Approaches to Combinatorial Synthesis of Heterocycles: A Solid-Phase Synthesis of 1,4-Dihydropyridines

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N-Immobilized enamino esters **2** derived from amine-functionalized PAL or Rink polystyrene resins react with preformed 2-arylidene β-keto esters or directly with β-keto esters and aldehydes to afford, upon trifluoroacetic acid cleavage, 1,4-dihydropyridine (DHP) derivatives in good yields. The mechanism of this transformation on solid support has been studied using ^{13}C NMR and IR spectroscopies. This new solid-phase synthesis has been applied to the preparation of several bioactive DHPs and is designed to be amenable to the "split and pool" protocol for combinatorial library synthesis.

Introduction

Combinatorial chemistry has recently emerged as a powerful tool for drug discovery.[1] While methods for the generation of combinatorial libraries of peptides and oligonucleotides are now well established, preparation of libraries of small organic molecules remains a relatively unexplored and rapidly evolving area of research.[2] Significantly, it is this aspect of combinatorial chemistry which may hold the most promise for efficient discovery of nonpeptidic drug candidates. An important feature of combinatorial chemistry is the synthesis of compounds on solid supports, allowing Furka's[3] "split and pool" methodology to be employed for library construction. Thus, a challenging prerequisite to combinatorial drug discovery[1] is to develop solid-phase syntheses of biologically active molecules on solid supports[4] and to explore the utility of such synthetic methodologies for preparation of combinatorial libraries. In this communication, we report our findings toward the development of a general method for the solid-phase synthesis of 1,4-dihydropyridines (DHPs).

The DHP nucleus is common to numerous bioactive compounds which include various vasodilator, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents.[5] DHPs have found commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as Nifedipine (**7a**),[6a] Nitrendipine (**7b**),[6b] and Nimodipine (**7c**).[6c] Second-generation calcium antagonists include DHP derivatives with improved bioavailability, tissue selectivity, and/or stability,

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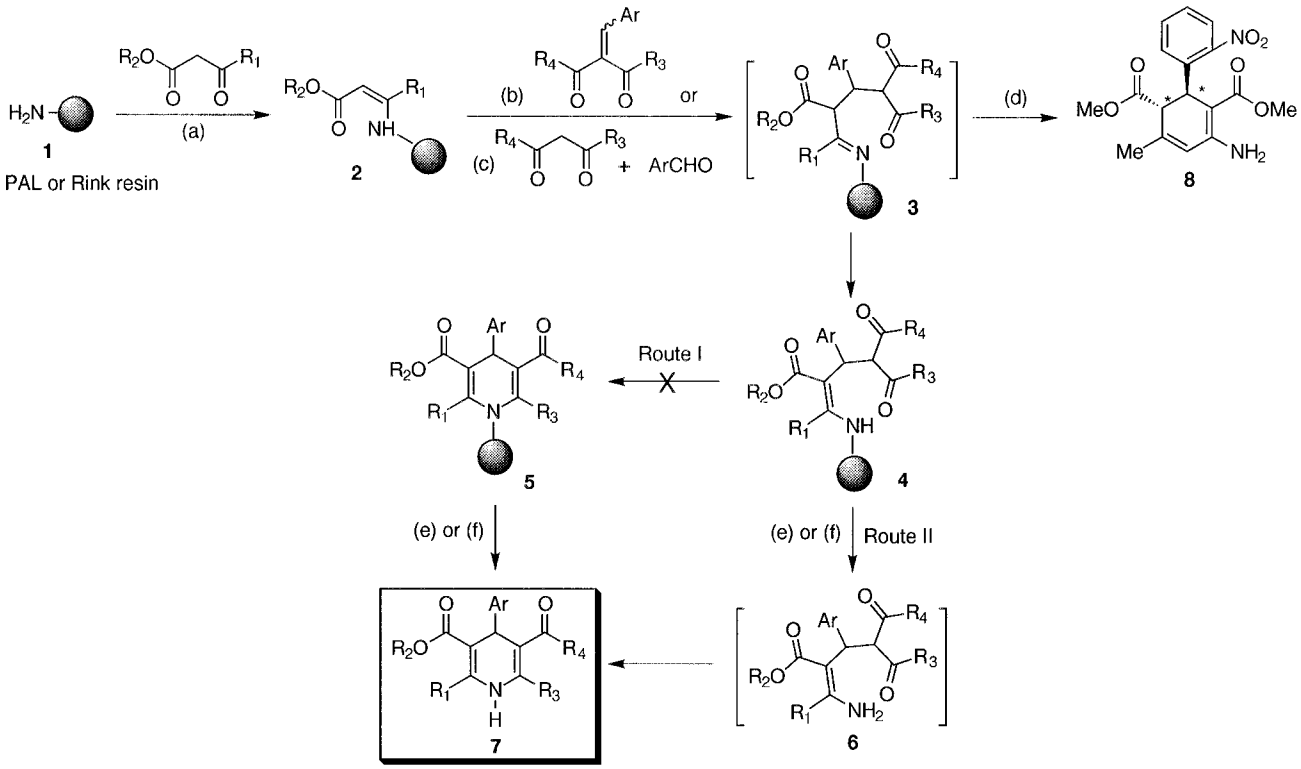
Scheme 1[a]



