New Applications of the Imine-Ketenimine Intramolecular [2+2] Cycloaddition Reaction: Highly Stereocontrolled Synthesis of Azeto[1,2-*a*]pyrimidines

Mateo Alajarín,*[a] Angel Vidal,[a] and Raúl-Angel Orenes[a]

Keywords: Cycloaddition / Diastereoselectivity / Imines / Ketenimines / Nitrogen heterocycles

Imino-ketenimines **7**, in which the reactive functionalities are linked by an allylic tether connecting the imino and ketenimino nitrogen atoms, undergo a formal intramolecular [2+2] cycloaddition to yield azeto[1,2-*a*]pyrimidines **8**. When enantiotopic ketenimine and imine fragments are combined, the resulting azeto[1,2-*a*]pyrimidines **8e–i** contain two stereogenic carbon atoms C-6 and C-7, and the cycloaddition takes place with complete diastereoselectivity in favor of the *cis* diastereoisomers. This methodology has also been applied to the preparation of some azeto[1,2-*a*][1,3]thiazolo[4,5-*d*]pyrimidines **16**, representative examples of a new fused heterocyclic system.

Introduction

Ketenimines are able to participate in [2+2] cycloaddition reactions through either their C=N or their C=C bonds.[1,2] Usually these heterocumulenes undergo [2+2] cycloaddition reactions through their cumulated C=C bond, thus contributing two carbon atoms to the new four-membered ring, which should also contain an exocyclic imino group. This chemical behavior of ketenimines has already been successfully exploited in the synthesis of four-membered heterocycles,[3] based on the reaction between ketenimines and compounds containing carbon−heteroatom (C=X) or heteroatom−heteroatom (X=Y) double bonds, such as heterocumulenes, azo and nitroso compounds, aldehydes and (thio)ketones, and imines.

Reactions between ketenimines and imines to furnish azetidin-2-imines were first reported by Regitz in 1979, who showed that *N*-cyano-*C*-(diphenylamino)ketenimine cycloadded to benzylideneaniline in an intermolecular fashion.[4] A year later, Ghosez studied the reactions of *N*-alkyl- and *N*-arylketenimines with imines, proving that enhancement of the electrophilic character of the ketenimine by the introduction of an electron-withdrawing substituent (such as tosyl) on its nitrogen atom was mandatory for the occurrence of the cycloaddition.[5] Since then, these reactions remained unexplored until recently, when we undertook the study of the intramolecular [2+2] cycloaddition reaction between ketenimine and imine functions supported on an *ortho*-benzylic scaffold (e.g., **1**), which afforded the azeto[2,1-*b*]-quinazolines **2** in a highly stereocontrolled manner (Figure 1).[6−10]

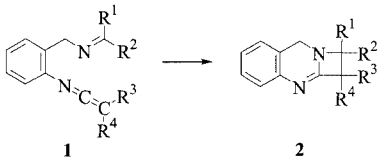


Figure 1. Intramolecular [2+2] cycloaddition of imino-ketenimines on an *ortho*-benzylic scaffold

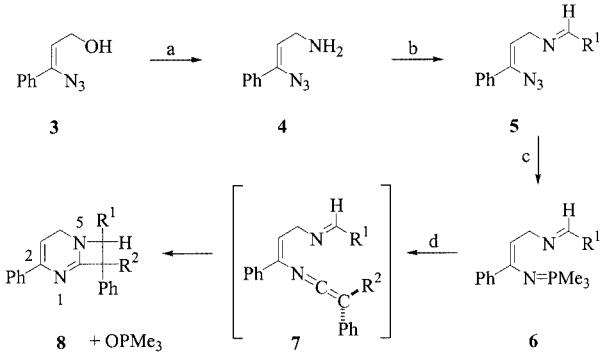
As result of a study aimed towards exploration of the efficiency of these [2+2] cycloaddition reactions in other imino-ketenimines related to **1**, bearing different tethers between their reactive functionalities, we present here a new synthetic approach to azeto[1,2-*a*]pyrimidines and a method for the preparation of the previously unknown azeto[1,2-*a*][1,3]thiazolo[4,5-*d*]pyrimidine ring system. In these cases, the C=C double bond of the allylic system connecting the nitrogen atoms of the ketenimine and imine functions is part of an acyclic alkene or a thiazole ring, respectively.

