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retro-Cheletropic ene reactions with 2-carbena-1,3-dioxolane as chelefuge

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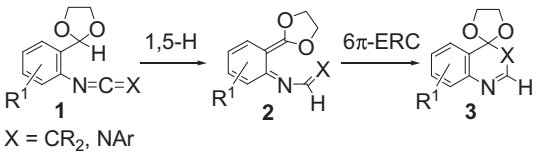
ABSTRACT

N[β-(Hetero)arylvinyl] ketenimines and carbodiimides bearing adequately positioned 1,3-dioxolane functions experience a new class of tandem process consisting of a 6π electrocyclic ring closure followed by a rare *retro*-cheletropic ene reaction, the extrusion of 2-carbena-1,3-dioxolane. This mechanistic sequence is supported by a computational study using DFT methods, showing that the simultaneous recovery of aromaticity at two rings is the clue for the low energy barrier of the *retro*-cheletropic step. Moreover, the highly exergonic decomposition of 2-carbena-1,3-dioxolane into CO_2 plus ethylene contribute to the success of the tandem sequences.

1. Introduction

The translocation of a hydrogen atom along a polyene chain is a well recognized event in organic chemistry. Woodward and Hoffmann characterized and classified this type of sigmatropic rearrangement, the hydrogen shift. Orbital symmetry rules establish in which cases these reactions are either thermally or photochemically allowed, as well as the suprafacial or antarafacial trajectory that the hydrogen atom follows from the atom to which is initially bonded to the migration terminus.[1] Sigmatropic hydrogen shifts are reactions that play an important role in some significant biosynthetic transformations. Probably the most typical example is the one occurring in the biosynthesis of the biologically active form of vitamin D_3: previtamin D_3 converts into vitamin D_3 by thermal isomerization involving an antarafacial 1,7 hydrogen shift.[2] Also in the biosynthesis of Giffordene, an olefinic hydrocarbon [(2*Z*,4*Z*,6*E*,8*Z*)-2,4,6,8-undecatetraene] isolated from the brown alga *Giffordia mitchellae*, evidences of a [1,7]-H migration have been found.[3]

Within the frame of our long-lasting efforts on the chemistry of heterocumulenes,[4] we have recently reported a study on 1,5 hydrogen shifts in acetal-ketenimines **1** (X=CR_2) and acetal-carbodiimides **1** (X=NAr) in which the acetalic H atom migrates to the electrophilic carbon atom of the heterocumulenic function (Scheme 1).[5] The 1,3-dioxolane function was demonstrated to be an excellent H donor fragment and these rearrangements were characterized as intramolecular hydride-like transfers by means of computational studies. The resulting *ortho*-azaxylylene intermediates **2** further undergo 6π electrocyclic ring closure (6π-ERC) to give quinolines **3** (X=CR_2) and quinazolines **3** (X=NAr).



Scheme 1. Cyclization of acetal-ketenimines and -carbodiimides **1**.

Based on these interesting **1**→**3** tandem processes, we targeted the preparation of several ketenimines and carbodiimides of general structure **4** (Scheme 2), in which that of substrates **1** has been modified by inserting a carbon–carbon double bond between the heterocumulenic function and the fragment bearing the dioxolane ring. In these new species the carbon–carbon double bond connecting the 1,3-dioxolane with the vinylheterocumulenic function is part of an aromatic or heteroaromatic ring. Our main aim was to examine the suitability of heterocumules **4** for experiencing a 1,7 hydride-like transfer[6] from the acetalic carbon atom to the electron deficient central carbon atom of the ketenimine or carbodiimide fragment. The putative 3-aza-1,3,5,7-octatetraenic intermediates **5**, resulting from such H shift, could further cyclize by two alternative 6π-ERC modes, either by closure of the X1–C2–N3–C4–C5–C6 3-azatriene system via X1–C6 bond formation or by cyclization of

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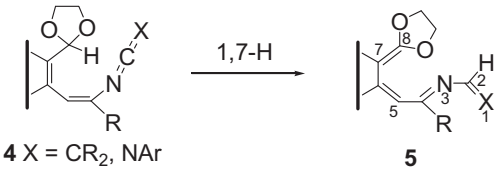
the N3–C4–C5–C6–C7–C8 1-azatriene fragment through N3–C8 bond formation, to give diverse pyridines. An alternative cyclization mode is the 8π-ERC with X1–C8 bond formation to afford azocines. The potential periselectivity of this cyclization step adds further interest to the study of this type of 1,7-H shift.



Scheme 2. *N*-[β-(Hetero)arylvinyl] ketenimines and carbodiimides bearing 1,3-dioxolane functions.

