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Dedicated to Paul A. Wender on the occasion of his 60th year

Abstract: Photodimers of 2-pyridones are cyclocta-1,5-dienes with two lactam bridges. These, and related structures, undergo halogenation to give rearranged products in which an amide nitrogen has intercepted an initial halonium ion. For the trans isomer, a transient four-membered azetidinium ion reacts via dealkylation, giving a dihalide-diamide product in high yield. This readily available intermediate reacts with nucleophiles in a process that begins with intramolecular amide N-alkylation, reforming the azetidinium intermediate. Reaction of this intermediate with the nucleophile can take two different paths, depending on the reversibility of the nucleophilic attack, with reversible nucleophiles giving N-dealkylation and irreversible nucleophiles reacting with the carbonyl group.

Key words: cycloadditions, dimerizations, ketones, photochemistry, pyridines

Photodimerization of 2-pyridones 1 yields highly functionalized cyclocta-1,5-dienes regioselectively and often with good stereoselectivity (Scheme 1). This singlet-mediated [4+4] cycloaddition is selective for head-to-tail isomers 2 and 3, frequently favoring trans-isomer 2 (Scheme 1). Procedures for favoring either trans-2 or cis-3 have been described.2-4

Each of these conformationally rigid structures has been found to undergo transannular reactions with amide nitrogen migration when treated with chlorine (Scheme 1). Treatment of trans-dimer 2 with chlorine results in a 1,3-migration of one amide nitrogen to yield 4, whereas a similar treatment of 3 leads to participation of both alkenes, creating a diquinane structure 5, whose formation is also accompanied by migration of an amide nitrogen (Scheme 1).

Diquinane 5 has obvious applications in natural product synthesis,5,6 but is derived from the less stable dimer 3 and is formed in moderate yield. In contrast, product 4 forms in high yield from the most common and most stable dimer 2. We describe here groundwork for the use of this readily available intermediate: investigations into the halogenation of trans-2 and related structures, and the reactivity of nucleophiles with product 4, which contains both an allylic and a non-allylic secondary halide. A preliminary report on this work has appeared.7

Formation of 4 from 2 involves an intermediate chloronium ion 6, in which the chlorine has been added to the least-hindered face of one alkene group (Scheme 2). This chloronium ion is then intercepted by the amide nitrogen that lies on the other side. The resulting azetidinium amide 7 is reminiscent of a von Braun intermediate, primed to undergo dealkylation.6,9 Three possible bonds can be broken in the next step, following paths a, b, and c (Scheme 2). In terms of orbital overlap, path a initially appeared to be the most likely; however, this potential product 8 is not observed, possibly because of the electro-negative influence of the neighboring chloride. The von Braun reaction is well known for dealkylation of cyclic amines. This path b, however, would lead to the frustrated amide 9, and it also not observed. Path c appears less obvious, but leads to the sole product 4 that is isolated (Scheme 2). Initially it was believed that the allylic nature of this position led to this site of reactivity; however, the actual reason is apparently more subtle (see below).

Three N-alkylpyridone dimers have been subjected to halogenation (Scheme 3, Table 1). Addition of chlorine to

Scheme 1 Photodimerization of 2-pyridones and chlorination of the cis- and trans-dimers...
the N-butyl dimer 2a gave product 4a in almost quantitative yield, with the structure confirmed by X-ray crystallography. The more labile N-benzyl and N-(methoxymethyl) derivatives also gave the dichlorides 4c and 4d in high yield. Bromination of 2a smoothly gave the dibromide 4b.

Dihalides 4 present a unique array of functionality, with a secondary aliphatic halide and a secondary allylic halide, flanked by tertiary amides on both sides of the central cyclooctene. An initial probe of the reactivity of 4a was conducted by treating this dichloride with sodium ethoxide (Scheme 4). Inspection of the structure of 4a (Figure 1) reveals that SN2 attack on both chlorides is blocked by an amide near the alkene face syn to the chloride. The rate determining bond to be broken in nucleophilic attack via path a is longer by 0.005 Å. The selectivity for path c is therefore likely to be a consequence of the steric and electronic effect of the chloride substitution next to the azetidinium ion.

Modeling of intermediate 7 found the rather symmetric structure shown in Figure 2. The azetidinium ion has two bonds between carbon and nitrogen that would be broken by nucleophilic attack by paths a and c. In this analysis, the two bonds are nearly identical in length; the bond to be broken in nucleophilic attack via path a is longer by 0.005 Å. The selectivity for path c is therefore likely to be a consequence of the steric and electronic effect of the chloride substitution next to the azetidinium ion.