Results and Discussion

The starting compound for the synthesis of azeto[1,2-*a*]pyrimidines was the previously unreported (*Z*)-3-azido-3-phenyl-2-propen-1-amine (**4**). A Mitsunobu reaction between the 2-propen-1-ol **3**[11] and triphenylphosphane, diethyl azodicarboxylate and phthalimide followed by hydrazinolysis afforded the amine **4**. Treatment of **4** with aromatic, heteroaromatic and α,β-unsaturated aldehydes under mild conditions, in diethyl ether solution and in the presence of anhydrous magnesium sulfate,[12] provided the corresponding aldimines **5** in almost quantitative yields. Azido-

[a] Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, Espinardo, 30100 Murcia, Spain
Fax: (internat.) + 34-968/364149
E-mail: alajarin@um.es

imines **5** were used in the next reaction step as crude products, due to the hydrolytic sensitivity of the imine function. In fact, all attempts to purify compounds **5** either by crystallization or column chromatography failed, yielding mixtures of the amine **4** and the corresponding aldehyde. Staudinger treatment[13] of azidoimines **5** with trimethylphosphane, in toluene solution at room temperature, yielded the *P*,*P*,*P*-trimethyl-λ^5-phosphazenes **6**. The conversion **5** → **6** was complete in less than 30 min, as monitored by IR (disappearance of the azide vibration near 2100 cm^{-1}). In the same reaction flask, the trimethylphosphazenes **6** were treated with 1 equiv. of diphenyl ketene or methyl phenyl ketene, giving the intermediate ketenimines **7**, which could be detected in the reaction medium by IR spectroscopy (2000 cm^{-1}, N=C=C) shortly after the addition of the ketene. Compounds **7** underwent a straightforward transformation within minutes in toluene solution at room temperature, yielding 6,7-dihydro-4*H*-azeto[1,2-*a*]pyrimidines (**8**) (Scheme 1). The separation of the reaction products from the trimethylphosphane oxide was carried out by column chromatography. Azetopyrimidines **8** were obtained in low to acceptable overall yields (20−60%) for the conversion **5** → **8**, three reaction steps in a one-pot process (Table 1). The low yields may be the result of partial



Scheme 1. Reagents and conditions: (a) (i) PPh_3, $EtO_2CN{=}NCO_2Et$, phthalimide, THF, 0 °C 1 h, room temp. 36 h; (ii) $N_2H_4{\cdot}H_2O$, THF/EtOH, room temp. 16 h, 50 °C 2 h; (b) R^1CHO, $MgSO_4$, room temp., 16 h; (c) PMe_3, toluene, room temp., 30 min (d) $R^2PhC{=}C{=}O$, toluene, room temp., 30 min

Table 1. 2-Phenyl-6,7-dihydro-4*H*-azeto[1,2-*a*]pyrimidines **8** and 2,5,5-triphenyl-5,8-dihydro-6*H*-azeto[1,2-*a*][1,3]thiazolo[4,5-*d*]-pyrimidines **16**

Compound	R^1	R^2	Yield [%]
8a	4-BrC_6H_4	C_6H_5	42
8b	4-$O_2NC_6H_4$	C_6H_5	39
8c	3-furyl	C_6H_5	20
8d	(*E*)-2-$O_2NC_6H_4CH{=}CH$	C_6H_5	34
8e	4-BrC_6H_4	CH_3	60
8f	4-ClC_6H_4	CH_3	48
8g	4-$O_2NC_6H_4$	CH_3	52
8h	3-furyl	CH_3	41
8i	(*E*)-2-$O_2NC_6H_4CH{=}CH$	CH_3	30
16a	4-BrC_6H_4		51
16b	4-ClC_6H_4		64

decomposition of compounds **8** during the purification step. We have observed that heterocycles **8** are not stable in solution at room temperature, slowly decomposing to yield complex mixtures that we were not able to resolve.

The structural characterization of compounds **8** is mainly based on their ^1H and ^{13}C NMR spectroscopic data. Their ^1H NMR spectra show 3-H as a triplet at δ = 5.36−5.53 ppm (^3J = 2.9−3.3 Hz) and 6-H as a singlet [except for **8d** and **8i**, in which R^1 = (*E*)-2-$O_2NC_6H_4CH{=}CH$] at δ = 4.59−5.55 ppm. The two methylene protons at C-4 appear as diastereotopic (each one as a doublet of doublets, with a geminal coupling constant of 12.0−12.8 Hz) in compounds **8a**−**d**, whereas for the remaining compounds **8e**−**i** these protons just appear as doublets. The protons of the 7-CH_3 methyl group in compounds **8e**−**i** appear as singlets at δ = 1.82−1.94 ppm. In their ^{13}C NMR spectra the signals at δ = 67.0−75.3 ppm and δ = 61.6−71.3 ppm are attributable to the methine and quaternary carbon atoms C-6 and C-7, respectively. The IR, MS and analytical data of compounds **8** are in perfect agreement with the proposed structures.