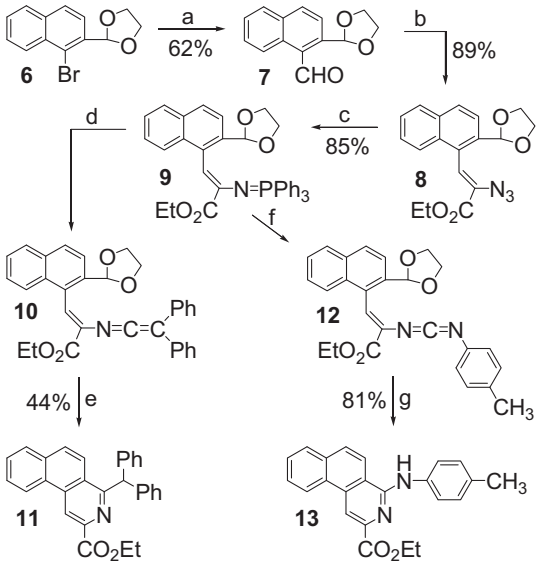
Herein we report our results on the thermal treatment of some examples of ketenimines and carbodiimides of general structure **4**. We show that they experience an unexpected 6π-ERC/*retro*-cheletropic ene reaction tandem process, instead of any of the above sequences involving as the first step a [1,7]-H shift.

2. Results and discussion

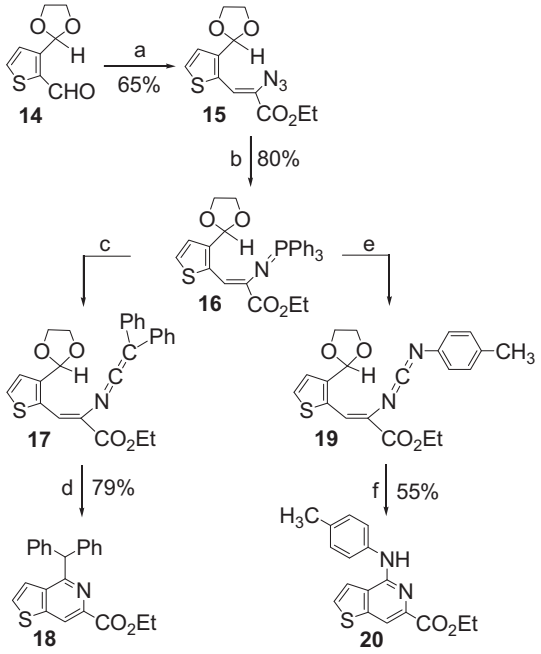
We first prepared ketenimine **10** and carbodiimide **12**. Bromolithium exchange in 2-(1-bromo-2-naphthyl)-1,3-dioxolane **6** using *n*-butyllithium, in diethyl ether at −78 °C, and further reaction with DMF provided 2-(1,3-dioxolan-2-yl)-1-naphthaldehyde **7** in 62% yield. Condensation of aldehyde **7** with ethyl azidoacetate in the presence of sodium ethoxide in ethanol at −15 °C led to β-(1-naphthyl)vinyl azide **8** (89% yield). The imination reaction of triphenylphosphine with the azide **8**, in anhydrous diethyl ether at room temperature, yielded the triphenyliminophosphorane **9** (85% yield). The aza-Wittig reaction of iminophosphorane **9** with diphenylketene in toluene solution at room temperature led to the ketenimine **10**. Its formation was confirmed by an IR spectrum of the reaction mixture showing a very strong absorption band close to 2000 cm^{-1} associated to the N=C=C grouping. This compound was used in the following step without purification. When the toluene solution containing ketenimine **10** was heated at reflux temperature for 1 h the 4-diphenylmethylbenz[*f*]isoquinoline **11** was formed and isolated in moderate yield (44%) (Scheme 3). The reaction of iminophosphorane **9** with 4-methylphenylisocyanate in toluene at room temperature gave carbodiimide **12**, as evidenced the IR spectrum of the reaction mixture showing a strong absorption band close to 2270 cm^{-1} associated to the N=C=N grouping. Under severe thermal conditions (toluene, 170 °C, sealed tube, 24 h) carbodiimide **12** converted into the 4-(4-methylphenyl)aminobenz[*f*]isoquinoline **13** (81% yield).

Benz[*f*]isoquinolines **11** and **13** were characterized following their analytical and spectroscopic data. In their ^{1}H NMR spectra the C(1)H proton resonates as a singlet at δ=9.25 ppm for **11** and δ=8.79 for **13**. The ^{13}C NMR spectrum of benz[*f*]isoquinoline **11** shows the signal of the aliphatic methine carbon atom of the diphenylmethyl substituent at δ=55.9 ppm.

