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Studies on Intramolecular Diels−Alder Reactions of Furo[3,4-*c*]pyridines in the Synthesis of Conformationally Restricted Analogues of Nicotine and Anabasine

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Received October 11, 2002

En route to conformationally restricted analogues of nicotine and anabasine, a novel synthetic route to bridged anabasines is described that hinges on a domino intramolecular [4 + 2]-cycloaddition/ring opening−elimination sequence of 3-amino-substituted furo[3,4-*c*]pyridines. Extension of this route to bridged nicotines, however, proved abortive, even when the dienophile tether is activated by a *p*-tolylsulfonyl group or when the diene moiety is activated by an electron-releasing methoxy substituent. A detailed density functional theoretical study (B3LYP/6-31+G**) was undertaken to provide insight into the factors that facilitate an intramolecular Diels−Alder reaction in the former case.

Introduction

During the past 2 decades or so a great stride has been made to probe the role of particular conformations on the pharmacological properties of important biologically active molecules such as amino acids,[1] peptides,[2] sugars,[3] nucleosides,[4] nucleotides,[4a,5] nucleic acids,[6] vitamins,[7] raloxifene,[8] and dihydropyrimidines.[9] In almost all of these studies the parent molecule is modified in such a fashion that its original conformational mobility is severely limited to one particular conformation. For tobacco alkaloids nicotine (**1**) and anabasine (**2**), the synthesis and evaluation of conformationally restricted analogues should help to determine the conformation(s) that induce ion channel opening.[10] Indeed, selective nicotine receptor ligands have potential as therapeutic agents for central nervous system disease and other disorders.[11] A limited number of constrained analogues **3**−**13** have already been synthesized (Figure 1),[12−22] and among these, the bridged nicotinoid **8** was found to be very potent in binding and functional assays.[14] Of the remaining analogues, **3**, **4**, **7**, **10**, and **11** were evaluated as

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10.1021/jo026555p CCC: $25.00
Published on Web 04/26/2003

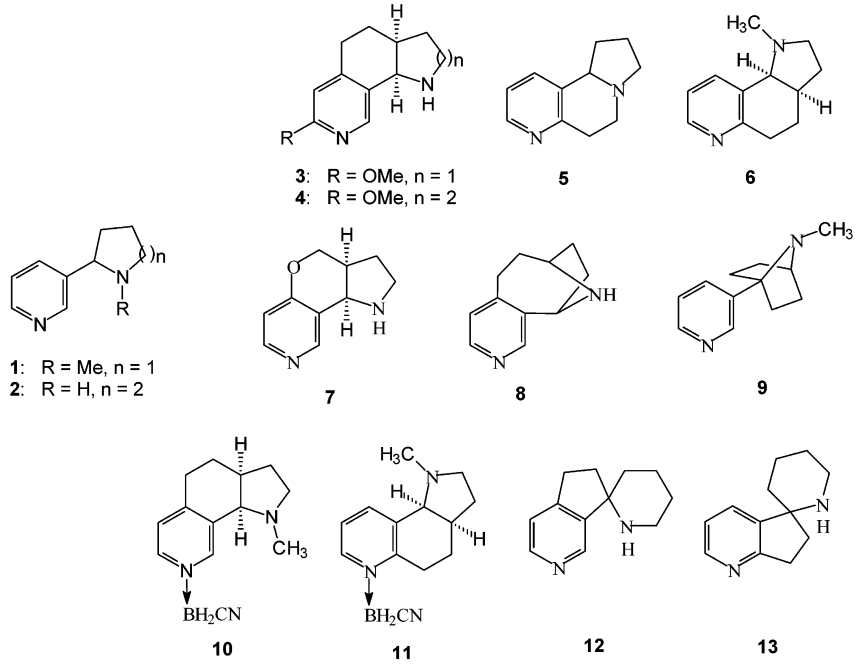


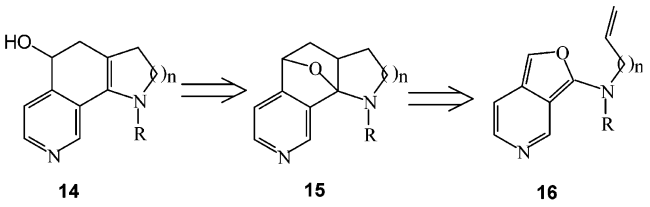
FIGURE 1.

agonists/antagonists of neuronal acetylcholine receptors (nAChRs).[17,21,22] In particular, compound **3**, which selectively activates human recombinant α2*β*4 and α4*β*4 nAChRs, has been shown to be active in animal models of Parkinson's disease and pain. The long and circuitous synthetic route described for the ring systems **3** and **4** does not appear to be viable for the synthesis of the large variety of bridged nicotines and anabasines required to probe the conformation of (*S*)-nicotine that induces ion channel opening. Hence, the development of an alternative and more flexible route that overcomes these limitations was felt desirable. In conjunction with our work on the synthesis of polysubstituted isoquinoline derivatives,[23−25] we recently reported[26] a synthetic route to bridged anabasine **4** based on a domino[27] cycloaddition/ring opening−elimination sequence of 3-amino-substituted furo[3,4-*c*]pyridines. In this paper, we report a full account of our efforts in this area, including inter alia development of a theoretical model to explain the failure of a key intramolecular Diels−Alder reaction leading to bridged nicotines (cf. **3**).

Results and Discussions

Our strategy toward conformationally restricted nicotines and anabasines **3** and **4** is depicted in Scheme 1. On the basis of the pioneering work of Friedrichsen et al. and also Padwa et al., we anticipated that **14**, which incorporates the basic skeleton of bridged nicotines and

SCHEME 1



anabasines, should be available from **15** via a ring opening and elimination sequence;[28,29] **15**, in turn, can be readily assembled from 3-amino-substituted furo[3,4-*c*]pyridines, e.g. **16**, by an intramolecular Diels−Alder reaction.To deal with this plan we initiated our investigation with the known acid **17**,[23,24] which on treatment with oxalyl chloride in refluxing benzene and subsequent reaction of the crude acid chloride with *N*-methylpent-4-enylamine in dichloromethane provided the corresponding amide **18** in 72% overall yield (Scheme 2). The amide exits as a mixture of rotamers (^{1}H NMR) in solution.[30] Lithiation of amide **18** with 2.2 equiv of lithium diisopropylamide (LDA)[31] followed by quenching with carbon dioxide gave the corresponding acid, which was easily separated from any unconverted **18**; a follow-up treatment of the acid with diazomethane provided **19** in 78% overall yield. It may be mentioned here that treatment of the lithiated amide from **18** with dimethyl carbonate yielded **19** directly, albeit with lower isolated yield in view of the difficulty associated with the separation of a rotameric mixture of **19** from an unconverted