Imino-ketenimines **7e**−**i**, in which R^2 = CH_3, combine imine and ketenimine fragments with enantiotopic faces. Consequently, the intramolecular cyclization of these compounds could provide mixtures of *cis*- and *trans*-azeto[1,2-*a*]pyrimidines **8e**−**i** (Figure 2). However, the intramolecular cyclization of **7e**−**i** in each case provided a single diastereoisomer, *cis*-**8**, as corroborated by ^1H NMR analysis of the crude reaction mixtures before chromatography.

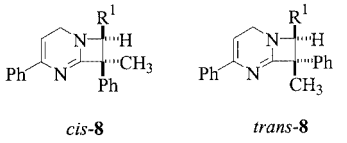


Figure 2. Azeto[1,2-*a*]pyrimidines *cis*-**8** and *trans*-**8**

The relative configurations of the two stereogenic centers (C-6 and C-7) in compounds **8e**−**i** were assigned on the basis of the values of the chemical shifts of the 7-CH_3 protons, and on analysis of their gate-decoupled ^{13}C NMR spectra. Figure 3 presents the chemical shifts of the 7-CH_3 protons of the azeto[1,2-*a*]pyrimidines **8e**−**i**, and those of the 2-CH_3 protons of the structurally related azeto[2,1-

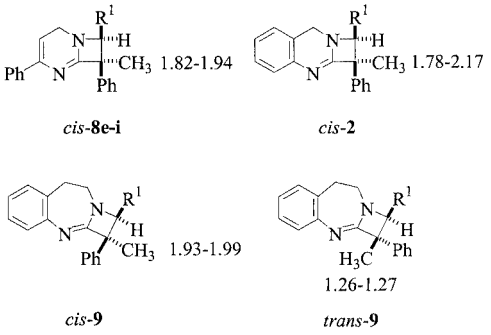


Figure 3. Selected ^1H NMR (δ, ppm) data for compounds *cis*-**8e**−**i**, *cis*-**2**, *cis*-**9** and *trans*-**9**

b]quinazolines *cis*-**2** and azeto[2,1-*b*][1,3]benzodiazepines *cis*-**9** and *trans*-**9**, for which the relative *cis*/*trans* configurations have been determined unequivocally.[8] By analysis of these data, relative *cis* configurations could be reliably assigned to the compounds **8e−i** prepared in this work.

Moreover, the gate-decoupled ^{13}C NMR spectra of compounds **8e−i** allowed observation of the coupling between the CH_3 carbon atom linked to C-7 and the proton 6-H. From the values of these coupling constants ($^3J_{C,H}$ = 3.5−4.2 Hz) a dihedral angle close to 35° between the mentioned nuclei can be calculated,[14] which is also in agreement with a *cis* geometry (Figure 4). Nearly no coupling would be expected for the *trans* isomers.

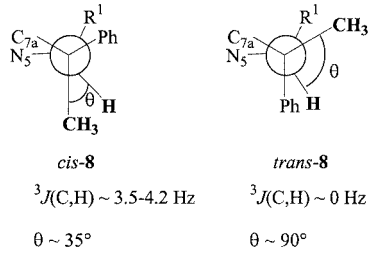


Figure 4. Newman projection of *cis*-**8** (R^2 = CH_3) and *trans*-**8** (R^2 = CH_3) along the C-6−C-7 bond