Investigation of the chlorination reaction was expanded to include the pyridone–naphthalene cycloadduct 15.
formed by irradiation of 13 and produced as a mixture with the cis-isomer 14 (Scheme 5). Substrate 15 has two non-equivalent alkenes, and there is little discrimination between them: two products were formed in this reaction and both were definitively proven by X-ray crystallography. One product of this reaction is the equivalent of that described above, from chloronium ion interception by a nearby amide nitrogen. The resulting azetidinium ion 16 is then cleaved by chloride to give 18 (Scheme 5).

Where chlorination of the alternative alkene occurs, the chloronium is intercepted by the nearby aromatic ring, via cyclobutane 17 (Scheme 5). In this case, the structure of 19 suggests that the chloride opening of intermediate 17 occurs in an $S_2^2$ fashion to give 19. In this case, however, a direct $S_2$ opening of cyclobutane 17 would yield a tertiary allylic chloride, which might be expected to rear-

Scheme 5  Products 18 and 19 produced by chlorination of 15; both the amide nitrogen and the phenyl group migrate

range to 19. It is notable that there are two different phenyl migrations possible for 15, one leading through 17 to 19 (Scheme 5). The alternative phenyl migration isomer is not observed.

Nucleophilic substitution of the allylic chloride in 4a was studied with nucleophiles in addition to ethoxide (Scheme 6). With nucleophiles that can add reversibly to a carbonyl, substitution of the chloride proceeded smoothly. The reaction with sodium methoxide gave substitution analogous to that of sodium ethoxide, although with a slightly reduced yield. Thiophenol and pyrrolidine, both in the presence of sodium hydride, gave sulfur and nitrogen displacement examples. Malononitrile also gave substitution in good yield.
Harder nucleophiles revealed another reaction path, attacking the carbonyl group of the intermediate azetidinium 7a (Scheme 7, Table 2). When the amide in 4a displaces the chloride to give 7a, the amide carbonyl becomes susceptible to nucleophilic attack (see arrow, Scheme 7). In the case of reversible nucleophiles such as ethoxide, addition to this acyl ammonium carbonyl is of little consequence. When the nucleophile addition is irreversible, however, the addition leads to formation of a ketone or aldehyde, which then suffers a second addition. Allyl Grignard addition proceeds in good yield, to give essentially one product 21a (Scheme 7, Table 2). Other Grignard reagents (phenyl, ethyl, phenylethynyl) were less satisfactory, yielding mixtures of products, although these reactions were not optimized.

With hydride as the nucleophile, the reaction was slower and produced a range of products (Scheme 7, Table 2). With sodium borohydride in ethanol at ambient temperature for eight hours, starting 4a remained, but was fully consumed after an additional two hours at reflux. In this case, the major product was 10a, by chloride displacement by solvent, with a lesser amount of the dechlorinated 23b formed in substantial amounts (Scheme 7, Table 2). With lithium borohydride in THF for seven days, only azetidine products were isolated; however, two-thirds of this product included loss of the allylic chloride, to give 22b (Scheme 7, Table 2). It is tempting to suggest that this product results from internal delivery of a hydride from the newly formed primary alcohol.

Photocycloaddition of 2-pyridones with themselves, or with other 1,3-diene equivalents (1,3-dienes, furan, naphthalene), yields well-functionalized cycloocta-1,5-dienes, often in high yield and with good regio- and stereoselectivity. When these cycloocta-1,5-diene products are treated with chlorine or bromine, transannular participation leads to novel structures. For the reactions of the trans-cycloadducts described here, capture of the intermediate halonium ion by the amide nitrogen forms a reactive four-membered ammonium intermediate that then reacts with modest nucleophiles such as chloride, giving the product in high yield and as a single stereoisomer. When the halogenation substrate is the achiral pyridone dimer 4, which has a center of symmetry, the product is chiral, with six contiguous stereogenic centers. The allylic halide is readily displaced with relatively soft nucleophiles, but this reaction is governed by one of the nearby amide nitrogens. These studies are continuing.

Et₂O, THF and CH₂Cl₂ were dried using a Glass Contour (now Seca Solvent Systems) purification system. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker WM-400 spectrometer. Exact mass measurements were performed with a VG70SE instrument at Drexel University.