[a] Key: (a) $R_1COCH_2CO_2R_2$, 4A molecular sieves, CH_2Cl_2, rt. (b) $ArCH{=}C(COR_3)CO_2R_4$, 4A molecular sieves, pyridine, 45 °C. (c) $R_3COCH_2CO_2R_4$ or $MeCOCH_2COMe$, ArCHO, 4A molecular sieves, pyridine, 45 °C. (d) 4A molecular sieves, EtOH, 80 °C (For $R_1 = R_2 = R_3 = R_4 = Me$, Ar = 2-$O_2NC_6H_4$). (e) 95% TFA/THF. (f) 3% TFA/CH_2Cl_2.

such as the antihypertensive/antianginal drugs Elgodipine,[6d] Furnidipine,[6e,f] Darodipine,[6g] Pranidipine,[6h] Lemildipine,[6i] Dexniguldipine,[6j] Lacidipine,[6k] and Benidipine,[6l] Following discovery of the compound Bay K 8644,[6m] a number of DHP calcium agonists have been introduced as potential drug candidates for treatment of congestive heart failure.[6n,o] Among DHPs with other types of bioactivity, Cerebrocrast[6p] has been recently introduced as a neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered.[6r] These recent examples highlight the level of ongoing interest toward new DHP derivatives and have prompted us to explore this pharmacophoric scaffold in a combinatorial format as a fertile source of bioactive molecules.

Results and Discussion

The reported synthesis of 1,4-dihydropyridines on solid supports is based on a two- or three-component cyclocondensation of enamino esters with 2-arylidene β-keto esters or β-keto esters and aldehydes, respectively (cf. Scheme 1).[5b,c] As a model study, the solid-phase synthesis of the calcium channel blocker drug Nifedipine (**7a**) was undertaken. Thus, methyl acetoacetate was reacted with polystyrene-based acid-cleavable PAL[7] or Rink[8] amine resins to afford the methyl aminocrotonate **2** immobilized on a solid support (Scheme 1; $R_1 = R_2 = Me$). Next, the N-tethered enamino ester **2** ($R_1 = R_2 = Me$) was reacted with preformed methyl 2-(2-nitrobenzylidene)acetoacetic ester or directly with 2-nitrobenzaldehyde and methyl acetoacetate in pyridine, followed by cleavage of the final product **7a** from resin with trifluoroacetic acid (TFA; Scheme 1, Table 1).

Table 1. 1,4-Dihydropyridine Derivatives 7 (Scheme 1)

	derivative					yield
compound	Ar	R_1	R_2	R_3	R_4	(%)[a]
7a[b]	*o*-$NO_2C_6H_4$	Me	Me	Me	OMe	65[c] (70)[d]
7b[e]	*m*-$NO_2C_6H_4$	Me	Me	Me	OEt	75[d]
7c[f]	*m*-$NO_2C_6H_4$	Me	^{i}Pr	Me	$O(CH_2)_2OMe$	78[d]
7d	*p*-$NO_2C_6H_4$	Me	Me	Me	Me	75[d]
7e[g]	*p*-$NO_2C_6H_4$	$^{13}CH_3$	Et	Me	OMe	70[c]
7f	*p*-$NO_2C_6H_4$	Et	Me	Ph	OEt	70[d]
7g	*p*-NCC_6H_4	Me	Me	Me	OMe	74[d]
7h	Ph	Me	Me	Me	OAll	72[h]
7i	4-Py	Me	Me	Me	OMe	75[d]

[a] Yields are based on loading of the starting resin. [b] Nifedipine. [c] Prepared by two-component condensation with $ArCH{=}C(COR_3)$-CO_2R_4 using PAL resin. [d] Prepared by three-component condensation using Rink resin. [e] Nitrendipine. [f] Nimodipine. [g] Contains ^{13}C C-3 labeling. [h] Prepared by two-component condensation with $PhCH{=}C(COMe)CO_2All$ using Rink resin.