From a mechanistic point of view, the formation of the bicyclic compounds **8** from imino-ketenimines **7** can be explained by a two-step sequence: initial nucleophilic addition of the nitrogen atom of the imine function to the sp-hybridized carbon atom of the ketenimine, and subsequent conrotatory 4π-electrocyclization of the resulting zwitterionic intermediate.[8−10] On the basis of this mechanistic sequence, the conversion of imino-ketenimines **7e−i**, which bear two different substituents (CH_3 and Ph) on the sp^2 carbon terminus of the ketenimine fragment, into the [2+2] cycloadducts *cis*-**8** should occur through the zwitterionic intermediate (*E*)-INT (Figure 5), resulting from the nucleophilic ring-closure of compounds **7e−i** through a Ph-*exo*[8] transition state. Conrotation of (*E*)-INT should produce *cis*-**8**. The experimental results show that [2+2] cycloadditions of compounds **7e−i** to produce **8** occur with high diastereoselectivity, as the *trans*-**8** adducts were never isolated nor detected. This fact can be explained by considering that the cyclization of compounds **7** giving rise to the zwitterionic intermediates occurs exclusively by the sterically less congested Ph-*exo* mode of addition.

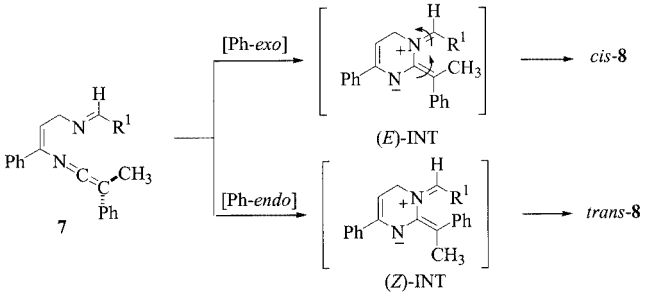
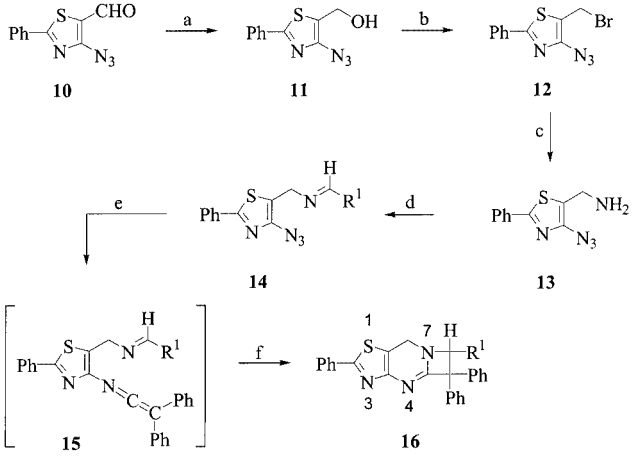


Figure 5. Mechanism for the conversion **7** → **8**

Some methods have been reported in the literature for the synthesis of azeto[1,2-*a*]pyrimidines (also known as aza analogues of cephams). The one most generally applicable involves the formation of the azetidine ring on a preformed pyrimidine system, by means of a [2+2] cycloaddition reaction between ketenes and dihydro- or tetrahydropyrimidines.[15−20] Other less versatile procedures for the synthesis of azeto[1,2-*a*]pyrimidines have also been developed.[21,22]

The synthetic sequence resulting in azeto[1,2-*a*][1,3]thiazolo[4,5-*d*]pyrimidines **16** started with the new 5-(aminomethyl)thiazole **13**, which could be obtained in four steps by standard procedures in 35% overall yield starting from the known azido aldehyde **10**.[23] This involved: i) sodium borohydride reduction to alcohol **11**, ii) conversion into bromide **12** with Ph_3PBr_2 and iii) Gabriel-style synthesis of amine **13**. Treatment of **13** with 4-bromo- or 4-chlorobenzaldehyde in diethyl ether solution in the presence of anhydrous magnesium sulfate yielded the expected aldimines **14**. Sequential treatment of toluene solutions of aldimines **14** with trimethylphosphane and diphenyl ketene provided imino-ketenimines **15**. Compounds **15** were found to be fairly stable in toluene solution at room temperature, and no cycloaddition was observed at this temperature after 24 h. Indeed, the formal intramolecular [2+2] cycloaddition of imino-ketenimines **15** only took place after heating of the reaction mixture at reflux for 1 h. Azeto[1,2-*a*][1,3]thiazolo[4,5-*d*]pyrimidines **16** were obtained in moderate yields after column chromatography (Scheme 2, Table 1). Compounds **16** were fully characterized by their analytical and spectroscopic data.