The outcome of the conversions of heterocumulenes **10** and **12** into **11** and **13**, respectively, was striking as the 1,3-dioxolane fragment was absent from the structure of the reaction products. One H atom of such fragment, presumably the most labile acetalic proton, becomes incorporated into **11** and **13**, apparently at the exocyclic C and N atoms linked to C(4) of the benz[*f*]isoquinoline ring system. In order to prove that this outcome is not privative of the 1,2-disubstituted naphthalene scaffolding linking the vinyl-heterocumulene and dioxolane fragments, we next aborded the study of two new similar heterocumulenes built on a 2,3-disubstituted thiophene nucleus. Thus, the condensation of 3-(1,3-dioxolan-2-yl)thiophene-2-carbaldehyde **14** with ethyl azidoacetate and subsequent Staudinger reaction of the azide **15** with triphenylphosphine provided iminophosphorane **16**. Ketenimine **17** was generated in toluene solution by reaction of compound **16** with diphenylketene and activated by heating at 80 °C for converting into the 4-diphenylmethylthieno[3,2-*c*]pyridine **18** (79% yield) (Scheme 4). Carbodiimide **19**, synthesized by reacting **16** with 4-methylphenylisocyanate experienced cyclization to the 4-(4-methylphenyl)aminothieno[3,2-*c*]pyridine **20** (55% yield) by thermal treatment in toluene solution at 160 °C in a sealed tube.



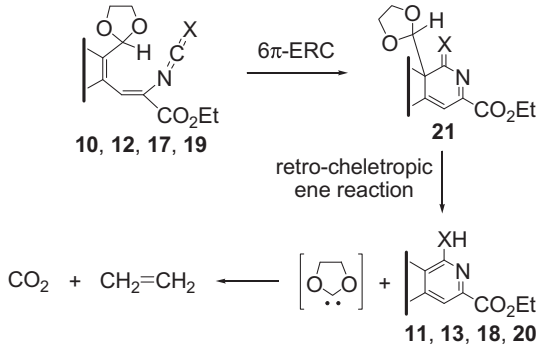
Scheme 3. Reagents and conditions: (a) *n*-BuLi, DMF, Et_2O, −78 °C→rt, 16 h. (b) $N_3CH_2CO_2Et$, Na, EtOH, −15 °C 3 h, then rt 12 h. (c) PPh_3, Et_2O, rt, 16 h. (d) $Ph_2C{=}C{=}O$, toluene, rt, 30 min. (e) Toluene, reflux, 1 h. (f) 4-CH_3–C_6H_4–N=C=O, toluene, rt, 1 h. (g) Toluene, 170 °C, sealed tube, 24 h.



Scheme 4. Reagents and conditions: (a) $N_3CH_2CO_2Et$, Na, EtOH, −15 °C 3 h, then rt 12 h. (b) PPh_3, Et_2O, rt, 16 h. (c) $Ph_2C{=}C{=}O$, toluene, rt, 30 min. (d) Toluene, 80 °C, 2 h. (e) 4-CH_3–C_6H_4–N=C=O, toluene, rt, 1 h. (f) Toluene, 160 °C, sealed tube, 24 h.

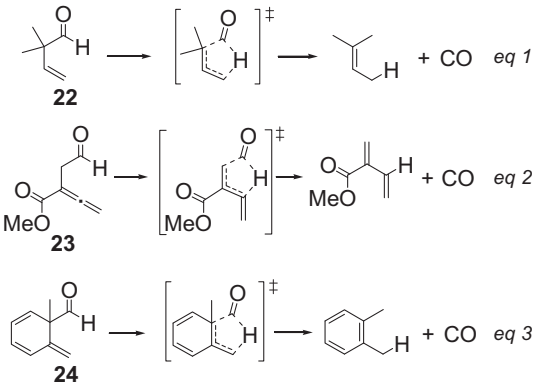
We have envisaged a reasonable mechanism for explaining the conversion of ketenimines **10** and **17** and carbodiimides **12** and **19** into the corresponding fused pyridines **11**, **13**, **18** or **20**.[7] It involves

a 6π-ERC of the heterocumulenic acetals at the first step to give intermediates **21** (Scheme 5). These species would then experience a *retro*-cheletropic ene reaction[8] with extrusion of 2-carbena-1,3-dioxolane to provide the final fused pyridines, a process, that is, probably favoured because the newly formed double bond completes an aromatic system (the pyridine ring). As being previously disclosed, the generated ethylenedioxycarbene should immediately fragment into carbon dioxide and ethylene.[9,10]



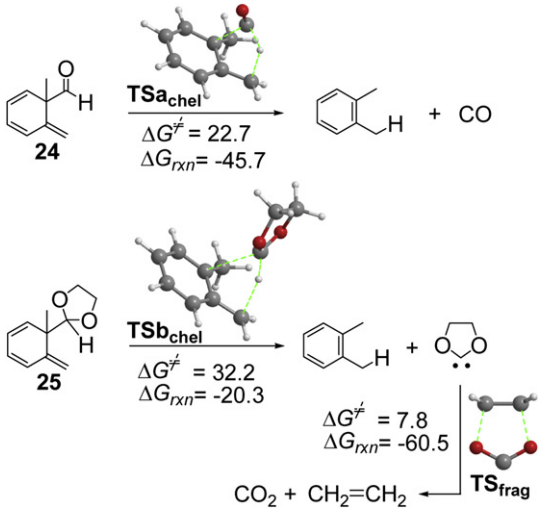
Scheme 5. Proposed mechanism for the conversions **10**→**11**, **12**→**13**, **17**→**18** and **19**→**20**.