Following the synthesis of **7a** on solid supports, a set of related compounds (**7b-i**) was prepared using an analogous synthetic protocol. Specifically, this involved (i) preparation of the immobilized N-tethered enamino component **2**, (ii) condensation of the latter with either 2-benzylidene β-keto ester or β-keto ester and aldehyde,

(7) PAL resin: polystyrene resin possessing amine terminal linker derived from 5-[4-(aminomethyl)-3,5-dimethoxy)phenoxy]valeric acid. Albericio, F.; et al. *J. Org. Chem.* **1990**, *55*, 3730.

(8) Rink resin: polystyrene resin possessing amine terminal linker derived from 4-[((2′,4′-dimethoxyphenyl)amino)methyl]phenol. Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787. While this reaction proceeds faster with less sterically hindered PAL resin, the Rink support is preferable in most cases due to milder cleavage conditions from this superacid-labile resin (3% TFA in DCM, 45 min, as opposed to 95% TFA in THF, 1.5 h, required for the cleavage from PAL resin).

(9) Reverse phase HPLC purity of the crude Nifedipine thus obtained was ca. 70−80% (detection at 220 nM).

and (iii) TFA cleavage to afford the desired DHP **7** (Scheme 1, Table 1). As evident, the solid-phase synthesis appears to tolerate variations of both ester (substituents R_1, R_2, R_3, R_4) and aromatic (or heteroaromatic) groups in β-keto esters or aldehydes, respectively. β-Diketones can also be successfully employed at the second step of these Hantzsch-type reactions on solid supports, as exemplified by the synthesis of compound **7d** from the Rink resin N-tethered methyl aminocrotonate **2** ($R_1 = R_2$ = Me) and acetylacetone (Scheme 1, Table 1).[10]

Useful insight into the mechanism of the DHP formation was obtained during optimization of the solid-phase synthesis. Thus, the presence of pyridine in the reaction media is essential for successful transformation of immobilized enamino esters **2** into DHPs **7**. For example, our attempted preparation of **7a** by a standard Hantzsch reaction[5b] of enamino ester **2** ($R_1 = R_2$ = Me) N-tethered to the PAL resin with methyl 2-(2-nitrobenzylidene)-acetoacetic ester in refluxing ethanol failed to afford the expected product **7a**. Instead, 2-amino-1,3-cyclohexadiene derivative **8** was isolated as a principal product (yield ca. 60%), resulting from apparent cyclocondensation of an intermediate of type **3** on the α-methyl group of the enamine component (R_1 = Me; see Scheme 1).[11] The presence of pyridine[12] probably facilitates isomerization of intermediate imines **3** into thermodynamically more stable conjugated enamines of type **4**, thus preventing undesired carbon-to-carbon cyclocondensation. Final cleavage and isolation of products was typically performed under inert atmosphere to avoid the conversion of readily oxidizable DHPs **7** into the corresponding pyridines.[5c]

In principle, DHPs of type **7** could be formed on solid supports *via* cyclic intermediate **5** (route I in Scheme 1) or, alternatively, *via* acyclic adduct **4**. The latter under TFA cleavage conditions would release the penultimate enamino ester **6**, which can spontaneously cyclize in solution to afford the product **7** (route II). Reaction of ^{13}C-labeled immobilized ethyl aminocrotonate **2** (derived from PAL or Rink amine resins with ethyl [2,4-$^{13}C_2$]-acetoacetate) with methyl 2-(*p*-nitrobenzylidene)acetoacetate indicated no formation of the N-tethered 1,4-dihydropyridine of type **5** ($R_1 = {}^{13}CH_3$, R_2 = OEt, $R_3 = R_4$ = Me, ^{13}C C-3 labeling), as evidenced by the absence of an expected 1,4-dihydropyridine C-3 resonance at ca. 103 ppm in gel-phase ^{13}C NMR spectra of resins.[13] Instead, two signals at δ 90.3−92.9 ppm were observed for both PAL- and Rink-supported products. These can be tentatively assigned to C-2 enamino ester resonances of *E*- and *Z*-forms of an intermediate of type **4e** ($^{13}CH_3$ resonances at δ 15.0−15.3 ppm were also detected). Subsequent TFA cleavage of both PAL- and Rink-tethered intermediates resulted in isolation of the expected 1,4-dihydropyridine **7e** (Table 1; δ ^{13}C-3 103.3 ppm, δ $^{13}CH_3$ 19.7 ppm). In addition, the IR spectrum of the Rink-supported compound **4e** in KBr displayed a signal of the unconjugated ester group at 1735 cm^{-1} (along with other carbonyl absorbances at 1715 cm^{-1}). By contrast, the IR spectrum of the 1,4-dihydropyridine **7e** in KBr displayed only the expected signal of a conjugated ester carbonyl at 1705 cm^{-1}. These data suggest that the solid-phase synthesis of 1,4-dihydropyridines **7** probably proceeds *via* immobilized acyclic intermediates of type **4**, although the alternative route *via* N-tethered heterocycles **5** cannot be excluded in all cases (cf. preparations of N-substituted 1,4-dihydropyridine derivatives[11−13]).