1-Benzylpyridin-2(1H)-one (1c)⁴
To a soln of 2-pyridone (7.1 g, 75 mmol) in MeOH (100 mL) was added K₂CO₃ (21 g, 150 mmol) and BnBr (13 mL, 112 mmol). The mixture was heated to reflux for 2.5 h, filtered, and concentrated. The residue was diluted with H₂O (150 mL) and extracted with EtOAc (4 x 50 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc).

Yield: 12.3 g (89%); colorless solid; Rᵥ = 0.42 (hexanes–EtOAc, 1:2); mp 68 °C (Lit. 72 °C).

¹H NMR (400 MHz, CDCl₃): δ = ca. 7.28–7.19 (m, 7 H), 6.56 (d, J = 9.2 Hz, 1 H), 6.08 (dd, J = 6.4, 1.2 Hz, 1 H), 5.09 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 163.0, 139.7, 137.6, 136.7, 129.2, 128.5, 128.8, 121.6, 106.6, 52.4.

1-(Methoxymethyl)pyridin-2(1H)-one (1d)⁵
To a soln of 2-pyridone (5.0 g, 53 mmol) in THF (200 mL) at 0 °C was added NaH (1.9 g, 79 mmol). After 0.5 h, MOMCl (4.8 mL, 63 mmol) was added, and the mixture was stirred at 0 °C for an additional 0.5 h. The soln was diluted with sat. NH₄Cl (100 mL), extracted with EtOAc (4 x 100 mL), dried (Na₂SO₄), and concentrated in vacuo. Yield: 7.4 g (100%); oil; Rᵥ = 0.47 (MeOH–CH₂Cl₂, 1:20).

¹H NMR (400 MHz, CDCl₃): δ = 7.29 (m, 2 H), 6.48 (d, J = 8.4 Hz, 1 H), 6.13 (t, J = 6.4 Hz, 1 H), 5.24 (s, 2 H), 3.32 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 163.2, 140.3, 136.4, 121.7, 106.4, 78.5, 57.3.

(1R*,2R*,5S*,6S*)-3,7-Dibenzyl-3,7-diaza-tricyclo[4.2.2.2²⁷]deca-9,11-diene-4,8-dione (2c)
An 8.0 M soln of 1-benzylpyridin-2(1H)-one (1c; 12.0 g, 64.78 mmol) in MeOH (8 mL) was irradiated with a water-cooled Pyrex-
filtered 450-W medium-pressure mercury lamp for 3 d. The solvent was concentrated in vacuo and the residue was washed with hexanes.

Yield: 3.6 g (30%); colorless solid.

1H NMR (400 MHz, CDCl3): δ = 7.25 (m, 3 H), 7.07 (m, 2 H), 6.47 (t, J = 6.9 Hz, 1 H), 5.97 (t, J = 8.1 Hz, 1 H), 5.05 (d, J = 15.0 Hz, 1 H), 3.95 (m, 1 H), 3.53 (m, 2 H).

13C NMR (100 MHz, CDCl3): δ = 174.3, 136.3, 135.4, 130.7, 129.1, 128.4, 128.1, 55.4, 50.9, 50.7.

(1R,2R,5S,6S)-3,7-Bis(methoxymethyl)-3,7-diazatricyclo[4.2.2.2\textsuperscript{2,5}]dodeca-9,11-diene-4,8-dione (2d)

Neat 1-(methoxymethyl)pyridine-2(1H)-one (1d; 7 g; 52.46 mmol) was irradiated with a water-cooled Pyrex-filtered 450-W medium-pressure mercury lamp for 22 h. The colored impurities were removed by flash chromatography (MeOH–CH₂Cl₂, 5:100). Other impurities were washed out with Et₂O; this gave pure 2d.

Yield: 700 mg (10%); colorless solid; R<sub>f</sub> = 0.42 (MeOH–CH₂Cl₂, 1:20); mp 200 °C.

IR (KBr): 2958, 2930, 2871, 1661, 1467, 1176, 737 cm\textsuperscript{-1}.


To a soln of 2a (107 mg, 0.35 mmol) in CH₂Cl₂ (5 mL) was added 4a (0.16 mmol) in CH₂Cl₂ (5 mL). The resulting mixture was stirred at r.t. for 0.5 h. The soln was diluted with sat. NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (4 × 20 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo.

Yield: 135 mg (100%); colorless solid; R<sub>f</sub> = 0.57 (hexanes–EtOAc, 1:2); mp 165–167.5 °C.