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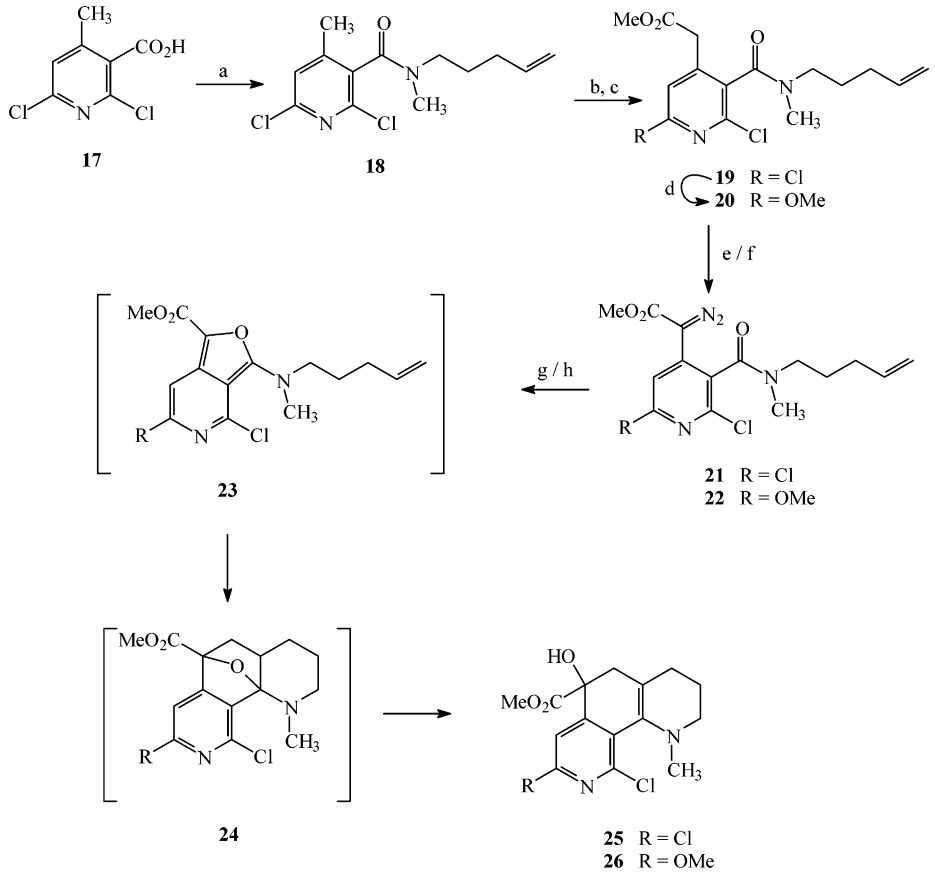
(31) It should be noted that use of 1 equiv of LDA did not give any lithiated product from amide **18**.

SCHEME 2[a]



[a] (a) $(COCl)_2$, PhH, reflux and then *N*-methylpent-4-enylamine, py, rt, 72%; (b) LDA, THF, −78 °C and then CO_2, 83%; (c) CH_2N_2, 94%; (d) (i) 40% aq KOH, MeOH, 12 h, rt; H_3O^+; (ii) CH_2N_2; 94%; (e) 4-acetamidobenzenesulfonyl azide, Et_3N, 0 °C → rt, 12 h, 93%; (f) 4-acetamidobenzenesulfonyl azide, DBU, CH_3CN, 83%; (g) $Rh_2(OAc)_4$, PhH, reflux, 1 h, 52%; (h) $Rh_2(OAc)_4$, PhH, rt, 24 h, 62%.

rotameric mixture of **18**. The substituted diazoacetic ester **21**, the substrate for the transition metal-catalyzed domino reaction, was made from **19** by the Davies protocol[32] via treatment with 4-acetamidobenzenesulfonyl azide (PABSA) in the presence of Et_3N. When **21** was exposed to 1 mol % $Rh_2(OAc)_4$ in refluxing benzene for 1 h, the bridged anabasine **25** (mp 165−167 °C) was obtained in 52% yield as a yellow crystalline solid via intramolecular cycloaddition **23** → **24** (R = Cl) followed by ring opening of **24** (R = Cl) and subsequent proton transfer. The structural assignment of **25** was confirmed by its ^1H and ^{13}C NMR spectra and elemental analysis, as well as X-ray crystal structure determination.[33]

With this encouraging result, we proceeded to apply this methodology to the synthesis of bridged nicotine analogues (cf. **3**). As shown in Scheme 3, diazoacetic ester **30**, the dienophile tether of which is shortened by one methylene unit, was synthesized according to the sequence of reactions described for **21** (Scheme 2). When diazoacetic ester **30** was subjected to the Rh(II)-catalyzed domino reaction, no intramolecular cycloaddition leading to a bridged nicotine analogue **34** (R = Cl) was obtained, even after heating in refluxing benzene for a prolonged time. However, in this case it was possible to trap the corresponding azaisobenzofuran **32** with methyl acrylate to furnish cycloadduct **33**. It is of interest to note that if the $-NCH_3$ group of the amine tether in azaisobenzofuran **32** is replaced by a CH_2 group and the $-CO_2Me$ group by a SPh group, then intramolecular Diels−Alder reactions proceed smoothly.[34] This suggests that the chain length may not be an important criterion for lack of facility of the Diels−Alder reaction of azaisobenzofuran

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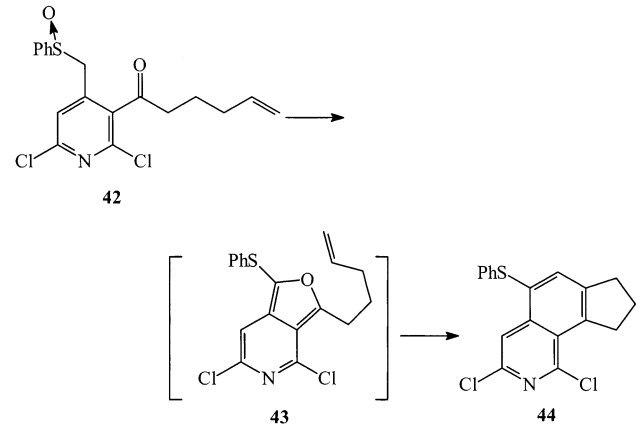
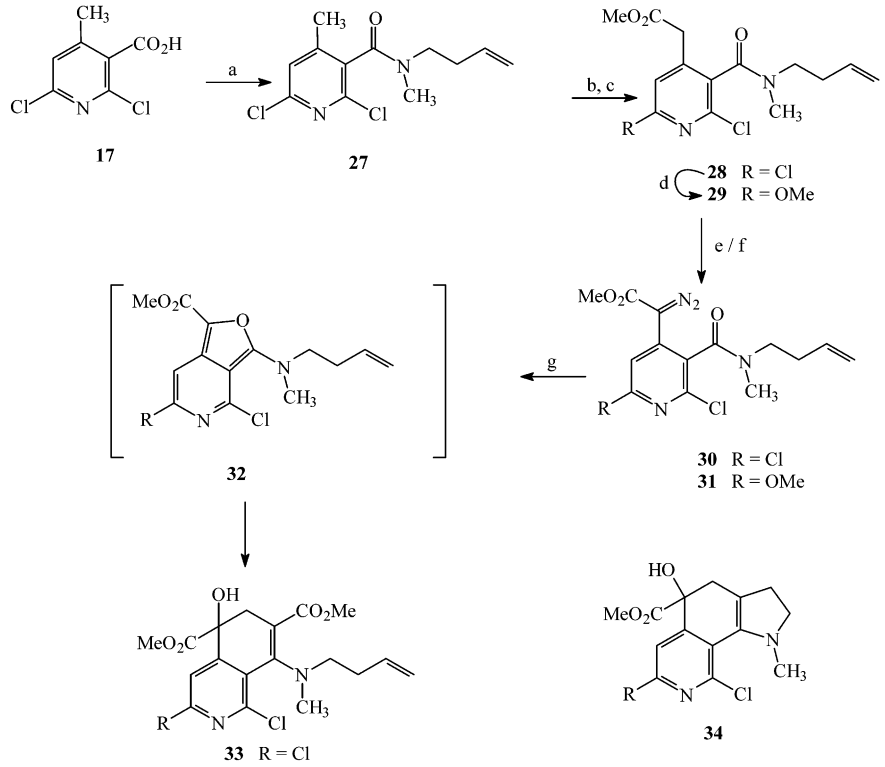
(34) Subjection of **42** to the Pummerer reaction conditions[25] [$(C_3F_7CO)_2O$, p-TsOH (cat.), tol] smoothly gave **44** via IMDA reaction of **43** and ring opening−aromatization of the resultant cycloadduct (Sarkar, T. K.; Panda, N. and Basak, S., unpublished results).