Conclusions

Until recently, the majority of reported heterocyclic syntheses on a solid support were based on amide bond-forming transformations utilizing amino acids.[1b,j,14,15] Our route to 1,4-dihydropyridines is based on non-amide heterocyclic chemistry and does not require the use of amino acid building blocks. Significantly, this synthesis enables preparation of diverse 1,4-dihydropyridine derivatives **7** which encompasses various compounds reported in connection with structure−activity relationship studies for calcium channel blocking 1,4-dihydropyridines.[5a,b,d,e] The compounds that can be conveniently prepared by this solid-phase synthesis (see Table 1) include potent cardiovascular drugs Nifedipine (**7a**), Nitrendipine (**7b**), and Nimodipine (**7c**).

The presently described method enables simple and expedient solid-phase syntheses of 1,4-dihydropyridines in good overall yields and is well suited for the combinatorial split and pool protocols.[1] In addition, solid-phase-supported functionalized enamines of the type **1** are also convenient precursors for combinatorial syntheses of

(10) β-Diketones can also be employed at the first step of the synthesis. However, the formation of corresponding N-tethered enamino ketones (cf. **2**, Scheme 1) required harsher reaction conditions (e.g., refluxing benzene), and the HPLC purity of resulted crude DHPs was significantly lower (ca. 40−60%). The condensation of the immobilized enamino ester **2** ($R_1 = R_2$ = Me) with benzoylacetone and 4-nitrobenzaldehyde resulted in isolation of two regioisomeric DHPs [cf. **7**; $R_1 = R_2$ = Me, R_3 = Me (Ph), R_4 = Ph (Me)].

(11) Similar byproducts in preparations of N-substituted 1,4-dihydropyridines have recently been isolated: Feliciano, A. S.; Caballero, E.; Pereira, J. A. P.; Puebla, P. *Tetrahedron Lett.* **1991**, *47*, 6503. In agreement with spectral data reported for compounds of this type by Feliciano et al., the lack of coupling of H-1 and H-2 protons suggests the relative *trans*-configuration between the aryl and 1-(methoxycarbonyl) group in compound **8**. The ^{1}H NMR spectrum of compound **8** in $CDCl_3$ displayed two Me ester resonances (δ 3.48 and 3.76 ppm) along with a Me-6 signal at 1.92 ppm involved in a coupling (J = 1.5 Hz) with an olefinic H-5 proton (δ 5.88 ppm). The ^{13}C NMR spectrum of **8** displayed the characteristic signal of the C-3 carbon of the enamino ester fragment at 89.0 ppm. Among other attempted experiments, this reaction in the presence of 5 mol % of Py, Ni(acac)$_2$, or TsOH also afforded predominantly compound **8**, and no Nifedipine was obtained from transformation in the presence of DIEA in DMF.

(12) Three-component condensations of an aldehyde, β-keto ester, and benzylamine hydrochloride in Py at ca. 100 °C were previously reported to afford DHP derivatives in low to moderate yields, and no possible mechanism of the py action in these transformations has been discussed: (a) Bossert, F.; Elberfeld, W.; Vater, W. U.S. Patent 3,647,-807, March 7, 1972. (b) Funer, A. V.; Strehl, P.; Schubel-Hopf, U.; Ebbinghaus, D.; Finck, D. German Patent 2,908,738, March 6, 1979.