IR (KBr): 2958, 2932, 2872, 1662, 1467, 1176, 753 cm\textsuperscript{-1}.

1H NMR (400 MHz, CDCl₃): δ = 5.93 (dt, J = 12.0, 1.6 Hz, 1 H), 5.77 (t, J = 10.8 Hz, 1 H), 4.85 (q, J = 2.0 Hz, 1 H), 4.22 (dd, J = 4.0, 1.6 Hz, 1 H), 3.91–3.81 (m, 2 H), 3.66–3.58 (m, 3 H), 3.49 (dt, J = 10.0, 1.6 Hz, 1 H), 3.11–2.98 (m, 2 H), 1.56–1.23 (m, 8 H), 0.90 (t, J = 7.2 Hz, 3 H), 0.86 (t, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 166.2, 166.7, 137.1, 127.1, 60.1, 59.7, 58.1, 56.1, 51.1, 48.7, 48.2, 47.5, 30.1, 30.0, 20.7, 20.6, 14.1, 14.0.

(1R,4S,7S,8S,11R,12R)-7,12-Dibromo-2,10-dibutyl-2,10-diazatricyclo[6.4.0.0\textsuperscript{4,11}]dodeca-5,9-diene (4d)

To a soln of 4a (100 mg, 0.2 mmol) in CH₂Cl₂ (5 mL) was added a 0.63 M soln of Cl₂ in CH₂Cl₂ (0.38 mL, 0.24 mmol), and the resulting mixture was stirred at 0 °C for 0.5 h. The soln was diluted with sat. NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo.

Yield: quantitative; colorless solid; R<sub>f</sub> = 0.54 (MeOH–CH₂Cl₂, 1:20); mp 58–60 °C.

HRMS–FAB: m/z [M + H]+ calcd for C₁₄H₁₈N₂O₂Br₂: 463.041879; found: 463.0410.


(1R,4S,7S,8S,11R,12R)-7,12-Dichloro-2,10-bis(methoxymethyl)-2,10-diazatricyclo[6.4.0.0\textsuperscript{4,11}]dodeca-5,9-diene (4d)

To a soln of 2a (55 mg, 0.2 mmol) in CH₂Cl₂ (5 mL) was added a 0.63 M soln of Cl₂ in CH₂Cl₂ (0.38 mL, 0.24 mmol), and the resulting mixture was stirred at r.t. for 1 h. The soln was diluted with sat. NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo.

Yield: quantitative; colorless solid; R<sub>f</sub> = 0.54 (MeOH–CH₂Cl₂, 1:20); mp 158–160 °C.

HRMS–FAB: m/z [M + H]+ calcd for C₁₄H₁₈N₂O₂Cl₂: 349.0722; found: 349.0733.
1H NMR (400 MHz, CDCl3): δ = 5.85 (d, J = 12.8 Hz, 1 H), 5.75 (m, J = 10.4 Hz, 2.8 Hz, 1 H), 4.22 (dd, J = 4.4, 1.6 Hz, 1 H), 4.19 (q, J = 2.4 Hz, 1 H), 3.85 (m, 2 H), 3.63 (m, 4 H), 3.40 (q, J = 7.2 Hz, 1 H), 3.34 (d, J = 10.4 Hz, 1 H), 3.07 (m, 2 H), 1.37 (m, 2 H), 1.20 (m, 6 H), 1.20 (t, J = 6.8 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 3 H), 0.84 (t, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 167.1, 166.5, 137.8, 125.4, 65.3, 60.2, 58.9, 58.0, 48.2, 48.1, 47.5, 46.4, 30.1, 30.0, 20.66, 20.59, 15.5, 14.1.


To a soln of compound 4c (69 mg, 0.20 mmol) in absolute EtOH (15 mL) was added 0.5 M NaOEt in EtOH (0.55 mL, 0.27 mmol), and the mixture was heated at reflux for 0.5 h. The solvent was cooled and concentrated in vacuo. The residue was diluted with sat. NH4Cl (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried (MgSO4) and concentrated. The residue was purified by flash chromatography (hexanes–EtOAc, 1:1:1); mp 261–263 °C.

Yield: 45 mg (23%); colorless solid; Rf = 0.41 (hexanes–EtOAc, 1:1); mp 261–263 °C.