Obviously the main interest of the conversions of heterocumulenes **10**, **12**, **17** and **19** into their corresponding fused pyridines **11**, **13**, **18** and **20** is not synthetic but mechanistic. In fact, these final heterocyclic products should reasonably result from similar reaction sequences by starting from less elaborated materials, the respective (hetero)aromatic aldehydes lacking the 1,3-dioxolane functions [H instead of $CH(OCH_2)_2$ in the structures **7** and **14**]. Indeed, compound **20** has been previously prepared in this way.[11] By contrast the herein disclosed synthetic sequences are relevant on mechanistic grounds as they belong to a new class of tandem processes and involve the scarcely reported *retro*-cheletropic ene reaction as the key step. As far as we are aware, no examples of cheletropic ene reactions are known, whereas only a few fragmentations that can be interpreted as the reversal of these processes have been reported: the decarbonylation of 2,2-dimethyl-3-butenal **22**[8b,d] (Eq. 1 in Scheme 6) and those of the structurally related 3,4-pentadienal **23**[8c] (Eq. 2) and 6-methylenecyclohexa-2,4-diene-1-carbaldehyde **24**[8a,b] (Eq. 3).



Scheme 6. Decarbonylation of 2,2-dimethyl-3-butenal (Eq. 1), 3,4-pentadienal (Eq. 2) and 6-methylenecyclohexa-2,4-diene-1-carbaldehyde (Eq. 3).

The transformations in Eqs. 1 and 3 have been computationally studied by DFT methods and shown to proceed by asynchronous concerted mechanisms via five-membered cyclic transition states.[8b] A differentiating fact of the *retro*-cheletropic ene reactions involved in the herein reported experiments is the new divalent species acting as the chelefuge, 2-carbena-1,3-dioxolane instead of the habitual carbon monoxide in the previously disclosed instances represented in Scheme 6. We aimed to compare, by computational evaluation, these two chelefuges. DFT calculations at the B3LYP/6-31+G** theoretical level predict an energy barrier of 22.7 kcal mol^{-1} for the transformation of 1-methyl-6-methylenecyclohexa-2,4-diene-1-carbaldehyde **24** into *ortho*-xylene and carbon monoxide, whereas that calculated for the conversion of 1-methyl-6-methylenecyclohexa-2,4-dienyl-1,3-dioxolane **25** into *ortho*-xylene and ethylenedioxycarbene is higher (32.2 kcal mol^{-1}) (see Scheme 7). However, as the first reaction is considerably more exergonic than the latter (−20.3 vs −45.7 kcal mol^{-1}), we have used the Marcus theory[12] for excluding the effects of the different thermodynamic contributions to the magnitude of these energy barriers by calculating the intrinsic $\Delta G^{\neq}_{Marcus}$ barrier. The calculated $\Delta G^{\neq}_{Marcus}$ values are 45.6 and 42.4 kcal mol^{-1}, respectively, showing that the ability of 2-carbena-1,3-dioxolane as chelefuge is intrinsically comparable, even slightly better, than that of carbon monoxide in these transformations.

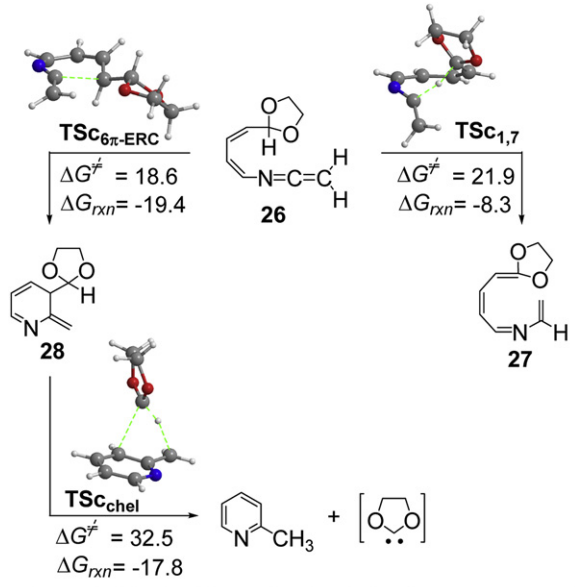


Scheme 7. Comparison of carbon monoxide and ethylenedioxacarbene as chelefuges.

