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Intramolecular Ketenimine−Ketenimine [2 + 2] and [4 + 2] Cycloadditions[†]

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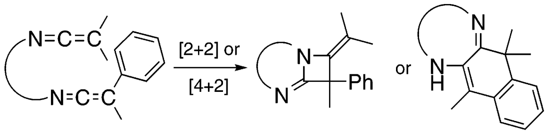
Received March 6, 2007



Bis(ketenimines), in which the two heterocumulenic functions are placed in close proximity on a carbon skeleton to allow their mutual interaction, show a rich and not easily predictable chemistry. Intramolecular [2 + 2] or [4 + 2] cycloadditions are, respectively, observed when both ketenimine functions are supported on either *ortho*-benzylic or 2,2′-biphenylenic scaffolds. In addition, nitrogen-to-carbon [1,3] and [1,5] shifts of arylmethyl groups in *N*-arylmethyl-*C*,*C*-diphenyl ketenimines are also disclosed.

Ketenimines are excellent building blocks for the synthesis of differently ring-sized nitrogen heterocycles, thanks to their ability for adding nucleophiles[1] and carbon-centered radicals[2] to their central carbon atom. They are also commonly involved in pericyclic events[1] such as cycloaddition reactions, 6π-electrocyclic ring closures, and sigmatropic rearrangements.[3] Among these types of reactions, only a few symmetric and unsymmetric [2 + 2] dimerizations of ketenimines have been reported. The known [2 + 2] modes have provided 2-iminoazetidines,[4] an unsymmetrical type of dimer, and the symmetrical dimers 1,2- or 1,3-bis(imino)cyclobutanes[5] and 1,3-diazetidines.[4b,6]

Despite the fascinating chemistry of ketenimines, only a few reactions have been conducted on bis(ketenimines): (1) the addition of dicarboxylic acids,[7] diamines,[8] and phosphinidene complexes[9] to bis(ketenimines) of general structure $R_2C{=}C{=}N{-}Z{-}N{=}C{=}CR_2$ ($Z = p$-C_6H_4, m-C_6H_4, p-$C_6H_4{-}CH_2{-}C_6H_4$-p) forming poly(*N*-acylamides), polyamidines, and bis(phosphindoles), respectively; (2) double electrocyclic ring closures of bis(ketenimines) in which two *N*-vinyl ketenimine moieties are placed on a heteroaromatic five-membered ring (pyrrole, furan, or thiophene) that occur with the simultaneous formation of two pyridine rings for producing dipyridopyrroles, furodipyridines, and thienodipyridines;[10] (3) double [1,5] migrations of alkyl(aryl)thio groups from carbonyl carbon atoms to the central carbon of ketenimine functions, to yield bis(3*H*-quinolin-4-ones) linked via their respective C2 carbon atoms by dithioether chains;[3a] and (4) an intramolecular Diels−Alder cycloaddition involving two different ketenimine functions, *N*-aryl and *N*-vinyl, yielding a benzonaphthyridine.[11]

Our interest in the chemistry of ketenimines led us to prepare some new examples of bis(ketenimines) in which the two functions are supported in proximal positions of a variety of carbon scaffolds, with the aim of exploring putative intramolecular [2 + 2] cycloadditions between the two ketenimine moieties, in their different regiochemical modes.

To this end, we first chose an *ortho*-xylene scaffold as the platform for placing two ketenimine functions. The preparation of the diazide **1** was carried out simply by reaction of α,α'-dichloro-*o*-xylene with sodium azide, as previously reported.[12] The sequential treatment, at room temperature, in the same reaction flask, of a toluene solution of **1** with triphenylphosphine and diphenylketene led to the bis(ketenimine) **2** (Scheme 1), whose formation was secured by a very strong absorption band near 2000 cm^{-1} in the IR spectrum of the reaction mixture, associated with the N=C=C groupings. Bis(ketenimine) **2** remained unaltered when kept in the toluene solution at room temperature. However, when it was heated at reflux temperature until the total disappearance of the cumulenic band in its IR spectrum (approximately 2 h), the dinitrile **3** was formed in 51% yield (calculated global yield from **1**). A similar chemical behavior was observed for the bis(ketenimine) **5**, derived from 2,2′-bis(azidomethyl)biphenyl **4**, which yielded the related

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[†] Dedicated to Prof. Miguel Yus on his 60th birthday.

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[§] Servicio Universitario de Investigación Científica.