IR (KBr): 2934, 2873, 1671, 1465, 1357, 1305, 1296, 1295, 1294, 1284, 1256, 65.2, 60.3, 58.6, 56.2, 51.8, 51.4, 47.2, 46.3, 15.6.


To a soln of compound 4d (69 mg, 0.20 mmol) in absolute EtOH (5 mL) was added 0.5 M NaOEt in EtOH (0.6 mL, 0.30 mmol), and the mixture was heated at reflux for 1 h. The solvent was cooled and concentrated in vacuo. The residue was diluted with sat. NH4Cl (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organics were dried (MgSO4) and concentrated. The residue was purified by flash chromatography (MeOH–CH2Cl2, 5:100); mp 192–193 °C.

Yield: 60 mg (98%); colorless solid; Rf = 0.34 (hexanes–EtOAc, 1:1); mp 192–193 °C.

IR (KBr): 3475, 3301, 3032, 2976, 2870, 1595, 1464, 1264, 1169, 1096, 732 cm⁻1.


To a soln of compound 15 (157 mg, 0.56 mmol) in CH2Cl2 (10 mL) was added 0.46 M MeCl in CH2Cl2 (1.6 mL, 0.73 mmol), and the mixture was heated at reflux for 1 h. The solvent was diluted with sat. NaHCO3 (30 mL) and extracted with EtOAc (4 × 40 mL). The combined organics were dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 2:1). This gave 18a and 19a.

Compound 18a Yield: 33 mg (17%); colorless solid; Rf = 0.65 (hexanes–EtOAc, 1:1); mp 261–263 °C.

IR (KBr): 2924, 2853, 1666, 1478, 1087, 953, 741 cm⁻1.


Compound 19a Yield: 45 mg (23%); colorless solid; Rf = 0.49 (hexanes–EtOAc, 1:1); mp 182–184 °C.

IR (KBr): 3052, 2975, 2926, 2843, 1665, 1460, 1266, 1070, 734 cm⁻1.
1H NMR (400 MHz, CDCl3): δ = 7.24–7.14 (m, 2 H), 7.10 (dd, J = 7.2, 0.8 Hz, 1 H), 6.07 (dd, J = 7.2, 1.2 Hz, 1 H), 5.50 (dd, J = 7.2, 1.6 Hz, 1 H), 4.93 (d, J = 8.8 Hz, 1 H), 4.64 (dd, J = 6.4, 2.0 Hz, 1 H), 4.25 (dd, J = 4.0, 1.2 Hz, 1 H), 4.18 (d, J = 13.2 Hz, 1 H), 3.97 (m, 2 H), 3.75 (dt, J = 12.8, 2.0 Hz, 1 H), 3.65 (d, J = 9.2 Hz, 1 H), 3.11 (s, 3 H), 3.06 (d, J = 2.0 Hz, 1 H).

13C NMR (100 MHz, CDCl3): δ = 170.9, 146.8, 141.0, 134.6, 129.2, 128.8, 128.4, 126.3, 71.9, 70.0, 67.6, 60.5, 59.8, 55.4, 52.4, 50.3, 40.8.


Dibromides 18b and 19b
To a soln of 15 (72 mg, 0.25 mmol) in CH2Cl2 (10.0 mL) at 0 °C was added Br2 (14.5 µL, 0.28 mmol) in CH2Cl2, and the mixture was stirred at 0 °C for 1 h. The soln was diluted with sat. NaHCO3 (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 2:1); this gave 18b and 19b.

Compound 18b
Yield: 39 mg (35%); Rf = 0.51 (hexanes–EtOAc, 2:1); mp 225–227 °C.

1H NMR (400 MHz, CDCl3): δ = 7.69 (m, 1 H), 7.44 (m, 2 H), 7.33 (m, 1 H), 5.63 (d, J = 11.7 Hz, 1 H), 5.31 (d, J = 1.5 Hz, 1 H), 5.25 (dd, J = 11.7, 2.4 Hz, 1 H), 5.10 (d, J = 9.0 Hz, 1 H), 4.60 (d, J = 10.2 Hz, 2 H), 4.28 (d, J = 10.8 Hz, 1 H), 4.20 (d, J = 10.8 Hz, 1 H), 4.08 (d, J = 10.2 Hz, 1 H), 3.74 (d, J = 9.3 Hz, 1 H), 3.32 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 168.0, 138.4, 135.9, 132.7, 132.4, 130.2, 127.5, 127.4, 123.6, 78.7, 74.3, 61.8, 60.4, 58.4, 56.9, 51.7, 48.8, 35.8.