SCHEME 3[a]



[a] (a) $(COCl)_2$, PhH, reflux and then *N*-methylbut-3-enylamine, py, rt, 66%; (b) LDA, THF, −78 °C and then CO_2, 80%; (c) CH_2N_2, 92%; (d) (i) 40% aq KOH, MeOH, 12 h, rt; H_3O^+; (ii) CH_2N_2; 83%; (e) 4-acetamidobenzenesulfonyl azide, Et_3N, 0 °C → rt, 12 h, 92%; (f) 4-acetamidobenzenesulfonyl azide, DBU, CH_3CN, 93%; (g) $Rh_2(OAc)_4$, PhH, CH_2=CH−CO_2Me, rt, 24 h, 47%.

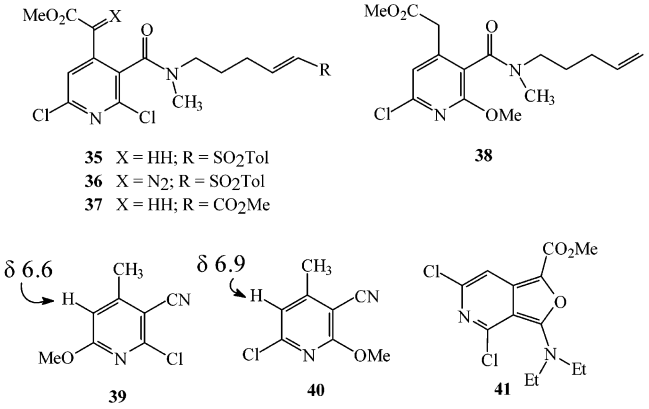


FIGURE 2.

32. One possibility could be that the unactivated olefinic tether present in **32** may not be sufficiently reactive to participate in the intramolecular Diels–Alder reaction. This speculation led us to introduce an electron-withdrawing group, such as a *p*-tolylsulfonyl group, to activate the olefinic tether for the intramolecular Diels–Alder reaction. After many unsuccessful attempts, the synthesis of **36** (Figure 2) was accomplished via the copper-catalyzed addition of tosyl iodide to **19** followed by triethylamine-assisted dehydroiodination of the initially formed *β*-iodo sulfone[35] and a diazo transfer reaction using a polymer-supported benzene sulfonyl azide reagent[36] in place of PABSA.[37] Unfortunately, once again no intramolecular cycloaddition was encountered when **36** was subjected to 1 mol % $Rh_2(OAc)_4$ in refluxing benzene for a prolonged time, even though intermolecular trapping products were formed when methyl acrylate was present in the reaction mixture. This failure may be a consequence of unfavorable steric interactions in the transition state.[38] Extension of this chemistry to the case of **32** was, therefore, unwarranted. The ester-activated substrate **37** was also made from **19** via oxidative scission (OsO_4/$NaIO_4$) of the π-bond and a Horner–Wittig olefination of the resulting aldehyde. Unfortunately, the very poor overall yield of this sequence coupled with the observation (^{1}H NMR) that **37** was not pure discouraged further elaboration for the studies on intramolecular Diels–Alder reactions.

In addition to activating the olefinic tether, we also conceived of activating the diene segment to effect an intramolecular Diels–Alder reaction, leading to a bridged nicotine. This consideration prompted us to synthesize methoxy-substituted bridged anabasine **26** from **20** via the intermediate **23**. The selective introduction of the methoxy group in **25** is also important, since Vernier et al.[17] reported that the constrained analogue **3** increases the selectivity and the efficacy for $\alpha2\beta4$ and $\alpha4\beta4$ cell lines compared to the desmethoxy analogue (**3**, R = H, *n* = 1). Thus, treatment of **19** (Scheme 2) with aqueous alkali in methanol at room temperature for 24 h and a follow-up treatment with diazomethane gave practically a single product (**20**) contaminated with a trace of its

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(37) Use of PABSA did not give **36** in a pure form.

regioisomer (**38**) (Figure 2). In the major regioisomer, the C-5 proton resonates at $\delta = 6.69$ and 6.64 (two rotamers), whereas in the trace isomer, the C-5 proton resonates at $\delta = 6.96$ and 6.92 (two rotamers); all of these signals were moved upfield in comparison to the C-5 signals ($\delta = 7.34$ and 7.28) in **19**. Recently, Clive et al. reported[39] the chemical shifts of C-5 protons of **39** and **40**. The chemical shifts of the C-5 proton in the major regioisomer match with the chemical shifts of the C-5 proton in **39** ($\delta = 6.6$) but not **40** ($\delta = 6.9$). From the above ^{1}H NMR analysis, structure **20** was thus assigned to the major isomer and structure **38** to the minor one. Clearly steric hindrance to nucleophilic attack at C-2 in **19** allowed selective introduction of the −OMe group. The transformation of **20** → **26** then followed an analogous route to that described for **19**. For the diazo transfer reaction **20** → **22**, DBU was found to be the effective base, not Et_3N, and the transformation **22** → **26** took place even at ambient temparature. The structure of **26** is fully supported by ^{1}H and ^{13}C NMR as well as X-ray crystal structure determination.[40]

Encouraged by this observation, the methoxy-substituted diazoacetic ester **31** was synthesized according to the procedure described for **22** and was subjected to 1 mol % $Rh_2(OAc)_4$ in benzene at room temperature. Disappointingly, no trace of Diels−Alder adduct was formed, even after heating at 80 °C for a prolonged time.

One way to explain the failure of the synthesis of bridged nicotines would be to assume that the nitrogen atom of the amine tether in **23** and **32** is planar, due to conjugation with the rest of the π-system of the azaisobenzofuran moiety. Drieding models indicate that the intramolecular Diels−Alder reaction of **23** is feasible under this condition, whereas **32** requires pyramidalization of the nitrogen atom of the amine tether for effective overlap of the π-systems of the diene and dienophile units and consequent increase in the transition state energy level. However, this explanation is not wholly tenable, since X-ray crystal structure determination[41] of a stable furo[3,4-*c*]pyridine **41**[24,42] clearly shows not only that the nitrogen atom of the diethylamino group is partially pyramidal but also that the dihedral angle between the mean N2/C8/C10 plane and the heterocyclic ring is 33.2(2)°, which should actually facilitate the desired reaction. Although it can be argued that crystal packing forces can skew such an angle,[43] it is certainly true that the presence of the *o*-chloro substituents in **23** and **32** would sterically encourage nonplanarity of the amines. The recalcitrance of transient azaisobenzofurans, e.g. **32** with a shorter olefinic tether toward cycloaddition, is thus enigmatic. As in some other Diels−Alder cycloadditions,[38] FMO theory is totally inadequate to explain the results in these cases. Accordingly, full-scale ab initio transition-state optimizations were carried out to get insight as to why the cycloaddition in the case of azaisobenzofuran **23** (R = Cl) is so much more facile than that of **32** (R = Cl).