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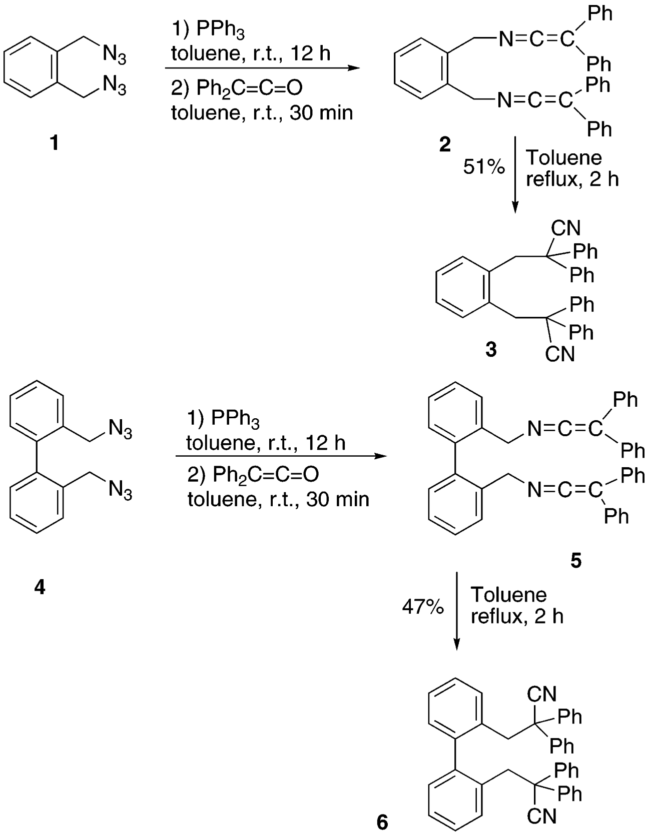
10.1021/jo0704661 CCC: $37.00

SCHEME 1. Bis(ketenimines) 2 and 5



dinitrile **6**. These results were not unprecedented. It is known that *N*-benzyl ketenimines experience, under thermal conditions, 1,3-migration of the benzyl group from nitrogen to carbon for yielding rearranged 3-phenylpropionitriles.[13]

The failure of the intramolecular ketenimine−ketenimine [2 + 2] cycloaddition in compounds **2** and **5** led us to look for other scaffolds. In a series of articles,[14] we have demonstrated that imino−ketenimines in which the nitrogen atoms of the imine and ketenimine functions are linked by an *ortho*-benzylic framework undergo intramolecular [2 + 2] cycloadditions involving both nitrogenated functions. We reasoned that the substitution of the imine group in this type of imino−ketenimines by a second ketenimine function should give us a chance for finding an intramolecular ketenimine−ketenimine [2 + 2] cycloaddition.

The reaction of the 2-azidobenzyl halides **7** with sodium azide, in DMSO solution, and the subsequent Staudinger reaction of the diazides **8** with triphenylphosphine in diethyl ether provided the bis(iminophosphoranes) **9**. Bis(ketenimines) **10** were generated in dichloromethane by reaction of **9** with diphenylketene (Scheme 2). Compounds **10** converted at room temperature into the azeto[2,1-*b*]quinazolines **11**, which were isolated from the final reaction mixtures in moderate yields (Table 1).

SCHEME 2. Bis(ketenimines) 10

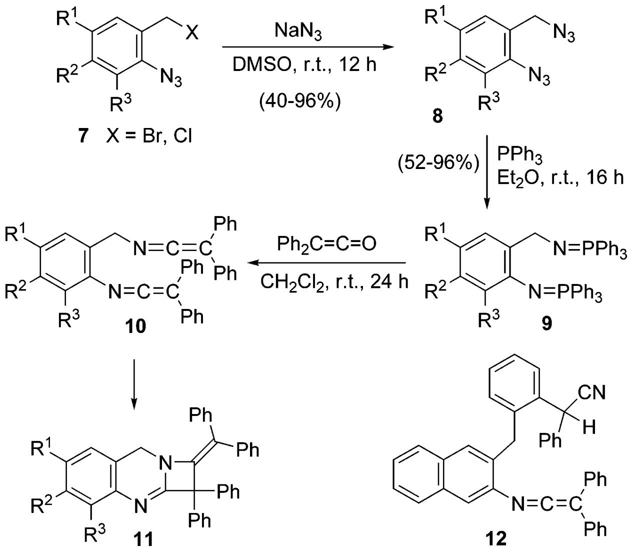


TABLE 1. Azeto[2,1-*b*]quinazolines 11

compound	R^1	R^2	R^3	yield (%)
11a	H	H	H	49
11b	H	H	CH$_3$	77
11c	Br	H	H	78
11d	Cl	H	H	76
11e	CH$_3$	H	H	51
11f	*o*-C$_6$H$_4$		H	16[a]

[a] The major product was nitrile **12** (61%).

The structure of these fused 2-iminoazetidines was determined following their analytical and spectral data and was confirmed by the X-ray structure determination of a monocrystal of **11d** (R^1 = Cl, R^2 = R^3 = H) (see Supporting Information).