(13) An example of preparation of N-immobilized 1,4-dihydronicotinamide (NADH) from nicotinamide with Merrifield resin followed by reduction of the intermediate pyridinium salt has been previously reported (see publications below and refs therein): (a) Lindsay, A. S.; Hunt, S. E.; Savill, N. G. *Polymer* **1966**, *7*, 479. (b) Dupas, G.; Decormeille, A.; Bourguignon, J.; Queguiner, G. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4492. (c) Dupas, G.; Decormeille, A.; Bourguignon, J.; Queguiner, G. *Tetrahedron Lett.* **1989**, *45*, 2579. The formation of polymer-grafted NADH in the latter case has been judged on the basis of combustion analysis and reductive properties of the resulting material. In addition, the synthesis of immobilized 1,4-dihydro-2,6-dimethyl-3,5-bis(ethoxycarbonyl)pyridine from amine-functionalized resin with diethyl 3,5-diacetylhexane-1,6-dioate has been claimed on the basis of IR spectra of the condensation product obtained: (d) Zicmanis, A.; Nalivaiko, R. E. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1982**, 351. No DHP derivatives have been released from the solid support in these cases.[13a−d]

(14) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588.

(15) Solid-phase synthesis of isoxazolines and tetrahydrofurans *via* cycloaddition chemistry has also been reported: (a) Beebe, X.; Kurth, M. J.; Schore, N. E. *J. Am. Chem. Soc.* **1992**, *114*, 10061. (b) Beebe, X.; Schore, N. E.; Kurth, M. *J. Org. Chem.* **1995**, *60*, 4196. (c) Beebe, X.; Chiappari, C. L.; Olmstead, M. M.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1995**, *60*, 4204.

other bioactive heterocyclic targets. These efforts are currently in progress and will be reported in due course.

Experimental Section

General Considerations. The ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with TMS as the internal standard. IR spectra were recorded in KBr. Low-resolution mass spectra were obtained using the ESI technique, while high-resolution mass spectra were obtained using the FAB technique. HPLC analysis and purification were performed using 5 μm 3.9 × 150 mm reverse phase column (gradient from 100% of the aqueous 0.1% TFA (eluent A) to 40% eluent A−60% of 0.1% TFA in MeCN (eluent B) for compound **7i**, and gradient from 90% eluent A−10% eluent B to 30% eluent A−70% eluent B over 30 min in all other cases; flow rate 1.5 mL/min). All starting reagents were of the best grade available (Aldrich, Fluka, Lancaster) and were used without purification. A commercial specimen of Nifedipine (**7a**) was available from CalBiochem-NovaBiochem, whereas Nitrendipine (**7b**) and Nimodipine (**7c**) were obtained from Research Biochemicals Inc. Resins Fmoc-Rink and Fmoc-PAL were obtained from Advanced Chemtech. 2-Benzylidene keto esters were prepared according to ref 16. Spectral and/or HPLC properties for known 1,4-dihydropyridine derivatives **7a-c,g,i** were found to be in agreement with those for the previously reported compounds (see below).

General Procedure for Preparation of N-Immobilized Enamino Esters 2. An appropriate Fmoc-protected resin (0.23 mmol) is vortexed with 10% piperidine in DMF (5 mL) for 40 min. The resulting amine resin **1** is filtered, washed sequentially with DMF (4 × 7 mL), MeOH (3 × 7 mL), $CHCl_3$ (3 × 7 mL), and diethyl ether (7 mL) and dried in a vacuum desiccator (rt, 0.5 Torr). Resin **1** thus obtained is vortexed with an appropriate β-keto ester (6.9 mmol), and 4A molecular sieves (1 g) in CH_2Cl_2 (4 mL) for 3 days at rt. The product **2** is filtered, washed sequentially with $CHCl_3$ (3 × 7 mL), ethyl acetate (3 × 7 mL), and diethyl ether (7 mL), and dried in a vacuum desiccator (rt, 0.5 Torr).

Methyl [2,4-$^{13}C_2$]Aminocrotonate (2) N-Immobilized on PAL Resin: prepared as described above from commercial Fmoc-PAL resin (100 mg, 0.09 mmol) and $^{13}C_2$-2,4 ethyl acetoacetate (356 mg, 2.7 mmol). Fast gel-phase ^{13}C NMR (C_6D_6) δ: 19.7 ($^{13}CH_3$), 82.6 (^{13}CH═).

Methyl [2,4-$^{13}C_2$]Aminocrotonate (2) N-Immobilized on Rink Resin: prepared as described above from commercial Fmoc-Rink resin (200 mg, 0.09 mmol) and ethyl [2,4-$^{13}C_2$]-acetoacetate (356 mg, 2.7 mmol). Fast gel-phase ^{13}C NMR (C_6D_6) δ: 18.3 ($^{13}CH_3$), 83.4 (^{13}CH═).