TABLE 1. Calculated Heat of Activation ($\Delta E^{\ddagger}$) and the Heat of Reaction (ΔE) for the Diels−Alder Step

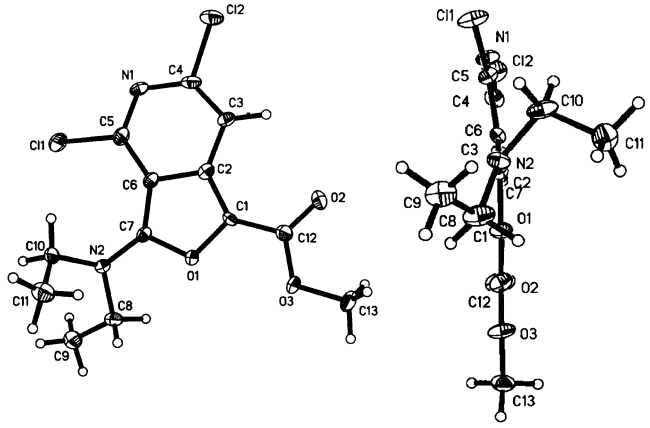
computational models		$\Delta E^{\ddagger}$ (kcal/mol)	ΔE (kcal/mol)
PM3	Scheme 3	35.9	−2.2
	Scheme 2	35.8	−15.0
HF/3-21G*//PM3	Scheme 3	39.4	−25.4
	Scheme 2	30.5	−58.8
B3LYP/3-21G*//PM3	Scheme 3	26.9	−14.6
	Scheme 2	19.3	−42.0
HF/6-31G*//PM3	Scheme 3	47.6	−16.3
	Scheme 2	39.8	−48.6
B3LYP/6-31G*//PM3	Scheme 3	32.4	−5.7
	Scheme 2	25.8	−32.0
B3LYP/6-31+G**//PM3	Scheme 3	33.2	−4.2
	Scheme 2	26.6	−30.5

Thermodynamics and kinetics of the key Diels−Alder step in Scheme 2, i.e., **23** (R═Cl) to **24** (R═Cl), and the related part in Scheme 3 were submitted to computations. Both semiempirical and nonempirical quantum-mechanical methods were performed. The semiempirical PM3 treatment implemented in the SPARTAN program package[44] was used subsequently on the optimized geometries with the GAUSSIAN program package[45] in the following approximations: HF/3-21G*, B3LYP/3-21G*, HF/6-31G*, B3LYP/6-31G*, and B3LYP/6-31+G**.

The calculated heats of activation for the transformations of **23** (R═Cl) → **24** (R═Cl) in Scheme 2 and related transformations in Scheme 3 are listed in Table 1. In the Diels−Alder step, the pathway for Scheme 2 exhibits a bit lower barrier than that of Scheme 3 at all levels of computation except PM3. The PM3 method is parametrized to heats of formation (i.e. to thermodynamics) and to equilibrium geometries and works well in these situations.[46] However, it does not automatically mean that it is also reliable for activated complexes. In our particular case, it appears that PM3 is not an adequate model for the estimation of activation energies, as it does not agree well with the higher levels of theory.

To have a further insight into the situation, we have carried out some additional calculations based on density functional theory within the LSDA approximation—the

(41) X-ray crystal structure determination of **41** was carried out by Prof. H.-K. Fun (Penang, Malaysia) (Unpublished results).



(42) Unlike **41**, intermediate **32** was not isolable in our hands.

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VWN functional using the DN basis set[44] (other acronym[45] SVWN/DN). At the VWN/DN level the geometries were reoptimized and it was found that the barrier in the five-membered cyclization case is by 10.6 kcal/mol higher than the other route, i.e., **23** (R═Cl) → **24** (R═Cl). Moreover, the activation energetics in the VWN/DN-optimized geometries was also evaluated with two larger basis sets, DN* and DN**. The barrier in the five-membered Diels−Alder step is higher by 9.8 and 9.6 kcal/mol in the VWN/DN* and VWN/DN** approach, respectively. Given the complexity of the systems, we cannot point out just a single factor responsible for this finding, consistently produced at various levels of theory. It is rather a result of a complex interplay of various factors.

A significant difference can be seen in the simple thermodynamics,[47] i.e., between the enthalpies of **23** (R═Cl) and **24** (R═Cl) in Scheme 2. The corresponding step in Scheme 3 was also calculated. It turns out that the thermodynamics of the Diels−Alder step is crucial for the reactions. The computations consistently show that there is a substantial drop in energy in this step for the case of Scheme 2; however, there is a considerably smaller decrease of potential energy for the case of Scheme 3 (Table 1). To get the Gibbs free energy changes rather than the potential energy (enthalpy) changes, we also computed the related PM3 entropy changes for the temperature of boiling benzene, $T = 353$ K (the enthalpy part was also updated for the temperature). The Gibbs energy change computed at the PM3 level at this temperature is −12.3 and +3.8 kcal/mol for Schemes 2 and 3, respectively. Thus, the calculations suggest that the difference in thermodynamics of the transformation from **23** (R═Cl) to **24** (R═Cl) may explain the difference in reactivities between both schemes.

Conclusion

In conclusion, the first example of an intramolecular Diels−Alder reaction involving a furo[3,4-*c*]pyridine is reported, which opens a novel route to conformationally restricted anabasines with potential as therapeutic agents for central nervous system disease and related disorders. Limitation of this strategy for the synthesis of conformationally restricted nicotines[48] has been noted. Heats of reaction calculated for two closely related reactions with DFT were used as a qualitative tool for explaining the Diels−Alder reactivity of furo[3,4-*c*]pyridines.

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Experimental Section

All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under an inert atmosphere in flame-dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: Tetrahydrofuran and benzene from sodium benzophenone ketyl; dichloromethane and acetonitrile from P_2O_5; DMSO from CaH_2; Et_3N, pyridine, and diisopropylamine from solid KOH; and methanol from Mg. After drying, organic extracts were evaporated under reduced pressure and the residue was flash chromatographed on silica gel (Acme's, particle size 230−400 mesh) using ethyl acetate−petroleum ether (60−80 °C) mixture as eluent unless specified otherwise. TLC was recorded using precoated plate (Merck, silica gel 60 F_{254}).