On the other hand, the fragmentation of 2-carbena-1,3-dioxolane into carbon dioxide plus ethylene is a well-known process. Several computational studies have concluded that this reaction takes place in a concerted pathway with a small energy barrier.[13] Our calculations show that 2-carbena-1,3-dioxolane fragments into ethylene and carbon dioxide via the transition state $\mathbf{TS}_{frag}$ involving an energy barrier of 7.8 kcal mol^{-1} (slightly higher than that computed at the CASPT2 level[13b]), and a reaction energy of −60.5 kcal mol^{-1} at the B3LYP/6-31+G**. This notable exergonic and irreversible second step of the conversion **25**→*ortho*-xylene+carbon dioxide+ethylene should be the major driving force for the success of the *retro*-cheletropic ene step.

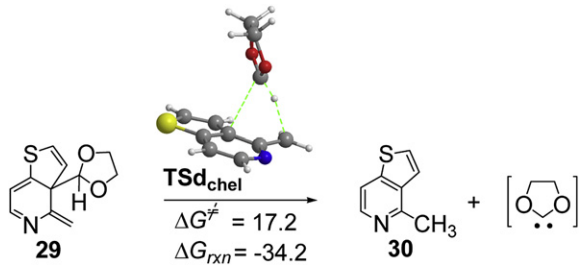
We also targeted to investigate by computations the transformations of the heterocumulenes used in the experimental study into the corresponding fused pyridines, trying to discern why these molecules do not experience the initially planned [1,7]-H shift but instead electrocycle and further extrude the dialkoxycarbene. We first chose the structurally simplest *N*-[(1*Z*,3*Z*)-4-(1,3-dioxolan-2-yl)buta-1,3-dienyl] ketenimine **26** as a model of the heterocumulenes used in the experimental work (Scheme 8). We located the transition state $\mathbf{TSc}_{1,7}$ connecting **26** with the 3-azaoctatetraenic system **27** by [1,7]-H shift of the acetalic proton. $\mathbf{TSc}_{1,7}$ shows a nice helical geometry as expected for this class of sigmatropic rearrangement. The alternative 6π electrocyclic ring closure of **26** leading to 3-(1,3-dioxolan-2-yl)-2,3-dihydro-2-

methylenepyridine (**28**) takes place via the transition structure **TSc**$_{6\pi\text{-ERC}}$,[14] slightly below in energy than **TSc$_{1,7}$** (18.6 vs 21.9 kcal mol^{-1}, respectively). In addition, the 2-methylenepyridine **28** is thermodynamically more stable than the azaoctatetraene **27**. The 2-methylenepyridine **28** further fragments into 2-carbena-1,3-dioxolane and 2-methylpyridine via the transition structure **TSc**$_{chel}$. The calculated energy barrier for this step is 32.5 kcal mol^{-1}, and the reaction energy −17.8 kcal mol^{-1}. The overall process, including the fragmentation of 2-carbena-1,3-dioxolane, i.e., the conversion of ketenimine **26** into 2-methylpyridine, CO_2 and ethylene, is highly exergonic (−90.0 kcal mol^{-1}). Consequently, on the basis of kinetic and thermodynamic grounds, the 1,7-H shift via **TSc$_{1,7}$** leading to **27** is predicted to be non competitive with the experimentally-observed reaction channel, the electrocyclization/extrusion tandem processes of the (het)arene fused analogous of **26**.[15]



Scheme 8. Mechanistic paths found for the conversion of ketenimine **26** into the azaoctatetraene **27** and into 2-methylpyridine+2-carbena-1,3-dioxolane.

Finally, in a closer approximation to the experimental processes, we have also computed the fragmentation of the slightly simplified model 3-(1,3-dioxolan-2-yl)-3,4-dihydro-4-methylenethieno[3,2-*c*]pyridine (**29**) into 4-methylthieno[3,2-*c*]pyridine (**30**) plus 2-carbena-1,3-dioxolane by a similar concerted process (Scheme 9). The value of the energy barrier calculated for this *retro*-cheletropic ene reaction, 17.2 kcal mol^{-1}, is notably lower than the one calculated for the previous conversion of **28** into 2-methylpyridine and the dialkoxycarbene, 32.5 kcal mol^{-1}. This low energy barrier is reasonably interpreted in terms of the gain in aromatization energy occurring not only at the pyridine ring but also at the thiophene fragment. For the same reason, the fragmentation of **29** is also considerably more exergonic, ΔG_{rxn}=−34.2 kcal mol^{-1}, than that of **28**, ΔG_{rxn}=−17.8 kcal mol^{-1}.



Scheme 9. Computed *retro*-cheletropic ene fragmentation of **29**.