Scheme 2. Reagents and conditions: (a) $NaBH_4$, THF/Et_2O, 0 °C → room temp., 12 h; (b) PPh_3Br_2, Et_3N, benzene, room temp., 12 h; (c) (i) potassium phthalimide, DMF, 80 °C, 12 h; (ii) $N_2H_4{\cdot}H_2O$, THF/EtOH, room temp. 16 h, 60 °C 1.5 h; (d) R^1CHO, $MgSO_4$, Et_2O, room temp., 16 h; (e) (i) PMe_3, toluene, room temp., 30 min; (ii) $Ph_2C{=}C{=}O$, toluene, room temp., 15 min; (f) toluene, reflux, 1 h

Conclusion

In summary, we have presented new synthetic applications proving the wide applicability of the formal intramole-

cular [2+2] cycloaddition between ketenimine and imine functions to yield 2-iminoazetidines. This methodology has now allowed us to prepare different types of azeto[1,2-*a*]-pyrimidines, either isolated or fused to a thiazole ring, with excellent diastereoselectivity in the newly formed C−C bond, when applicable.

Experimental Section

General Remarks: All melting points were determined with a Kofler hot-plate melting-point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions or films with a Nicolet Impact 400 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 200 or a Varian Unity 300 spectrometer and are reported in ppm on the δ scale. The signal of the solvent was used as reference. Mass spectra were recorded with a Hewlett−Packard 5993C spectrometer. Microanalyses were performed with a Carlo Erba EA-1108 instrument. (*Z*)-3-Azido-3-phenyl-2-propen-1-ol,[11] 4-azido-5-formyl-2-phenylthiazole,[23] diphenyl ketene[24] and methyl phenyl ketene[25] were prepared by literature procedures. Aldimines **5** and **14** were obtained by standard procedures.[12]

Amine 4: Diethyl azodicarboxylate (1.5 g, 8.57 mmol) was added at 0 °C to a solution of triphenylphosphane (2.25 g, 8.57 mmol) in dry THF (15 mL) and the reaction mixture was stirred for 30 min. A solution of **3** (1 g, 5.71 mmol) in dry THF (10 mL) and phthalimide (1.26 g, 8.57 mmol) were then added. The mixture was stirred for 1 h at 0 °C and for 36 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed [silica gel, hexanes/EtOAc (4:1, v/v)] to give *N*-[(*Z*)-3-azido-3-phenyl-2-propen-1-yl]phthalimide as a colorless oil (1.15 g, 68%). Hydrazine hydrate (7.5 equiv.) was then added to a solution of the *N*-[(*Z*)-3-azido-3-phenyl-2-propen-1-yl]phthalimide (1 g, 3.29 mmol) in a mixture of THF (40 mL) and EtOH (6 mL), and the reaction mixture was stirred for 16 h at room temperature and for 2 h at 50 °C. After cooling, the mixture was filtered, the solid was washed with THF (10 mL), and the solvent was removed from the filtrate. The resulting material was purified by column chromatography [silica gel, Et_2O/EtOH (1:1, v/v)] to yield amine **4** as a yellow oil (0.27 g, 48%). IR (neat): $\tilde{\nu}$ = 3376 (NH_2), 3314 (NH_2), 2112 (N_3) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.48 (br. s, 2 H), 3.50 (d, *J* = 6.8 Hz, 2 H), 5.27 (t, *J* = 6.8 Hz, 1 H), 7.39 (s, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 38.6, 120.9, 127.0, 128.7, 128.9, 134.6 (s), 137.5 (s) ppm. MS (70 eV, EI): *m*/*z* (%) = 174 (30) [M^+], 146 (100) [$M^+ - N_2$]. $C_9H_{10}N_4$ (174.20): calcd. C 62.05, H 5.79, N 32.16; found C 62.25, H 5.71, N 32.04.

General Procedure for the Preparation of the 7-Methyl(phenyl)-2,7-diphenyl-6,7-dihydro-4*H*-azeto[1,2-*a*]pyrimidines (8): Trimethylphosphane (1.4 mmol, 1.4 mL of a 1 M toluene solution) was added to a solution of the corresponding aldimine **5** (1.4 mmol) in dry toluene (10 mL) and the reaction mixture was stirred at room temperature until the evolution of nitrogen ceased (30 min). A solution of diphenyl ketene or methyl phenyl ketene (1.4 mmol) in the same solvent (2 mL) was then added. After the mixture had been stirred at room temperature for 30 min, the solvent was removed under reduced pressure and the resulting material was chromatographed on a silica gel column, with hexanes/EtOAc as eluent. After removal of the solvent from the relevant column chromatography fractions under reduced pressure, the resulting solid material was triturated, dried at room temperature under high vacuum for 12 h, and used as such for characterization. Compounds **8** were stored in the dark at 0 °C.