Compound 19b
Yield: 16 mg (14%); Rf = 0.32 (hexanes–EtOAc, 2:1); mp 105–107 °C.

1H NMR (400 MHz, CDCl3): δ = 7.29–7.24 (m, 2 H), 7.15 (dd, J = 7.6, 1.2 Hz, 1 H), 7.03 (dd, J = 7.6, 1.2 Hz, 1 H), 5.28 (d, J = 6.8 Hz, 1 H), 5.03 (d, J = 8.8 Hz, 1 H), 4.86 (t, J = 5.2 Hz, 1 H), 4.42 (dd, J = 4.4, 1.2 Hz, 1 H), 4.27 (d, J = 12.8 Hz, 1 H), 4.08–3.98 (m, 2 H), 3.85 (dt, J = 12.8, 2.0 Hz, 1 H), 3.73 (d, J = 9.2 Hz, 1 H), 3.27 (s, 3 H), 3.26 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 170.1, 146.4, 141.8, 134.9, 129.2, 128.9, 128.4, 126.2, 118.5, 79.4, 73.9, 60.9, 56.8, 55.6, 53.4, 51.0, 49.3, 42.0.

HRMS–FAB: m/z [M + Na]+ calcd for C18H17NO3Br2: 495.9523; found: 495.9522.

(1R*,4S*,7S*,8S*,11R*,12R*)-2,10-Dibutyl-7-chloro-12-methoxy-2,10-diazatricyclo[6.4.0.04,11]dodec-5-ene-3,9-dione (20a)
To a soln of 4a (100 mg, 0.27 mmol) in anhyd MeOH (5 mL) was added 0.16 M NaOMe in MeOH (2 mL, 0.32 mmol), and the mixture was heated at reflux for 30 h. The soln was cooled and concentrated in vacuo. The residue was diluted with sat. NH4Cl (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried (MgSO4) and concentrated. The residue was purified by flash chromatography (hexanes–EtOAc, 1:2) to give 20a.

Yield: 92 mg (93%); colorless solid; Rf = 0.25 (hexanes–EtOAc, 1:2); mp 63–66 °C.

1H NMR (400 MHz, CDCl3): δ = 5.90 (d, J = 12.0 Hz, 1 H), 5.83 (m, 1 H), 4.25 (dd, J = 4.0, 2.0 Hz, 1 H), 4.11 (m, 1 H), 3.93 (d, J = 10.0 Hz, 1 H), 3.86 (m, 1 H), 3.63 (m, 3 H), 3.42 (s, 3 H).
in THF (3 mL), and the mixture was warmed to r.t. overnight. The solution was diluted with H2O (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 1:5) to give 20d.

Yield: 87 mg (80%); colorless solid; Rf = 0.76 (EtOAc).

IR (KBr): 3416, 2959, 2932, 2872, 1643, 1468 cm⁻¹.


Compound 21b

Flash chromatography (hexanes–EtOAc, 1:2) gave 10a; yield: 51 mg (50%); 23b; yield: 27 mg (30%).

IR (KBr): 3052, 2961, 2842, 1666, 1265, 739 cm⁻¹.


References


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(10) See ref. 6
(11) Compound 10a crystallized in the rhombohedral space group $R\overline{3}$, with $a = 25.354 (2) \text{Å}, b = 25.354 (2) \text{Å}, c = 18.437 (2) \text{Å},$ and $Z = 18$. Direct solution using 4159 unique reflections with SHELXL-97 gave a final $R_1 = 0.0707$ and $R_2 = 0.1980$.
(12) This structure was calculated by initially building a structure with a carbon atom in place of the positively charged nitrogen, and minimizing the structure using molecular mechanics. The resulting structure was then modified by replacing the carbon with a positively charged nitrogen and minimizing the structure using PM3 (MOPAC). The calculation was performed using WebMO (www.webmo.net). Images were generated with PyMOL (pymol.sourceforge.net).
(13) Compound 18a crystallized in the monoclinic space group $P2_1/n$, with $a = 8.8752 (11) \text{Å}, b = 16.318 (2) \text{Å}, c = 13.575 (2) \text{Å}, \beta = 90.9270 (10)\degree$, $V = 1965.7 (5) \text{Å}^3$, and $Z = 4$. Direct solution using 3180 unique reflections with SHELXL-97 gave a final $R_1 = 0.0372$ and $R_2 = 0.0816$.