3. Conclusions

In summary, we here disclosed some examples of a new type of tandem process involving as key step the rare pericyclic fragmentation known as the *retro*-cheletropic ene reaction. The experimentally-assayed processes are thermally-activated tandem 6π-electrocyclization/fragmentation reactions of *N*-(hetero)aryl-vinyl substituted ketenimines and carbodiimides, bearing a 1,3-dioxolane ring at 2 position of the (hetero)aryl fragment, which were initially designed for testing potential [1,7]-H shifts. A computational DFT study predicts surmountable energy barriers at the experimental reaction conditions, gives account of the peri-selectivity towards the electrocyclization versus the competitive H shift in the first mechanistic step, and also shows that the *retro*-cheletropic ene fragmentation benefits, as presumed, from the simultaneous gain of aromatic stabilization at two nuclei. The unprecedented chelefuge in the *retro*-cheletropic ene step is a dialkoxycarbene, 2-carbena-1,3-dioxolane, which in turn should decompose to carbon dioxide and ethylene as soon as formed in a further fragmentation. This latter concerted step, with a low energy barrier and highly exergonic, should decisively contribute to the success of the experimental processes.

4. Experimental section

4.1. General methods

All melting points are uncorrected. Infrared (IR) spectra were recorded as Nujol emulsions. ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 or 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 100 MHz. The chemical shifts are expressed in parts per million, relative to Me_4Si at δ=0.00 ppm for ^{1}H, while the chemical shifts for ^{13}C are reported relative to the resonance of $CDCl_3$ δ=77.1.

2-(1-Bromo-2-naphthyl)-1,3-dioxolane **6**,[16] 3-(1,3-dioxolan-2-yl)thiophene-2-carbaldehyde **14**[17] and diphenylketene[18] were prepared following published experimental procedures.

4.2. Preparation of benz[*f*]isoquinolines 11 and 13

n-BuLi [4 mL, 2.5 M in hexane] was added dropwise to a solution of 2-(1-bromo-2-naphthyl)-1,3-dioxolane **6** (2.79 g, 10 mmol) in anhydrous diethyl ether (50 mL) at −78 °C under an atmosphere of nitrogen. The mixture was stirred at −78 °C for 30 min, after which a precipitate came out. Then, *N*,*N*-dimethylformamide (1.46 g, 22 mmol) was added. The mixture was stirred at −78 °C for 15 min, warmed to room temperature and stirred for 16 h. Saturated aqueous sodium hydrogen carbonate (50 mL) was added and the solvent was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (4×50 mL), and the combined organic extracts were washed with brine (100 mL) and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure The crude product was purified by column chromatography [silica gel; eluting with hexanes/diethyl ether (7:3, v/v)] to give 2-(1,3-*dioxolan*-2-*yl*)-1-*naphthaldehyde* **7** [yield 62% (1.41 g)].

A mixture of ethyl azidoacetate (5.16 g, 40 mmol) and 2-(1,3-dioxolan-2-yl)-1-naphthaldehyde **7** (2.28 g, 10 mmol) was added dropwise to a well-stirred solution containing sodium (0.92 g) in anhydrous ethanol (50 mL), under nitrogen at −15 °C. The reaction mixture was stirred at −15 °C for 3 h, allowed to warm to room temperature, and the stirring continued for 12 h. The mixture was poured into aqueous 30% ammonium chloride (100 mL) and extracted with diethyl ether (3×80 mL). The combined organic layers were washed with water (3×100 mL) and dried over

anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude material was chromatographed on silica gel, using dichloromethane as eluent to give *ethyl* 2-*azido*-3-[2-(1,3-*dioxolan*-2-*yl*)-1-*naphthyl*]*propenoate* **8** [yield 89% (3.02 g)].

A solution of triphenylphosphine (1.97 g, 7.5 mmol) in anhydrous diethyl ether (20 mL) was added dropwise, under nitrogen, at room temperature, to a solution of ethyl 2-azido-3-[2-(1,3-dioxolan-2-yl)-1-naphthyl]propenoate **8** (2.54 g, 7.5 mmol) in the same solvent (15 mL). The reaction mixture was stirred at room temperature for 16 h. The precipitated *ethyl* 3-[2-(1,3-*dioxolan*-2-*yl*)-1-*naphthyl*]-2-*triphenylphosphoranylideneaminopropenoate* **9** was filtered and air dried [yield 85% (3.65 g)].