Compound 8a: 0.29 g, 42%. IR (nujol): $\tilde{\nu}$ = 1663 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.98 (dd, *J* = 12.8, 3.1 Hz, 1 H), 4.04 (dd, *J* = 12.8, 3.1 Hz, 1 H), 5.30 (s, 1 H), 5.38 (t, *J* = 3.1 Hz, 1 H), 6.92−6.95 (m, 6 H), 7.05−7.08 (m, 2 H), 7.18−7.32 (m, 7 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.74 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 42.6, 70.6 (s), 73.8, 100.4, 125.6, 126.9, 127.3, 127.8, 128.0, 128.2, 128.7, 129.4, 131.5, 132.5 (s), 134.5 (s), 138.0 (s), 139.4 (s), 141.7 (s), 144.3 (s), 165.4 (s) ppm. MS (70 eV, EI): *m*/*z* (%) = 492 (24) [M^+, for ^{81}Br], 490 (26) [M^+, for ^{79}Br], 165 (100). $C_{30}H_{23}BrN_2$ (491.42): calcd. C 73.32, H 4.72, N 5.70; found C 73.19, H 4.79, N 5.59.

Compound 8b: 0.25 g, 39%. IR (nujol): $\tilde{\nu}$ = 1673 (C=N), 1521 (NO_2), 1349 (NO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.16−4.17 (m, 2 H), 5.53 (t, *J* = 3.3 Hz, 1 H), 5.55 (s, 1 H), 6.99−7.03 (m, 3 H), 7.10−7.13 (m, 2 H), 7.31−7.45 (m, 8 H), 7.78 (d, *J* = 7.2 Hz, 2 H), 7.83 (d, *J* = 7.2 Hz, 2 H), 8.04 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 42.8, 71.3 (s), 73.1, 100.5, 123.4, 125.5, 127.2, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.7, 137.4 (s), 139.0 (s), 141.0 (s), 143.1 (s), 144.1 (s), 147.6 (s), 164.9 (s) ppm. MS (70 eV, EI): *m*/*z* (%) = 457 (59) [M^+], 321 (100). $C_{30}H_{23}N_3O_2$ (457.52): calcd. C 78.75, H 5.07, N 9.18; found C 78.69, H 5.15, N 9.10.

Compound 8c: 0.11 g, 20%. IR (nujol): $\tilde{\nu}$ = 1670 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.01 (dd, *J* = 12.0, 3.1 Hz, 1 H), 4.05 (dd, *J* = 12.0, 3.1 Hz, 1 H), 5.29 (s, 1 H), 5.38 (t, *J* = 3.1 Hz, 1 H), 5.83−5.84 (m, 1 H), 7.03−7.34 (m, 13 H), 7.62−7.66 (m, 2 H), 7.72−7.77 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 42.4, 67.0, 100.5, 109.6, 121.4 (s), 125.6, 127.0, 127.3, 127.7, 128.1, 128.2, 128.3, 128.6, 138.7 (s), 139.5 (s), 141.3, 141.8 (s), 143.4, 144.4 (s), 165.4 (s) ppm. MS (70 eV, EI): *m*/*z* (%) = 402 (65) [M^+], 114 (100). $C_{28}H_{22}N_2O$ (402.49): calcd. C 83.56, H 5.51, N 6.96; found C 83.48, H 5.42, N 6.85.

Compound 8d: 0.23 g, 34%. IR (nujol): $\tilde{\nu}$ = 1665 (C=N), 1521 (NO_2), 1345 (NO_2) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.18 (dd, *J* = 12.8, 2.9 Hz, 1 H), 4.28 (dd, *J* = 12.8, 2.9 Hz, 1 H), 5.03 (d, *J* = 8.0 Hz, 1 H), 5.47 (t, *J* = 2.9 Hz, 1 H), 5.74 (dd, *J* = 15.7, 8.0 Hz, 1 H), 7.00 (dd, *J* = 7.5, 1.3 Hz, 1 H), 7.18−7.50 (m, 14 H), 7.71 (d, *J* = 7.3 Hz, 2 H), 7.80 (d, *J* = 6.8 Hz, 2 H), 7.95 (dd, *J* = 8.1, 1.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 42.7, 69.0 (s), 72.3, 100.6, 124.7, 125.6, 127.3, 127.5, 127.7, 127.8, 128.2, 128.4, 128.5, 128.7, 129.2, 130.2, 131.7, 132.3 (s), 133.4, 138.6 (s), 139.5 (s), 141.2 (s), 144.4 (s), 147.6 (s), 165.0 (s) ppm. MS (70 eV, EI): *m*/*z* (%) = 483 (8) [M^+], 164 (100). $C_{32}H_{25}N_3O_2$ (483.56): calcd. C 79.48, H 5.21, N 8.69; found C 79.33, H 5.10, N 8.83.