2,6-Dichloro-*N*,4-dimethyl-*N*-pent-4-enylnicotinamide (18). To a stirred suspension of 2,6-dichloro-4-methyl-3-pyridinecarboxylic acid (**17**)[24] (1.6 g, 7.76 mmol) in benzene (15 mL) was added oxalyl chloride (1 mL, 11.67 mmol) followed by one drop of DMF at room temparature. The solution was then refluxed for 5 h and concentrated under reduced pressure. The crude acid chloride was dissolved in dichloromethane (12 mL) and to this solution was added dropwise *N*-methylpent-4-enylamine (1.13 g, 11.41 mmol) followed by pyridine (0.63 mL, 7.76 mmol) at 0 °C under argon. After the reaction mixture was stirred at room temparature for 5 h, water was added and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed several times with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography (ethyl acetate−petroleum ether 10:90) to give **18** as a yellowish oil (1.6 g, 72% yield) that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 40:60) 0.29 and 0.17; IR (neat) 1643 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$–CCl_4 7:3) δ 7.19 and 7.15 (s, 1H), 5.92−5.70 and 5.68−5.5 (m, 1H), 5.12−4.85 (m, 2H), 3.73−3.35 (m) and 3.08 (t, $J = 8$ Hz) (2H), 3.11 and 2.84 (s, 3H), 2.29 (s, 3H), 2.22−1.54 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.8 (s), 164.3 (s), 150.3 (s), 149.8 (s), 149.5 (s), 149.3 (s), 145.7 (s), 145.5 (s), 137.0 (d), 136.2 (d), 131.1 (s), 130.8 (s), 124.2 (d), 123.7 (d), 115.3 (t), 114.9 (t), 49.5 (t), 46.3 (t), 35.1 (q), 31.8 (q), 30.6 (t), 30.0 (t), 26.7 (t), 25.5 (t), 18.7 (q), 18.5 (q). Anal. Calcd for $C_{13}H_{16}N_2OCl_2$: C, 54.37; H, 5.62; N, 9.75. Found: C, 54.31; H, 5.42; N, 9.97.

Methyl (2,6-Dichloro-3-{[methyl(pent-4-enyl)amino]-carbonyl}pyridin-4-yl)acetate (19). To a stirred solution of LDA (11.25 mmol) [prepared from 1.5 M *n*-BuLi in hexane (7.5 mL) and diisopropylamine (2 mL, 14. 27 mmol)] in THF (25 mL) at −78 °C under argon atmosphere was slowly added a solution of 2,6-dichloro-*N*,4-dimethyl-*N*-pent-4-enylnicotinamide (**18**) (1.5 g, 5.22 mmol) in THF (5 mL) by syringe injection over a period of 1.5 h. After being stirred for another 1 h at −78 °C, dried CO_2 gas was bubbled through the burgundy red solution over 30 min, and then the cooling bath was removed. The mixture was evaporated to dryness under reduced pressure, water was added, and the mixture was extracted with dichloromethane. The aqueous layer was acidified with concentrated hydrochloric acid and extracted several times with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give crude acid (1.43 g). The crude acid, thus formed, was then treated with excess ethereal diazomethane at 0 °C. The mixture was evaporated and the residue was purified by column chromatography (ethyl acetate−petroleum ether 10:90) to give **19** as a yellowish oil (1.4 g, 78% overall yield) that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 40: 60) 0.28 and 0.15; IR (neat) 1744, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 and 7.28 (s, 1H), 5.91−5.75 and 5.74−5.60 (m, 1H), 5.12−4.90 (m, 2H), 3.98−3.40 and 3.20−2.85 (m, 2H), 3.80 (d, $J_{AB} = 16.3$ Hz, 1H), 3.72 and 3.71 (s, 3H), 3.56 (d, $J_{AB} = 16.3$ Hz, 1H), 3.11 and 2.87 (s, 3H), 2.20−1.66 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8 (s), 168.7 (s), 164.4 (s), 149.8 (s), 146.1 (s), 146.0 (s), 145.8 (s), 145.7 (s), 137.2 (d), 136.5 (d), 131.4 (s), 131.1 (s), 124.9 (d), 124.7 (d), 115.4 (t),

115.1 (t), 52.3 (q), 49.9 (t), 46.7 (t), 37.4 (t), 35.5 (q), 31.9 (q), 30.7 (t), 30.3 (t), 26.8 (t), 25.6 (t). Anal. Calcd for $C_{15}H_{18}N_2O_3Cl_2$: C, 52.19; H, 5.26; N, 8.11. Found: C, 52.06; H, 5.43; N, 8.15.

Methyl Diazo(2,6-dichloro-3-{[methyl(pent-4-enyl)-amino]carbonyl}pyridin-4-yl)acetate (21). To a stirred solution of methyl (2,6-dichloro-3-{[methyl(pent-4-enyl)amino]-carbonyl}pyridin-4-yl)acetate (**19**) (220 mg, 0.64 mmol) and *p*-acetamidobenzenesulfonyl azide (156 mg, 0.65 mmol) in acetonitrile at 0 °C was added triethylamine (0.27 mL, 1.91 mmol) dropwise. The mixture was allowed to warm to room temparature and stirred for another 12 h. The solvent was evaporated under reduced pressure. The residue was triturated with ether−petroleum ether (1:1) and filtered, and the solvent was evaporated under reduced pressure. The crude diazo product, thus formed, was further purified by column chromatography (ether−petroleum ether 1:4) to give **21** as a yellow liquid (220 mg, 93% yield) that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 40:60) 0.38 and 0.29; IR (neat) 2111, 1717, 1642 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 and 7.90 (s, 1H), 5.94−5.69 and 5.68−5.48 (m, 1H), 5.12−4.81 (m, 2H), 3.82 (s, 3H), 3.81−3.65 and 3.25−3.01 (m, 2H), 3.03 and 2.85 (s, 3H), 2.19−1.40 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.9 (s), 163.2 (s), 150.1 (s), 147.2 (s), 147.0 (s), 137.3 (s), 137.2 (d), 136.3 (d), 125.0 (s), 124.3 (s), 119.7 (d), 119.4 (d), 115.8 (t), 115.3 (t), 62.8 (s), 62.4 (s), 52.7 (q), 52.6(q), 50.0 (t), 46.8 (t), 35.8 (q), 31.9 (q), 30.9 (t), 30.3 (t), 26.8 (t), 25.4 (t); DCI-MS: *m*/*z* (relative intensity) 371 [(M + H)$^+$, 100), 388 (M+ NH_4^+, 70); HRMS (FAB) calcd for $C_{15}H_{17}N_4O_3Cl_2$ [(M + H)$^+$] *m*/*z* 371.0678, found 371.0685.

Methyl 8,10-Dichloro-6-hydroxy-1-methyl-1,2,3,4,5,6-hexahydro-1,9-phenanthroline-6-carboxylate (25). A mixture of diazo compound **21** (210 mg, 0.57 mmol) and 1 mol % $Rh_2(OAc)_4$ in benzene (10 mL) was stirred at room temparature for 2−3 h. The mixture was then heated at reflux for 30 min. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography (ethyl acetate−petroleum ether 10:90) to afford **25** as a yellow-green crystalline solid (100 mg, 52% yield): mp 165−167 °C; R_f (EtOAc−petroleum ether, 40:60) 0.32; IR (KBr) 3378, 1745, 1616 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 (s, 1H), 3.69 (s, 3H), 3.20 (bs, 1H), 3.19−3.09 (m, 1H), 2.90−2.75 (m, 1H), 2.65 (dt, J = 15.1 and 1.8 Hz, 1H), 2.44 (d, J = 15.1 Hz, 1H), 2.40 (s, 3H), 2.20−2.06 (m, 2H), 1.82−1.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3 (s), 152.8 (s), 147.6 (s), 145.0 (s), 138.1 (s), 125.8 (s), 118.5 (d), 113.9 (s), 74.9 (s), 52.8 (q), 51.2 (t), 41.1 (q), 40.5 (t), 28.7 (t), 18.4 (t). Anal. Calcd for $C_{15}H_{16}N_2O_3Cl_2$: C, 52.49, H, 4.70, N, 8.16. Found: C, 52.73, H, 4.62, N, 8.10.