The regioselective conversion of **10** → **11**, involving the N═C bond of the *N*-benzyl ketenimine fragment and the C═C bond of the *N*-aryl ketenimine moiety, most likely occurs by a stepwise mechanism similar to that of the intramolecular ketenimine−imine [2 + 2] cycloaddition.[14] Thus, the more nucleophilic nitrogen atom, that of the *N*-benzyl ketenimine fragment, should add to the electrophilic sp-hybridized carbon atom of the other ketenimine unit to give a zwitterionic intermediate, which in the second step of the reaction would ring close to form the azetidine ring present in compounds **11**.

Surprisingly, bis(ketenimine) **10f**, built on a naphthalenemethyl scaffold, furnished as the major reaction product the nitrile **12**[15] (61%), accompanied by the expected [2 + 2] cycloadduct **11f** (16%). It seems reasonable to assume that the formation of **12** is the result of a 1,5-rearrangement of the (2-naphthyl)methyl group to an *ortho* position of one of the phenyl substituents at the ketenimine terminal carbon atom. This rearrangement probably involves a geminate radical pair, similarly to what has been proposed for the 1,3-migrations previously mentioned.[13] To our knowledge, this is the first observation of a 1,5-rearrangement in *N*-arylmethyl ketenimines.

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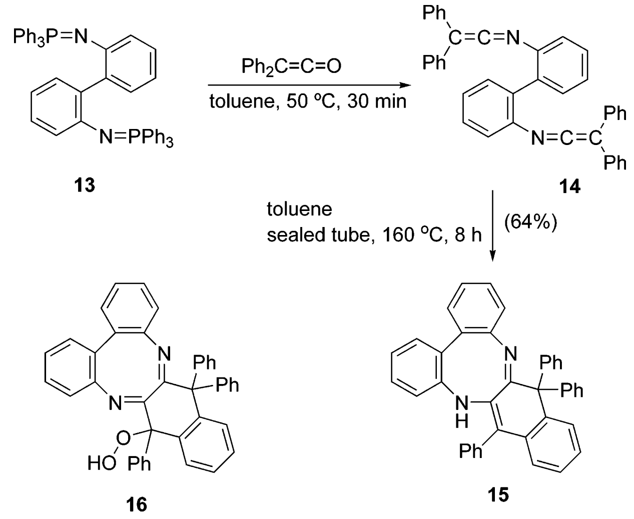
[15] The structure of nitrile **12** was unequivocally determined by X-ray analysis, although the collected data are of low quality for publication. Its analytical and spectral data are in full agreement with such structure.

SCHEME 3. Bis(ketenimine) 14



At this moment, we have no arguments to explain the difference in the reaction pathway for the bis(ketenimine) **10f** when compared with its *N*-benzyl analogous **10a**−**e**.

In addition, we explored the reactivity of biphenylene bis(ketenimine) **14**, in which both ketenimine nitrogens are linked to aryl carbon atoms. Treatment of a suspension of bis(iminophosphorane) **13**[16] with diphenylketene in toluene at 50 °C resulted in the smooth formation of bis(ketenimine) **14**. By heating in toluene solution at 160 °C in a sealed tube, this bis(ketenimine) underwent a clean intramolecular cyclization to furnish the pentacyclic compound **15** (Scheme 3). The structure of **15** could not be established unambiguously from its analytical and spectroscopic data, and so we directed our efforts to obtain monocrystals. The very low solubility of **15** in the usual organic solvents led us to crystallize it from nitrobenzene. Unexpectedly, the X-ray diffraction study of the crystals disclosed the structure of hydroperoxide **16** (see Supporting Information). Furthermore, part of this compound was recovered from the crystallization flask and could be fully characterized by its analytical and spectroscopic data. Hydroperoxide **16** probably formed by spontaneous oxidation of compound **15** by the action of the atmospheric oxygen during the crystallization process. Previous to this work, we have observed oxidations in air of compounds with NH−C═C fragments similar to the one which becomes oxidized in **15**, although in those cases, the reaction products were instead the corresponding tertiary alcohols.[17]

The conversion of **14** → **15** can be interpreted as a formal [4 + 2] cycloaddition, in which one of the ketenimine cumulated C═C bonds forms part of an all-carbon diene,[17,18] and the other one plays the role of the dienophile.[19]

In summary, here we have shown the preparation and chemical behavior of bis(ketenimines) with structures that allow the mutual interaction of their two heterocumulenic functions. Whereas the combination of two *N*-benzyl ketenimine moieties led to independent 1,3-migrations at both heterocumulene fragments, the adequate positioning of *N*-benzyl and *N*-aryl ketenimine functions in an *ortho*-benzylic scaffold resulted in regioselective intramolecular ketenimine−ketenimine [2 + 2] cycloadditions. In contrast, the disposition of two *N*-aryl ketenimine fragments on a 2,2′-biphenylene skeleton led to their interaction through an intramolecular Diels−Alder reaction.