Compound 8e: 0.36 g, 60%. IR (nujol): $\tilde{\nu}$ = 1668 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.87 (s, 3 H), 4.02 (d, *J* = 3.3 Hz, 2 H), 4.59 (s, 1 H), 5.39 (t, *J* = 3.3 Hz, 1 H), 6.80 (d, *J* = 8.3 Hz, 2 H), 6.95−7.00 (m, 5 H), 7.17 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 6.8 Hz, 1 H), 7.28 (t, *J* = 7.1 Hz, 2 H), 7.69 (d, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.6, 42.4, 63.1 (s), 75.3, 100.5, 121.9 (s), 125.5, 126.7, 127.2, 127.7, 128.0, 128.1, 128.9, 131.2, 134.7 (s), 138.2 (s), 139.3 (s), 144.3 (s), 167.0 (s) ppm. MS (70 eV, EI): *m*/*z* (%) = 430 (40) [M^+, for ^{81}Br], 429 (27), 428 (43) [M^+, for ^{79}Br], 105 (100). $C_{25}H_{21}BrN_2$ (429.35): calcd. C 69.94, H 4.93, N 6.52; found C 69.75, H 4.99, N 6.64.

Compound 8f: 0.26 g, 48%. IR (nujol): $\tilde{\nu}$ = 1659 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.85 (s, 3 H), 4.00 (d, *J* = 3.3 Hz, 2 H), 4.59 (s, 1 H), 5.38 (t, *J* = 3.3 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.93−7.03 (m, 6 H), 7.20−7.29 (m, 4 H), 7.67−7.70 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.6, 42.5,

63.2 (s), 75.3, 100.6, 125.6, 126.8, 127.2, 127.7, 128.0, 128.2, 128.3, 128.7, 133.8 (s), 134.3 (s), 138.3 (s), 139.4 (s), 144.4 (s), 167.1 (s) ppm. MS (70 eV, EI): *m/z* (%) = 386 (27) [M^+, for ^{37}Cl], 385 (26), 384 (57) [M^+, for ^{35}Cl], 117 (100). $C_{25}H_{21}ClN_2$ (384.90): calcd. C 78.01, H 5.50, N 7.28; found C 77.87, H 5.60, N 7.41.

Compound 8g: 0.29 g, 52%. IR (nujol): $\tilde{\nu}$ = 1665 (C=N), 1519 (NO_2), 1345 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.94 (s, 3 H), 4.08 (d, *J* = 3.3 Hz, 2 H), 4.74 (s, 1 H), 5.46 (t, *J* = 3.3 Hz, 1 H), 6.93−7.03 (m, 4 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 7.18−7.33 (m, 4 H), 7.68−7.71 (m, 2 H), 7.91 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.3, 42.8, 64.0 (s), 75.1, 100.8, 123.4, 125.6, 127.1, 127.2, 127.9, 128.0, 128.2, 128.3, 137.6 (s), 139.2 (s), 143.4 (s), 144.3 (s), 147.5 (s), 166.8 (s) ppm. MS (70 eV, EI): *m/z* (%) = 395 (42) [M^+], 259 (100). $C_{25}H_{21}N_3O_2$ (395.45): calcd. C 75.93, H 5.35, N 10.63; found C 76.04, H 5.25, N 10.78.