*4.2.1. 2-Ethoxycarbonyl-4-diphenylmethylbenz[f]isoquinoline **11**.* To a solution of ethyl 3-[2-(1,3-dioxolan-2-yl)-1-naphthyl]-2-triphenylphosphoranylideneaminopropenoate **9** (0.57 g, 1 mmol) in anhydrous toluene (20 mL) a solution of diphenylketene (0.19 g, 1 mmol) in the same solvent (5 mL) was added. The reaction mixture was stirred at room temperature for 30 min, and then heated at reflux for 1 h. After cooling, the solvent was removed to dryness under reduced pressure and the crude material was chromatographed on silica gel, using hexanes/diethyl ether (7:3, v/v) as eluent, to give 2-*ethoxycarbonyl*-4-*diphenylmethylbenz*[*f*]*isoquinoline* **11** [yield 44% (0.18 g)]; mp 163–164 °C (colourless prisms, diethyl ether); IR (Nujol) 1719 (vs), 1281 (vs), 1258 (vs), 1168 (m), 1143 (s), 1029 (m), 816 (m), 758 (s), 739 (s), 702 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (t, 3H, J=7.1 Hz), 4.45 (q, 2H, J=7.1 Hz), 6.47 (s, 1H), 7.18–7.41 (m, 10H), 7.70–7.74 (m, 2H), 7.84 (d, 1H, J=9.2 Hz), 7.87–7.90 (m, 1H), 8.10 (d, 1H, J=9.2 Hz), 8.79 (d, 1H, J=7.9 Hz), 9.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 55.9, 61.5, 117.4, 122.4, 123.7, 126.6, 127.3 (s), 127.8, 128.3, 128.7, 129.0, 129.5 (s), 129.8, 130.4, 132.9 (s), 135.8 (s), 142.4 (s), 142.7 (s), 160.8 (s), 166.3 (s); HRMS (ESI): calcd for $C_{29}H_{24}NO_2$ $[M+H]^+$ 418.1802; found 418.1806.

*4.2.2. 2-Ethoxycarbonyl-4-(4-methylphenyl)aminobenz[f]isoquinoline **13**.* To a solution of ethyl 3-[2-(1,3-dioxolan-2-yl)-1-naphthyl]-2-triphenylphosphoranylideneaminopropenoate **9** (0.57 g, 1 mmol) in anhydrous toluene (20 mL) a solution of 4-methylphenylisocyanate (0.13 g, 1 mmol) in the same solvent (5 mL) was added. The reaction mixture was stirred at room temperature for 1 h, and then heated at 170 °C in a sealed tube for 24 h. After cooling, the solvent was removed to dryness under reduced pressure and the crude material was chromatographed on silica gel, using hexanes/diethyl ether (7:3, v/v) as eluent, to give 2-*ethoxycarbonyl*-4-(4-*methylphenyl*)*aminobenz*[*f*]*isoquinoline* **13** [yield 81% (0.29 g)]; mp 187–189 °C (yellow prisms, diethyl ether); IR (Nujol) 1698 (vs), 1611 (vs), 1577 (vs), 1512 (vs), 1403 (vs), 1270 (vs), 1250 (vs), 1181 (s), 822 (s), 749 (s), 718 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52 (t, 3H, J=7.2 Hz), 2.34 (s, 3H), 4.51 (q, 2H, J=7.2 Hz), 7.16 (d, 2H, J=8.1 Hz), 7.18 (s, 1H), 7.68–7.74 (m, 4H), 7.79 (d, 1H, J=9.0 Hz), 7.86 (d, 1H, J=9.0 Hz), 7.88–7.91 (m, 1H), 8.65–8.68 (m, 1H), 8.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 20.8, 61.6, 111.6, 117.7 (s), 119.0, 119.4, 123.8, 127.7, 128.62, 128.64, 129.5, 131.9 (s), 133.1 (s), 136.2 (s), 138.4 (s), 141.3 (s), 152.3 (s), 166.4 (s); HRMS (ESI): calcd for $C_{23}H_{21}N_2O_2$ $[M+H]^+$ 357.1598; found 357.1604.

4.3. Preparation of thieno[3,2-*c*]pyridines 18 and 20

A mixture of ethyl azidoacetate (5.16 g, 40 mmol) and 3-(1,3-dioxolan-2-yl)thiophene-2-carbaldehyde **14** (1.84 g, 10 mmol) was added dropwise to a well-stirred solution containing sodium (0.92 g) in anhydrous ethanol (50 mL), under nitrogen at −15 °C. The reaction mixture was stirred at −15 °C for 3 h and then allowed to warm to room temperature, and the stirring continued for 12 h. The mixture was poured into aqueous 30% ammonium chloride (100 mL) and extracted with diethyl ether (3×80 mL). The combined organic layers were washed with water (3×100 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude material was chromatographed on silica gel, using dichloromethane as eluent to give *ethyl* 2-*azido*-3-[3-(1,3-*dioxolan*-2-*yl*)-2-*thienyl*]*propenoate* **15** [yield 65% (1.92 g)].