General Procedure for Solid-Phase Preparation of 1,4-Dihydropyridines. Method A. An appropriate resin N-immobilized enamino ester **2** (0.023 mmol) and β-keto ester (1 mmol) (or acetylacetone in the case of **7d** (1 mmol)) and *p*-nitrobenzaldehyde (1 mmol) with 4A molecular sieves (250 mg) in dry pyridine (0.75 mL) are stirred at 45 °C under argon in a sealed amber vial for 24 h. The resin is filtered, washed sequentially with MeOH (4 × 7 mL) and ethyl acetate (4 × 7 mL), and dried in a vacuum desiccator (rt, 0.5 Torr). The resulted resin is stirred under argon with 3% TFA in CH_2Cl_2 (1 mL, 45 min; for cleavage from Rink resin) or 95% TFA in THF (1 mL, 1.5 h; for cleavage from PAL resin). Degassed acetonitrile (4 mL) is added, and the supernatant layer is separated and quickly evaporated *in vacuo* with addition of toluene to ensure complete TFA removal. The crude products **7** can be further purified by gradient reverse phase HPLC using degassed solvents (see General Considerations for HPLC conditions).

Method B. Method B was carried out analogously to method A, but using an appropriate preformed benzylidene β-keto ester (1 mmol) instead of a mixture of β-keto ester and aldehyde for reaction with resin N-immobilized enamino ester **2**.

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PAL-Resin-Supported Intermediate 4e from Reaction of N-Immobilized Methyl [2,4-$^{13}C_2$]Aminocrotonate (2) with Methyl 2-(4-Nitrobenzylidene)acetoacetate: prepared as described above (method B) from PAL-immobilized **2** (50 mg, 0.045 mmol) and methyl 2-(4-nitrobenzylidene)-acetoacetate (496 mg, 2 mmol). Fast gel-phase ^{13}C NMR in (C_6D_6) δ: 15.3 ($^{13}CH_3$), 90.3 and 91.3 (^{13}CH═).

Rink-Resin-Supported Intermediate 4e from Reaction of N-Immobilized Methyl [2,4-$^{13}C_2$]Aminocrotonate (2) with Methyl 2-(4-Nitrobenzylidene)acetoacetate: prepared as described above (method B) from Rink-immobilized **2** (50 mg, 0.023 mmol) and methyl 2-(4-nitrobenzylidene)-acetoacetate (248 mg, 1 mmol). Fast gel-phase ^{13}C NMR (C_6D_6) δ: 15.0 and 15.3 ($^{13}CH_3$), 92.0 and 92.9 (^{13}CH═). IR (KBr) ν: 1735 (CO_2Me), 1715 (CO) cm^{-1}.

1,4-Dihydro-4-(2-nitrophenyl)-2,6-dimethyl-3,5-bis(methoxycarbonyl)pyridine (7a, Nifedipine). Following method A, 50 mg (0.023 mmol) of the Rink-supported methyl aminocrotonate **2** yielded 5.6 mg (70%) of **7a**.[6a] Alternatively, 50 mg (0.045 mmol) of PAL-supported methyl aminocrotonate **2** with methyl 2-(2-nitrobenzylidene)acetoacetate (496 mg, 2 mmol) according to method B yielded 10.1 mg (65%) of **7a**. t_R 17.0 min. ^1H NMR ($CDCl_3$) δ: 2.35 (s, 6 H), 3.59 (s, 6 H), 5.69 (s, 1H), 5.72 (s, 1 H), 7.23−7.28 (m, 1 H), 7.46 (ddd, J = 7.9, 7.1, and 1.3 Hz, 1 H), 7.51 (dd, 1 H, J = 8.0 and 1.6 Hz, Ar), 7.68 (dd, 1 H, J = 8.1 and 1.4 Hz, Ar). Mass spectrum *m/z* 347.1 $(M + H)^+$.

1,4-Dihydro-4-(3-nitrophenyl)-2,6-dimethyl-3-(ethoxycarbonyl)-5-(methoxycarbonyl)pyridine (7b, Nitrendipine). Following method A, 50 mg (0.023 mmol) of Rink-supported methyl aminocrotonate **2** yielded 6.2 mg (75%) of **7b**.[6b] t_R 22.8 min. ^1H NMR ($CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.37 (s, 3 H, Me), 2.38 (s, 3 H), 3.65 (s, 3 H), 4.10 (m, 2 H), 5.10 (s, 1 H), 5.71 (s, 1 H), 7.38 (dd, J = 8.0 and 7.9 Hz, 1 H), 7.65 (m, 1 H), 8.02 (m, 1 H), 8.12 (m, 1 H). Mass spectrum *m/z* 383.0 $(M + Na)^+$.