Methyl (2-Chloro-6-methoxy-3-{[methyl(pent-4-enyl)-amino]carbonyl}pyridin-4-yl)acetate (20). To a stirred solution of methyl (2,6-dichloro-3-{[methyl(pent-4-enyl)amino]-carbonyl}pyridin-4-yl)acetate (**19**) (620 mg, 1.8 mmol) in methanol (5 mL) was added 40% aqueous solution of KOH (15 mL) dropwise at room temparature. After being stirred for 24 h at ambient temparature, the mixture was concentrated under reduced pressure, diluted with water, and extracted with dichloromethane. The aqueous layer was acidified with concentrated hydrochloric acid, saturated with NaCl, and extracted several times with Et_2O. The combined organic extracts were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give crude hydroxy-substituted acid (600 mg). The crude acid, thus formed, was then treated with excess ethereal diazomethane at 0 °C. The mixture was evaporated and the residue was purified by column chromatography (ethyl acetate−petroleum ether 10:90) to give **20** as a yellowish oil (450 mg, 73% overall yield) that appears as a mixture of two rotamers in solution: R_f (EtOAc− petroleum ether, 40:60) 0.35 and 0.20; IR (neat) 1743, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 and 6.64 (s, 1H), 5.93−5.77 and 5.76−5.60 (m, 1H), 5.11−4.90 (m, 2H), 3.95 and 3.94 (s, 3H), 3.77 (d, 1H, J_{AB} = 16.2 Hz), 3.70 and 3.68 (s, 3H), 3.62−3.37 and 3.17−3.01 (m, 2H), 3.51 (d, 1H, J_{AB} = 16.3 Hz), 3.09 and 2.88 (s, 3H), 2.25−1.6 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.6 (s), 169.4 (s), 165.7 (s), 163.0 (s), 145.4 (s), 145.3 (s), 144.3 (s), 144.2 (s), 137.5 (d), 136.8 (d), 125.1 (s), 125.0 (s), 115.2 (t), 115.0 (t), 111.2 (d), 110.9 (d), 54.0 (q), 52.2 (q), 52.1 (q), 50.0 (t), 46.6 (t), 37.6 (t), 35.6 (q), 31.9 (q), 30.8 (t), 30.5 (t), 26.9 (t), 25.7 (t). Anal. Calcd for $C_{16}H_{21}N_2O_4Cl$: C, 56.39, H, 6.21, N, 8.22. Found: C, 56.27, H, 6.42, N, 8.23.

Methyl Diazo(2-chloro-6-methoxy-3-{[methyl(pent-4-enyl)amino]carbonyl}pyridin-4-yl)acetate (22). To a stirred solution of the methyl (2-chloro-6-methoxy-3-{[methyl(pent-4-enyl)amino]carbonyl}pyridin-4-yl)acetate (**20**) (180 mg, 0.53 mmol) and *p*-acetamidobenzenesulfonyl azide (0.21 g, 0.88 mmol) in acetonitrile (2 mL) at 0 °C was added DBU (0.17 mL, 1.17 mmol) dropwise. After stirring for 1 h at 0 °C, the mixture was allowed to warm to room temparature and stirred overnight. Saturated aqueous NH_4Cl solution was then added and the mixture was extracted twice with dichloromethane. The organic layer was dried (Na_2SO_4) and filtered and the solvent was evaporated under reduced pressure. The residue was triturated with ether−petroleum ether (1:1) and filtered and the solvent was evaporated under reduced pressure. The crude diazo product was purified by column chromatography (ether−petroleum ether 1:4) to afford **22** as a yellowish oil (160 mg, 83% yield) that appears as a mixture of two rotamers in solution: IR (neat) 2121, 1711, 1637 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14 (s, 1H), 5.95−5.70 and 5.69−5.50 (m, 1H), 5.15−4.84 (m, 2H), 3.91 and 3.90 (s, 3H), 3.81 and 3.80 (s, 3H), 3.78−3.62 and 3.30−2.75 (m, 2H), 3.03 and 2.86 (s, 3H), 2.25−1.45 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2 (s), 164.0 (s), 163.1 (s), 145.6 (s), 145.4 (s), 137.5 (d), 136.7 (d), 136.4 (s), 120.4 (s), 119.4 (s), 115.5 (t), 115.2 (t), 107.3 (d), 106.8 (d), 61.8 (s), 54.2 (q), 52.5 (q), 52.4 (q), 50.2 (t), 46.8 (t), 36.0 (q), 32.1 (q), 31.0 (t), 30.4 (t), 26.9 (t), 25.6 (t).

Methyl 10-Chloro-6-hydroxy-8-methoxy-1-methyl-1,2,3,4,5,6-hexahydro-1,9-phenanthroline-6-carboxylate (26). To a stirred solution of the α-diazo ester **22** (140 mg, 0.38 mmol) in dry benzene under an argon atmosphere at ambient temparature was added a catalytic amount of $Rh_2(OAc)_4$. After stirring the mixture for 24 h, the solvent was removed in vacuo and the residue was purified by flash chromatography (alumina; ethyl acetate−petroleum ether 20:80). Recrystallization from a dichloromethane−diethyl ether−petroleum ether (3:3:1) solution afforded **26** as yellow green crystals (80 mg, 62% yield): mp 152−154 °C; IR (KBr) 3440, 1735, 1635 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.82 (s, 1H), 3.93 (s, 3H), 3.68 (s, 3H), 3.25−3.05 (m, 1H), 2.95−2.75 (m, 1H), 2.58 (dt, 1H, J = 14.7 Hz), 2.43 (d, J = 14.7 Hz), 2.42 (s, 3H), 2.12 (t, 2H, J = 6.3 Hz), 1.85−1.55 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.9 (s), 161.6 (s), 153.1 (s), 143.1 (s), 138.4 (s), 119.9 (s), 111.1 (s), 105.0 (d), 75.1 (s), 53.9 (q), 52.7 (q), 51.4 (t), 41.1 (q), 40.9 (t), 28.8 (t), 18.4 (t). Anal. Calcd for $C_{16}H_{19}N_2O_4Cl$: C, 56.72, H, 5.65, N, 8.27. Found: C, 56.83, H, 5.69, N, 8.24.

***N*-but-3-enyl-2,6-dichloro-*N*,4-dimethylnicotinamide (27).** Similar to the preparation of the amide **18**, a sample of acid **17** (1.4 g, 6.79 mmol) gave amide **27** (1.22 g, 66% yield) as a yellowish oil that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 40:60) 0.33 and 0.20; IR (neat) 1644 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$–CCl_4 7:3) δ 7.15 and 7.09 (s, 1H), 5.95−5.72 and 5.70−5.45 (m, 1H), 5.20−4.95 (m, 2H), 3.78−3.48 and 3.24−3.10 (m, 2H), 3.10 and 2.82 (s, 3H), 2.52−2.35 (m, 2H), 2.28 and 2.27 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.4 (s), 165.3 (s), 150.2 (s), 149.9 (s), 149.88 (s), 149.82 (s), 146.1 (s), 146.0 (s), 134.9 (d), 133.7 (d), 131.3 (s), 131.0 (s), 124.5 (d), 124.4 (d), 118.0 (t), 117.2 (t), 50.0 (t), 46.5 (t), 35.6 (q), 32.4 (t), 32.1 (q), 31.4 (t), 19.2 (q), 19.0 (q). Anal. Calcd for $C_{12}H_{14}N_2OCl_2$: C, 52.76, H, 5.17, N, 10.26. Found: C, 52.74, H, 5.59, N, 10.29.