Experimental Section

Sample Procedure for the Preparation of Azeto[2,1-*b*]quinazolines 11. To a solution of bis(iminophosphorane) **9** (1 mmol) in anhydrous dichloromethane (20 mL) was added a solution of diphenylketene (0.58 g, 3 mmol) in the same solvent (5 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the resulting material was purified by column chromatography using hexanes/diethyl ether as eluent.

2,2-Diphenyl-1-diphenylmethylidene-1,2-dihydroazeto[2,1-*b*]quinazoline 11a: eluent for column chromatography, hexanes/diethyl ether (7:3, v/v); yield 49%; mp 236 °C (colorless prism, diethyl ether/*n*-pentane); IR (Nujol) 1713 (s), 1635 (vs), 1601 (vs), 1570 (s), 1470 (s), 1294 (m), 1201 (s), 1131 (vs), 1119 (s), 1093 (m), 1073 (m), 1030 (m), 940 (w), 862 (w), 784 (m), 764 (vs), 723 (s), 701 (vs), 694 (vs), 664 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.23 (s, 2H), 6.69−6.73 (m, 3H), 6.93−7.00 (m, 3H), 7.03−7.07 (m, 1H), 7.13−7.16 (m, 2H), 7.26−7.37 (m, 15H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 44.7, 70.0 (s), 114.7 (s), 121.2 (s), 125.0, 126.4, 126.6, 127.0, 127.4, 127.7, 127.9, 128.0, 128.5, 128.6, 129.9, 131.1, 138.4 (s), 138.6 (s), 138.9 (s), 142.0 (s), 145.5 (s), 164.2 (s); MS (EI, 70 eV) *m/z* (rel int) 474 (M$^+$, 26), 204 (100). Anal. Calcd for C$_{35}$H$_{26}$N$_2$ (474.60): C, 88.58; H, 5.52; N, 5.90. Found: C, 88.30; H, 5.61; N, 6.03.

Procedure for the Preparation of Compound 15. To a suspension of bis(iminophosphorane) **13** (0.70 g, 1 mmol) in anhydrous toluene (30 mL) was added a solution of diphenylketene (0.43 g, 2.25 mmol) in the same solvent (5 mL). The reaction mixture was stirred at 50 °C for 30 min, and the resulting solution was heated in a sealed tube at 160 °C for 8 h. The solvent was removed to dryness, and the solid residue was triturated with dichloromethane (25 mL). The precipitated yellow solid was filtered and dried: yield 64%; mp 204 °C; IR (Nujol) 3350 (s), 1660 (vs), 1610 (s), 1558 (s), 1492 (s), 1268 (m), 1226 (w), 1158 (w), 1110 (w), 1093 (w), 1032 (w), 767 (vs), 752 (vs), 727 (s), 704 (vs) 656 (s) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, 100 °C) δ 5.27 (s, 1H), 6.21 (d, 1H, J = 7.8 Hz), 6.45−6.50 (m, 3H), 6.62 (dd, 1H, J = 7.7, 0.9 Hz), 6.92−7.19 (m, 16H), 7.28−7.37 (m, 4H), 7.42−7.46 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, 100 °C) δ 64.8 (s), 118.7 (s), 119.1, 122.4, 124.2, 124.9, 125.5, 125.7 (s), 125.8, 125.9, 126.1, 126.3, 126.7, 127.2, 127.3, 127.6, 127.8, 128.6, 128.8, 129.2, 129.4, 131.3, 134.6 (s), 135.1 (s), 135.4 (s), 136.2 (s), 139.4 (s), 139.8 (s), 140.1 (s), 142.9 (s), 148.1 (s), 166.2 (s); MS (EI, 70 eV) *m/z* (rel int) 536 (M$^+$, 100). Anal. Calcd for C$_{40}$H$_{28}$N$_2$ (536.67): C, 89.52; H, 5.26; N, 5.22. Found: C, 89.33; H, 5.38; N, 5.29.

Acknowledgment. This work was supported by the Ministerio de Educación y Ciencia of Spain and FEDER (Project

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CTQ2005-02323/BQU), and Fundación Séneca-CARM (Project 00458/PI/04). B.B. also thanks Fundación Séneca-CARM for a fellowship.

Supporting Information Available: Experimental details for the synthesis of compounds **3**, **6**, **8**, and **9**. Spectral data (NMR, IR, MS, elemental analyses) for compounds **3**, **6**, **8**, **9**, **11b**−**f**, **12**, and **16**. X-ray data and CIF files of **11d** and **16**. ^{1}H and ^{13}C NMR spectra of compounds **3**, **6**, **11a**−**f**, **12**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0704661