1,4-Dihydro-4-(3-nitrophenyl)-2,6-dimethyl-3-[(2-methoxyethoxy)carbonyl]-5-(isopropoxycarbonyl)pyridine (7c, Nimodipine). Following method A, 50 mg (0.023 mmol) of Rink-supported isopropyl aminocrotonate **2** yielded 7.5 mg (78%) of **7c**.[6c] t_R 20.3 min. ^1H NMR ($CDCl_3$) δ: 1.09 (d, J = 6.2 Hz, 3 H), 1.26 (d, J = 6.2 Hz, 3 H), 2.36 (s, 6 H), 3.54 (m, 2 H), 4.17 (m, 2 H), 4.93 (m, 1 H), 5.09 (s, 1 H), 5.70 (s, 1 H), 7.39 (dd, J = 7.9 and 7.8 Hz, 1 H), 7.67 (dd, J = 7.7 and 1.1 Hz, 1 H), 8.01 (m, 1 H), 8.13 (m, 1 H). Mass spectrum *m/z* 418.9 $(M + H)^+$.

1,4-Dihydro-4-(4-nitrophenyl)-5-acetyl-2,6-dimethyl-3-(methoxycarbonyl)pyridine (7d). Following method A, 50 mg (0.023 mmol) of Rink-supported isopropyl aminocrotonate **2** yielded 5.7 mg (75%) of **7d**. t_R 22.1 min. ^1H NMR ($CDCl_3$) δ: 2.19 (s, 3 H), 2.33 (s, 3 H), 2.38 (s, 3 H), 3.71 (s, 3 H), 5.16 (s, 1 H), 5.73 (s, 1 H), 7.43 (d, J = 6.8 Hz, 2 H), 8.10 (d, J = 6.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ: 19.7, 20.5, 29.9, 40.2, 51.3, 103.6, 111.8, 123.7 (2 C), 128.5 (2 C), 144.4, 144.5, 153.6, 167.4, 197.7. High-resolution mass spectrum calcd for $(C_{17}H_{18}N_2O_5 + H)^+$ *m/z* 331.1294, found 331.1290.

1,4-Dihydro-4-(4-nitrophenyl)-2,6-dimethyl-3-(ethoxycarbonyl)-5-(methoxycarbonyl)pyridine ($^{13}C_2$-3,2-Me) (7e). Following method B, 50 mg (0.045 mmol) of PAL-supported methyl [2,4-$^{13}C_2$]aminocrotonate **2** with methyl 2-(4-nitrobenzylidene)acetoacetate (496 mg, 2 mmol) yielded 11.4 mg (70%) of **7e**. t_R 15.9 min. ^1H NMR ($CDCl_3$) δ: 1.21 (t, J = 7.1 Hz, 3 H), 2.36 (s, 3 H), 2.36 (dd, J = 129.7 and 3.5 Hz, 3 H, $^{13}CH_3$), 3.62 (s, 3 H), 4.09 (m, 2 H), 5.09 (d, J = 7.4 Hz, 1 H), 5.65 (d, J = 5.0 Hz, 1 H), 7.35 (d, J = 8.7 Hz, 2 H), 8.08 (d, J = 8.7 Hz, 2 H). Fast ^{13}C NMR ($CDCl_3$) δ: 19.7 ($^{13}CH_3$), 103.3 (3-^{13}C). High-resolution mass spectrum calcd for $(C_{16}{}^{13}C_2H_{20}N_2O_6 + H)^+$ *m/z* 363.1466, found 363.1449.

1,4-Dihydro-4-(4-nitrophenyl)-6-ethyl-2-phenyl-3-(ethoxycarbonyl)-5-(methoxycarbonyl)pyridine (7f). Following method A, 50 mg (0.023 mmol) of the Rink-supported methyl 3-amino-2-butenoate **2** yielded 7.0 mg (70%) of **7f**. t_R 22.8 min. ^1H NMR ($CDCl_3$) δ: 0.83 (t, J = 7.2 Hz, 3 H), 1.24 (t, 3 H), 2.68 (m, 1 H), 2.90 (m, 1 H), 3.67 (s, 3 H), 3.83 (m, 2 H), 5.21 (s, 1 H), 5.89 (d, 1 H), 7.27−7.73 (m, 2 H), 7.38−7.46 (m, 3 H), 7.51 (d, J = 8.7 Hz, 2 H), 8.14 (d, J = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$) δ: 12.8, 13.6, 26.0, 40.1, 51.3, 60.0, 102.3, 102.4, 123.6, 127.9, 128.5, 128.6, 129.5, 136.4, 146.4, 150.6, 154.6, 167.0, 167.2. High-resolution mass spectrum calcd for $(C_{24}H_{22}N_2O_6 + Li)^+$ *m/z* 443.2482, found 443.2482.