Methyl (3-{[But-3-enyl(methyl)amino]carbonyl}-2,6-dichloropyridin-4-yl)acetate (28). A sample of amide **27** (1

g, 3.67 mmol) under similar conditions as described for the preparation of **19** gave methyl (3-{[but-3-enyl(methyl)amino]-carbonyl}-2,6-dichloropyridin-4-yl)acetate (**28**) as a yellowish oil (0.89 g, 74% overall yield) that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 40:60) 0.27 and 0.19; IR (neat) 1745, 1642 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 and 7.27 (s, 1H), 5.98−5.72 and 5.70−5.45 (m, 1H), 5.20−4.97 (m, 2H), 3.84−3.45 and 3.22−3.08 (m, 2H), 3.73 and 3.71 (s, 3H), 3.66 (d, J_{AB} = 16.7 Hz, 1H), 3.57 (d, J_{AB} = 16.7 Hz, 1H), 3.11 and 2.87 (s, 3H), 2.50−2.25 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9 (s), 168.8 (s), 164.5 (s), 150.1 (s), 150.0 (s), 146.4 (s), 146.2 (s), 145.9 (s), 145.7 (s), 134.8 (d), 133.7 (d), 131.4 (s), 131.0 (s), 124.8 (d), 124.7 (d), 117.7 (t), 117.0 (t), 52.5 (q), 52.4 (q), 49.9 (t), 46.6 (t), 37.5 (t), 35.7 (q), 32.1 (t), 32.0 (q), 31.1 (t); DCI-MS: *m*/*z* (relative intensity) 331 [$(M + H)^+$, 100], 348 [$(M + NH_4^+)$, 51], 661 [$(2M + H)^+$, 12], 678 [$2M + NH_4^+$, 18]; HRMS (FAB) calcd for $C_{14}H_{17}N_2O_3Cl_2$ [$(M + H)^+$] *m*/*z* 331.0616, found 331.0608. Anal. Calcd for $C_{14}H_{16}N_2O_3Cl_2$: C, 50.77, H, 4.87, N, 8.46. Found: C, 50.69, H, 4.99, N, 8.42.

Methyl diazo(3-{[but-3-enyl(methyl)amino]carbonyl}-2,6-dichloropyridin-4-yl)acetate (30). Following the procedure described in the preparation of diazo compound **21**, the reaction of **28** (320 mg, 0.96 mmol) with *p*-acetamidobenzenesulfonyl azide (265 mg, 1.1 mmol) was performed and gave **30** as a yellow liquid (320 mg, 92% yield) that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 40:60) 0.36 and 0.32; IR (neat) 2112, 1715, 1642 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$: CCl_4 7:3) δ 7.95 and 7.84 (s, 1H), 5.90−5.65 and 5.62−5.40 (m, 1H), 5.18−4.89 (m, 2H), 3.95−3.60 and 3.30−3.08 (m, 2H), 3.81 and 3.80 (s, 3H), 3.00 and 2.83 (s, 3H), 2.46−2.15 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4 7:3) δ 163.7 (s), 163.0 (s), 162.9 (s), 149.8 (s), 146.9 (s), 146.8 (s), 137.2 (s), 134.5 (d), 133.2 (d), 124.9 (s), 124.0 (s), 119.6 (d), 119.1 (d), 117.9 (t), 117.0 (t), 62.7 (s), 62.2 (s), 52.5 (q), 49.9 (t), 46.6 (t), 35.9 (q), 32.0 (t), 31.6 (q), 30.8 (t).

Dimethyl 8-[but-3-enyl(methyl)amino]-1,3-dichloro-5-hydroxy-5,6-dihydro isoquinoline-5,7-dicarboxylate (33). A mixture of diazo compound **30** (88 mg, 0.25 mmol) and 1 mol % $Rh_2(OAc)_4$ in benzene (6 mL) was stirred for 2.5 h at room temparature. After that methyl acrylate (0.11 mL, 1.26 mmol) was added to the mixture, which was stirred at ambient temparature for another 24 h. The mixture was then concentrated under reduced pressure to give the crude adduct, which was purified by column chromatography (ethyl acetate−petroleum ether 10:90) to give **33** as a yellowish oil (48 mg, 47% yield): R_f (EtOAc−petroleum ether, 40:60) 0.33; IR (neat) 3441, 1741, 1639 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48 (s, 1H), 5.80−5.55 (m, 1H), 5.05−4.88 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.10−2.92 (m, 3H), 2.85 (d, 1H, J_{AB} = 11.8 Hz), 2.80 (s, 3H), 2.77 (d, 1H, J_{AB} = 11.8 Hz), 2.47−2.25 (m, 1H), 2.15−1.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3 (s), 166.9 (s), 155.9 (s), 150.3 (s), 149.1 (s), 147.9 (s), 135.6 (d), 125.6 (s), 118.9 (d), 116.1 (t), 104.4 (s), 74.1 (s), 53.8 (t), 53.4 (q), 51.4 (q), 40.9 (q), 37.7 (t), 32.4 (t). Anal. Calcd for $C_{18}H_{20}N_2O_5Cl_2$: C, 52.06, H, 4.85, N, 6.75. Found: C, 52.29, H, 4.79, N, 6.77.

Methyl (3-{[but-3-enyl(methyl)amino]carbonyl}-2-chloro-6-methoxypyridin-4-yl)acetate (29). The reaction was carried out with **28** (330 mg, 1 mmol) following the conditions described in the preparation of **20** and afforded **29** as a yellow liquid (270 mg, 83% yield) that appears as a mixture of two rotamers in solution: IR (neat) 1745, 1637 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.68 and 6.63 (s, 1H), 5.98−5.72 and 5.71−5.48 (m, 1H), 5.21−4.92 (m, 2H), 3.936 and 3.930 (s, 3H), 3.82−3.42 and 3.27−3.12 (m, 4H), 3.69 and 3.68 (s, 3H), 3.08 and 2.88 (s, 3H), 2.50−2.22 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$-CCl_4 = 7:3) δ 169.4 (s), 169.3 (s), 165.6 (s), 162.9 (s), 145.5 (s), 145.4 (s), 144.2 (s), 144.0 (s), 135.0 (d), 134.0 (d), 125.0 (s), 124.5 (s), 117.3 (t), 116.6 (t), 111.0 (d), 110.9 (d), 53.8 (q), 52.0 (q), 51.9 (q), 49.8 (t), 46.5 (t), 37.5 (t), 35.7 (q), 32.2 (t), 31.8 (q), 31.0 (t). Anal. Calcd for $C_{15}H_{19}N_2O_4Cl$: C, 55.13, H, 5.86, N, 8.57. Found: C, 55.12, H, 5.64, N, 8.55.

