7.1 Hz, CH_2O), 4.22 (2H, q, 3J =7.1 Hz, CH_2O), 4.48 (1H, d, 2J =15.5 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.56 (1H, d, 2J =15.5 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 5.15 (1H, s, CH), 6.87 (2H, d, 2J =8.6 Hz, CH), 7.19 (2H, d, 2J =8.6 Hz, CH), 8.36 (1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =13.8 (Me), 14.1 (Me), 24.6 (CH_2), 24.9 (CH_2), 25.6 (CH_2), 31.4 (CH_2), 33.1 (CH_2), 50.5, 51.4, 55.1, 55.2, 55.8, 58.2, 60.4, 62.4 (3MeO , $2\text{CH}_2\text{O}$, CH_2N , 2CHN), 96.1 (C), 114.1 (2CH), 124.9 (C), 129.4 (2CH), 131.9 (C), 154.0 (C), 154.2 (C),

158.1 (C), 159.6 (COO), 163.9 (COO), 164.3 (COO), 171.1 (COO) ppm. MS: m/z (%)=559 (M^++1 , 25), 558 (M^+ , 3), 527 (20), 499 (80), 264 (10), 191 (10), 186 (20), 121 (90). Anal. Calcd for $\text{C}_{29}\text{H}_{38}\text{N}_2\text{O}_9$ (558.62): C, 62.35; H, 6.86; N, 5.01. Found: C, 62.0; H, 6.7; N, 5.1.

3.3.3. 2,3-Diethyl 5,6-dimethyl 1-(2-chlorobenzyl)-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5o). Yellow oil; yield: 0.95 g (85%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3360, 2930, 1745, 1705, 1665, 1592, 1529, 1434, 1282, 1231, 1140, 1013, 794, 753. ^1H NMR (500.1 MHz, CDCl_3): δ =1.09 (3H, t, 3J =7.1 Hz, CH_3), 1.22 (3H, t, 3J =7.1 Hz, CH_3), 1.26–1.35 (4H, m, CH_2), 1.46–1.57 (4H, m, CH_2), 1.67–1.74 (2H, m, CH_2), 3.14–3.16 (1H, m, CH), 3.74 (3H, s, MeO), 3.94 (3H, s, MeO), 4.10 (2H, q, 3J =7.1 Hz, CH_2O), 4.21 (2H, q, 3J =7.1 Hz, CH_2O), 4.70 (2H, s, CH_2), 5.12 (1H, s, CH), 7.25–7.28 (2H, m, CH), 7.30–7.32 (1H, m, CH), 7.37–7.39 (1H, m, CH), 8.38 (1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =14.0 (Me), 14.1 (Me), 24.6 (CH_2), 24.9 (CH_2), 25.5 (CH_2), 33.2 (CH_2), 34.5 (CH_2), 51.4, 53.2, 53.8, 55.4, 58.7, 59.0, 61.5 (2OCH_2 , 2MeO , CH_2N , 2CHN), 96.8 (C), 127.2 (CH), 129.3 (CH), 129.5 (CH), 129.7 (CH), 126 (C), 133.5 (C), 132.6 (C), 153.2 (C), 154.5 (C), 164.2 (COO), 165.7 (COO), 166.8 (COO), 170.5 (COO) ppm. MS: m/z (%)=564 (M^++1 , 25), 563 (M^+ , 3), 532 (35), 504 (75), 438 (85), 299 (50), 264 (10), 125 (5). Anal. Calcd for $\text{C}_{28}\text{H}_{35}\text{ClN}_2\text{O}_8$ (563.04): C, 59.70; H, 6.27; N, 4.98. Found: C, 59.5; H, 6.2; N, 4.9%.

3.3.4. 2,3-Dimethyl 5,6-diethyl 1-benzyl-4-(cyclohexylamino)-1,2-dihydropyridine-2,3,5,6-tetracarboxylate (5p). Yellow powder; mp: 111–113 $^\circ\text{C}$; yield: 0.75 g (71%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3436, 2921, 1744, 1682, 1668, 1571, 1507, 1412, 1345, 1283, 1255, 1115, 1076, 825, 789, 677. ^1H NMR (500.1 MHz, CDCl_3): δ =1.25 (3H, t, 3J =7.1 Hz, Me), 1.32 (3H, t, 3J =7.0 Hz, Me), 1.52–1.57 (4H, m, 2CH_2), 1.62–1.70 (4H, m, 2CH_2), 1.73–1.81 (2H, m, CH_2), 3.18–3.23 (1H, m, CH), 3.52 (3H, s, MeO), 3.57 (3H, s, MeO), 4.18 (2H, q, 3J =7.1 Hz, CH_2O), 4.39 (2H, q, 3J =7.0 Hz, CH_2O), 4.54 (1H, d, 2J =15.5 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.62 (1H, d, 2J =15.5 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 5.13 (1H, s, CH), 7.25 (2H, d, 3J =7.0 Hz, CH), 7.29–7.38 (2H, m, CH), 8.33 (1H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ =13.8 (Me), 14.2 (Me), 24.9 (CH_2), 25.2 (CH_2), 25.6 (CH_2), 33.1 (CH_2), 34.2 (CH_2), 50.5, 52.4, 55.1, 56.3, 58.6, 60.4, 62.4 (2OCH_2 , 2MeO , CH_2N , 2CHN), 96.3 (C), 121.8 (C), 125.1 (C), 127.8 (2CH), 128.2 (CH), 128.7 (2CH), 134.8 (C), 153.9 (C), 163.8 (COO), 164.5 (COO), 165.1 (COO), 171.1 (COO) ppm. MS: m/z (%)=529 (M^++1 , 9), 528 (M^+ , 5), 497 (35), 469 (11), 264 (20), 91 (45). Anal. Calcd for $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_8$ (528.59): C, 63.62; H, 6.86; N, 5.30. Found: C, 63.4; H, 7.0; N, 5.4.

References and notes

- Lavilla, R. J. *Chem. Soc., Perkin Trans. 1* **2002**, 1141.
- Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. J. *Am. Chem. Soc.* **2001**, 123, 11829.
- Chai, L.; Zhao, Y.; Sheng, Q.; Liu, Z.-Q. *Tetrahedron Lett.* **2006**, 47, 9283.
- Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, 82, 233.
- Comins, D. L.; Hong, H.; Salvador, J. M. J. *Org. Chem.* **1991**, 56, 7197.
- Bennasar, M. L.; Roca, R.; Moneris, M.; Juan, C.; Bosch, J. *Tetrahedron* **2002**, 58, 8099.
- Brunner, B.; Stogaitis, N.; Lautens, M. *Org. Lett.* **2006**, 8, 3473.
- Ugi, I.; Dömling, A.; Werner, B. J. *Heterocycl. Chem.* **2000**, 37, 647.
- Kappe, C. O. *Eur. J. Med. Chem.* **2000**, 35, 1043.
- Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, 44, 2521.
- Jones, G. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vol. 2, pp 482.
- Yavari, I.; Khalili, G.; Mirzaei, A. *Tetrahedron Lett.* **2010**, 51, 1190.
- Yavari, I.; Mirzaei, A.; Moradi, L.; Khalili, G. *Tetrahedron Lett.* **2010**, 51, 396.
- Yavari, I.; Soufi, S.; Sirouspour, M.; Bayat, M. J. *Synlett* **2009**, 1921.
- Yavari, I.; Piltan, M.; Moradi, L. *Tetrahedron* **2009**, 65, 2067.
- Burnett, A.M.N.; Johnson, C.K.; 'Oak Ridge National Laboratory Report ORNL-6895', 1996.