A solution of triphenylphosphine (1.97 g, 7.5 mmol) in anhydrous diethyl ether (20 mL) was added dropwise, under nitrogen, at room temperature, to a solution of ethyl 2-azido-3-[3-(1,3-dioxolan-2-yl)-2-thienyl]propenoate **15** (2.21 g, 7.5 mmol) in the same solvent (15 mL). The reaction mixture was stirred at room temperature for 16 h. The precipitated *ethyl* 3-[3-(1,3-*dioxolan*-2-*yl*)-2-*thienyl*]-2-*triphenylphosphoranylideneaminopropenoate* **16** was filtered and air dried [yield 80% (3.18 g)].

*4.3.1. 6-Ethoxycarbonyl-4-diphenylmethylthieno[3,2-c]pyridine **18**.* To a solution of ethyl 3-[3-(1,3-dioxolan-2-yl)-2-thienyl]-2-triphenylphosphoranylideneaminopropenoate **16** (0.53 g, 1 mmol) in anhydrous toluene (20 mL) a solution of diphenylketene (0.19 g, 1 mmol) in the same solvent (5 mL) was added. The reaction mixture was stirred at room temperature for 30 min, and then heated at 80 °C for 2 h. After cooling, the solvent was removed to dryness under reduced pressure and the crude material was chromatographed on silica gel, using hexanes/diethyl ether (1:1, v/v) as eluent, to give 6-*ethoxycarbonyl*-4-*diphenylmethylthieno*[3,2-*c*]*pyridine* **18** [yield 79% (0.29 g)]; mp 105–106 °C (colourless prisms, diethyl ether); IR (Nujol) 1728 (vs), 1541 (m), 1492 (m), 1297 (s), 1283 (s), 1251 (s), 1211 (m), 1183 (m), 1080 (m), 1031 (m), 796 (w), 751 (m), 724 (m), 706 (m), 690 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 3H, J=7.2 Hz), 4.45 (q, 2H, J=7.2 Hz), 6.19 (s, 1H), 7.22–7.37 (m, 11H), 7.55 (d, 1H, J=5.6 Hz), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 58.0, 61.6, 118.4, 122.7, 126.7, 128.4, 129.5, 130.2, 136.7 (s), 141.2 (s), 142.0 (s), 148.3 (s), 157.8 (s), 165.7 (s); HRMS (ESI): calcd for $C_{23}H_{20}NO_2S$ $[M+H]^+$ 374.1209; found 374.1212.

*4.3.2. 6-Ethoxycarbonyl-4-(4-methylphenyl)aminothieno[3,2-c]pyridine **20**.* To a solution of ethyl 3-[3-(1,3-dioxolan-2-yl)-2-thienyl]-2-triphenylphosphoranylideneaminopropenoate **16** (0.53 g, 1 mmol) in anhydrous toluene (20 mL) a solution of 4-methylphenylisocyanate (0.13 g, 1 mmol) in the same solvent (5 mL) was added. The reaction mixture was stirred at room temperature for 1 h, and then heated at 160 °C in a sealed tube for 24 h. After cooling, the solvent was removed to dryness under reduced pressure and the crude material was chromatographed on silica gel, using hexanes/diethyl ether (3:7, v/v) as eluent, to give 6-*ethoxycarbonyl*-4-(4-*methylphenyl*)*aminothieno*[3,2-*c*]*pyridine* **20** [yield 55% (0.17 g)].[11]

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Supplementary data

^1H and ^{13}C NMR spectra of compounds **11**, **13** and **18**. Details of computational procedures, cartesian coordinates, and energies for all the stationary points. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.05.119.

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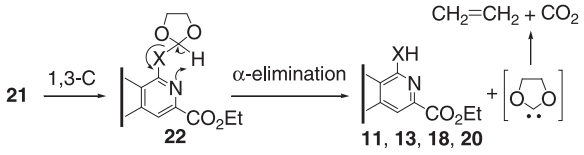

This alternative mechanistic sequence, in our view less convincing than the former one, was finally discarded on computational ground: see Ref. 14.

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14. We could locate an alternative isomeric transition state for the electrocyclic ring closure of **26** higher in energy than $\mathbf{TSc}_{6\pi\text{-ERC}}$ (see Supplementary data).
15. We have discarded the alternative mechanistic path involving 1,3 migration and α-elimination (see Ref. 7) on the following grounds: (i) we could not locate a first order transition structure for the 1,3 migration of the dioxolane ring; (ii) although we were able to locate a transition structure (see Supplementary data) for the 1,3-[CH_3] shift transforming 2,3-dihydro-3-methyl-2-methylenepyridine into 2-ethylpyridine, whose geometry correspond to a suprafacial migration with inversion at the migrating group (in agreement with the Woodwad–Hoffman rules), the energy barrier for this process is very high (57.6 kcal mol−1); (iii) all the attempts to optimize an analogous transition state for the migration of a 1,3-dioxolan-2-yl fragment failed or converged into the transition state corresponding to the *retro*-chelotropic ene reaction, $\mathbf{TSc}_{chel}$.
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