Methyl diazo(3-{[but-3-enyl(methyl)amino]carbonyl}-2-chloro-6-methoxypyridin-4-yl)acetate (31). Following the preparation of diazo compound **22**, a sample of **29** (100 mg, 0.30 mmol) gave diazo compound **31** (100 mg, 93% yield) as a yellowish oil that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 40:60) 0.39 and 0.33; IR (neat) 2109, 1714, 1639 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.27 and 7.14 (s, 1H), 5.98−5.71 and 5.70−5.45 (m, 1H), 5.22−4.94 (m, 2H), 3.92 (s, 3H), 3.85 and 3.82 (s, 3H), 3.80−3.68 and 3.42−3.12 (m, 2H), 3.04 and 2.87 (s, 3H), 2.52−2.15 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.4 (s), 165.3 (s), 164.1 (s), 163.2 (s), 145.6 (s), 145.4 (s), 136.7 (s), 136.6 (s), 135.0 (d), 133.8 (d), 120.6 (s), 119.4 (s), 117.7 (t), 117.0 (t), 107.5 (d), 106.9 (d), 62.5 (s), 61.8 (s), 54.2 (q), 52.5 (q), 52.4 (q), 50.3 (t), 46.9 (t), 36.2 (q), 32.3 (t), 32.0 (q), 31.0 (t).

Methyl (2,6-Dichloro-3-{[methyl-{(4*E*)-5-[(4-methylphenyl)sulfonyl]pent-4-enyl}amino]carbonyl}pyridin-4-yl)acetate (35). To a mixture of amide **19** (200 mg, 0.58 mmol), *p*-toluenesulfonyl iodide (200 mg, 0.71 mmol), anhydrous cupric chloride (5 mg, 0.04 mmol), triethylamine hydrochloride (5 mg, 0.04 mmol) was added dry acetonitrile (2 mL), and the resultant mixture was then stirred at room temperature under inert atmosphere in the dark for 3 h. The solvent was removed under reduced pressure, and the crude mixture was dissolved in CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. It was then purified quickly in the dark. The resulting residue was dissolved in dry benzene (4 mL) and treated with triethylamine (0.1 mL, 0.72 mmol) at room temperature. After being stirred for 15 min at same temparature, the mixture was diluted with ether and washed successively with 5% aqueous HCl and water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a dark oil that was purified by column chromatography (ethyl acetate−petroleum ether 20:80) to afford **35** as a yellowish oil (110 mg, 38% yield) that appears as a mixture of rotamers in solution: R_f (EtOAc−petroleum ether, 80:20) 0.34 and 0.26; IR (neat) 1742, 1639, 1317, 1145 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.8−7.6 (m, 2H), 7.32 (d, 2H, J = 8.02 Hz), 7.27 (s, 1H), 6.96 and 6.82 (dt, 1H, J = 6.68 Hz, 15.0 Hz), 6.49−6.16 (m, 1H), 3.75−3.28 (m, 2H), 3.75 (d, 1H, J_{AB} = 16.4 Hz), 3.67 (s, 3H), 3.63 (d, 1H, J_{AB} = 16.4 Hz), 3.15−2.75 (m, 3H), 2.42 (s, 3H), 2.40−2.20 and 2.18−2.0 (m, 2H), 1.98−1.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8 (s), 164.7 (s), 164.6 (s), 164.5 (s), 150.1 (s), 146.1 (s), 145.8 (s), 145.7 (s), 144.7 (d), 144.5 (d), 144.3 (s), 144.1 (s), 143.6 (d), 138.4 (s), 137.3 (s), 137.1 (s), 131.7 (d), 131.4 (d), 131.3 (d), 131.2 (s), 131.1 (s), 130.8 (s), 129.7 (d), 127.9 (d), 127.4 (d), 127.0 (d), 124.9 (d), 52.5 (q), 52.4 (q), 49.7 (t), 46.6 (t), 46.4 (t), 37.5 (t), 35.6 (q), 31.9 (q), 28.5 (t), 28.2 (t), 25.9 (t), 25.4 (t), 24.8 (t), 24.5 (t), 21.4 (q). Anal. Calcd for $C_{22}H_{24}N_2O_5Cl_2S$: C, 52.91, H, 4.84, N, 5.61. Found: C, 53.16, H, 4.90, N, 5.56.

Methyl [2,6-Dichloro-3-({methyl[(4*E*)-5-[(4-methylphenyl)sulfonyl]pent-4-enyl]amino}carbonyl)pyridin-4-yl]acetate (36). To a stirred suspension of sulfone (**35**) (70 mg, 0.14 mmol) and polymer-supported sulfonyl azide (1.2 mmol/g) (380 mg, 0.46 mmol) in acetonitrile (2 mL) was added triethylamine (0.06 mL, 0.42 mmol) dropwise at room temperature. The mixture was then stirred for another 48 h and filtered and the solvent was evaporated under reduced pressure. The diazo product, thus formed, was further purified by column chromatography (ethyl acetate−petroleum ether 20:80) to give **36** as a yellow liquid (50 mg, 68% yield) that appears as a mixture of two rotamers in solution: R_f (EtOAc−petroleum ether, 80:20) 0.39; IR (neat) 2113, 1714, 1641, 1306, 1147 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.96 and 7.89 (s, 1H), 7.82−7.62 (m, 2H), 7.31 (d, 2H, J = 8.05 Hz), 6.94 and 6.80 (dt, 1H, J = 15.0 Hz, 6.67 Hz), 6.42−6.18 (m, 1H), 3.83 (s, 3H), 3.78−2.78 (m, 2H), 3.02 and 2.85 (s, 3H), 2.41 (s, 3H), 2.38−2.21 and 2.15−2.0 (m, 2H), 1.98−1.62 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.3 (s), 164.2 (s), 164.1 (s), 163.3 (s), 150.4 (s), 147.2 (s), 147.0 (s), 144.8 (d), 144.5 (d), 144.4 (s), 143.5 (d), 137.6 (s),

137.5 (s), 132.1 (d), 131.7 (d), 131.6 (d), 129.9 (d), 128.2 (d), 127.6 (d), 127.2 (d), 125.1 (s), 124.9 (s), 119.9 (d), 62.5 (s), 52.8 (q), 50.1 (t), 46.6 (t), 36.0 (q), 32.0 (q), 28.8 (t), 28.4 (t), 26.0 (t), 25.5 (t), 25.0 (t), 24.5 (t), 21.6 (q).

Acknowledgment. Financial support from CSIR, Government of India is gratefully acknowledged. S.B. is thankful to CSIR, Government of India for a Senior Research Fellowship. We are also grateful to Prof. T. Gallagher (Bristol, U.K.), Dr. S. Djuric (Abbott, U.S.) Dr. C. Fehr (Firmenich, Geneva), and Prof. H.-K. Fun (Penang, Malaysia) for continuing help and support. Dr. W. Metz (Aventis, U.S.) is thanked for the gift sample of polymer-supported benzenesulfonyl azide. The authors thank both the National Center for High Performance Computing in Taiwan and the computing center of Academia Sinica for providing computing facilities. Z.S. acknowledges support from the Japan Society for the Promotion of Science. We also thank all the reviewers for their expert comments and helpful suggestions.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of **18**, **19**, **25**, **20**, **26**, **33**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026555P