1,4-Dihydro-4-(4-cyanophenyl)-2,6-dimethyl-3,5-bis-(methoxycarbonyl)pyridine (7g). Following method A, 50 mg (0.023 mmol) of Rink-supported methyl aminocrotonate **2** yielded 5.9 mg (74%) of **7g**.[17] t_R 17.0 min. ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3 H), 3.64 (s, 3 H), 5.04 (s, 1 H), 5.68 (s, 1 H), 7.37 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 8.5 Hz, 2 H). Mass spectrum *m/z* 348.9 $(M + H)^+$.

1,4-Dihydro-4-phenyl-2,6-dimethyl-3-(allyloxycarbonyl)-5-(methoxycarbonyl)-1,4-dihydropyridine (7h). Following method B, 50 mg (0.023 mmol) of Rink-supported methyl aminocrotonate **2** with allyl 2-benzylideneacetoacetate (230 mg, 1 mmol) yielded 5.4 mg (72%) of **7h**. t_R 19.6 min. ^{1}H NMR ($CDCl_3$) δ: 1.60 (s, 3 H), 2.05 (s, 3 H), 3.64 (s, 3 H), 4.54 (m, 2 H), 5.03 (s, 1 H), 5.13−5.21 (m, 2 H), 5.67 (s, 1 H), 5.83−5.93 (m, 1 H), 7.11−7.28 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ: 19.9, 20.0, 39.6, 51.2, 64.8, 104.1, 104.3, 117.6, 126.4, 127.9, 128.0, 128.2, 133.0, 144.3, 144.6, 147.7, 167.4, 168.2. High-resolution mass spectrum calcd for $(C_{19}H_{21}NO_4 + Li)^+$ *m/z* 334.1628, found 334.1626.

1,4-Dihydro-4-(pyridin-4-yl)-2,6-dimethyl-3,5-bis(methoxycarbonyl)pyridine (7i). Following method A, 50 mg (0.023 mmol) of Rink-supported methyl aminocrotonate **2** yielded 5.2 mg (75%) of **7i**.[18] t_R 18.5 min. ^{1}H NMR ($CDCl_3$) δ: 2.37 (s, 3 H), 3.65 (s, 3 H), 5.23 (s, 1 H), 6.76 (s, 1 H), 7.85 (m, 2 H), 8.65 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ: 19.4, 41.09, 51.5, 100.7 (2 C), 126.2, 140.8, 147.1, 166.9, 167.0. Mass spectrum *m/z* 302.5 $(M + H)^+$.

Dimethyl 4-Amino-6-methyl-2-(2-nitrophenyl)-3,5-cyclohexadiene-1,3-dicarboxylate (8). PAL-supported methyl aminocrotonate **2** (50 mg, 0.045 mmol) with methyl 2-(2-nitrobenzylidene)acetoacetate (496 mg, 2 mmol) and 4A molecular sieves (0.25 g) in ethanol (2 mL) were heated with stirring in a sealed vial at 80 °C for 24 h. The resin was filtered, washed sequentially with MeOH (4 × 7 mL) and ethyl acetate (4 × 7 mL), and dried in a vacuum desiccator (rt, 0.5 Torr). The resulted resin was stirred under argon with 95% TFA in THF (1 mL) for 60 min. The supernatant was separated and evaporated *in vacuo* with addition of toluene to ensure complete removal of TFA. The resulted product **8** was further purified by reverse phase HPLC (see General Considerations), yield 9.3 mg (60%). t_R 16.0 min. ^{1}H NMR ($CDCl_3$) δ: 1.92 (d, J = 1.5 Hz), 3.33 (s, 1 H), 3.48 (s, 3 H), 3.76 (s, 3 H), 4.99 (s, 1 H), 5.88 (d, J = 1.5 Hz, 1 H), 7.30−7.46 (m, 3 H), 7.79 (d, J = 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 35.2, 51.0, 51.8, 53.0, 89.0, 122.7, 124.5, 127.7, 130.1, 132.8, 138.7, 142.7, 149.5, 153.0, 169.8, 171.6. High-resolution mass spectrum calcd for $(C_{17}H_{18}N_2O_6 + H)^+$ *m/z* 347.0450, found 347.0443.

Supporting Information Available: ^{1}H NMR spectra for all new compounds (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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