Compound 8h: 0.20 g, 41%. IR (nujol): $\tilde{\nu}$ = 1669 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.82 (s, 3 H), 4.01 (d, *J* = 3.3 Hz, 2 H), 4.60 (s, 1 H), 5.36 (t, *J* = 3.3 Hz, 1 H), 5.69 (d, *J* = 1.1 Hz, 1 H), 7.03−7.28 (m, 10 H), 7.66−7.71 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.6, 42.2, 61.9 (s), 67.9, 100.6, 109.3, 125.6, 126.9, 127.2, 127.7, 128.1, 128.2, 139.1 (s), 139.6 (s), 141.0, 143.2, 144.2 (s), 144.5 (s), 167.1 (s) ppm. MS (70 eV, EI): *m/z* (%) = 340 (49) [M^+], 105 (100). $C_{23}H_{20}N_2O$ (340.42): calcd. C 81.15, H 5.92, N 8.23; found C 81.28, H 5.78, N 8.36.

Compound 8i: 0.18 g, 30%. IR (nujol): $\tilde{\nu}$ = 1670 (C=N), 1526 (NO_2), 1346 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.85 (s, 3 H), 4.13 (d, *J* = 3.2 Hz, 2 H), 4.27 (d, *J* = 8.0 Hz, 1 H), 5.36 (t, *J* = 3.2 Hz, 1 H), 5.47 (dd, *J* = 15.7, 8.0 Hz, 1 H), 6.83 (dd, *J* = 7.5, 1.7 Hz, 1 H), 6.98 (d, *J* = 15.7 Hz, 1 H), 7.12−7.45 (m, 10 H), 7.60−7.68 (m, 2 H), 7.83 (dd, *J* = 7.7, 1.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.1, 42.5, 61.6 (s), 73.4, 100.7, 124.5, 125.6, 127.2, 127.3, 127.7, 128.2, 128.4, 128.5, 129.0, 129.6, 131.9, 133.3, 138.8 (s), 139.5 (s), 144.4 (s), 147.3 (s), 147.5 (s), 166.7 (s) ppm. MS (70 eV, EI): *m/z* (%) = 421 (73) [M^+], 259 (100). $C_{27}H_{23}N_3O_2$ (421.49): calcd. C 76.94, H 5.50, N 9.97; found C 76.89, H 5.42, N 10.06.

Preparation of Alcohol 11: A solution of the aldehyde **10** (3 g, 13 mmol) in a mixture of THF (25 mL) and Et_2O (25 mL) was treated at 0 °C with a solution of sodium borohydride (0.61 g, 16.3 mmol) in H_2O (4 mL). The reaction mixture was stirred for 30 min at 0 °C and then allowed to warm to room temperature over 2 h. The organic solvents were then removed under reduced pressure, brine (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude material was chromatographed [silica gel, hexanes/EtOAc (7:3, v/v)] to yield alcohol **11** (2.75 g, 91%) as yellow prisms. M.p. 107−109 °C (Et_2O). IR (nujol): $\tilde{\nu}$ = 3304 (OH), 2161 (N_3) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.36 (br. s, 1 H), 4.67 (s, 2 H), 7.38−7.45 (m, 3 H), 7.83−7.90 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 55.2, 119.1 (s), 126.0, 129.0, 130.5, 132.8 (s), 145.1 (s), 166.1 (s) ppm. MS (70 eV, EI): *m/z* (%) = 232 (27) [M^+], 204 (33) [$M^+ - N_2$], 104 (100). $C_{10}H_8N_4OS$ (232.26): calcd. C 51.71, H 3.47, N 24.12; found C 51.63, H 3.41, N 24.01.

Preparation of Bromide 12: A solution of bromine (0.33 g, 2.08 mmol) in dry benzene (10 mL) was added dropwise at 0 °C to a solution of triphenylphosphane (0.52 g, 2.08 mmol) in the same solvent (15 mL), and the mixture was stirred at that temperature for 45 min. A solution of alcohol **11** (0.48 g, 2.08 mmol) and triethylamine (0.2 g, 2.08 mmol) in dry benzene (10 mL) was then added in one portion. After the mixture had been stirred at room temperature for 12 h, the white suspension was filtered off. The solvent was removed from the filtrate under reduced pressure and the residue was purified by column chromatography [silica gel, hexanes/EtOAc (2:1, v/v)] to give bromide **12** (0.45 g, 74%) as pale yellow prisms. M.p. 80−81 °C (Et_2O). IR (nujol): $\tilde{\nu}$ = 2143 (N_3) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.59 (s, 2 H), 7.39−7.46 (m, 3 H), 7.85−7.90 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 22.1, 116.4 (s), 126.2, 129.1, 131.0, 132.7 (s), 147.0 (s), 166.9 (s) ppm. MS (70 eV, EI): *m/z* (%) = 296 (2) [M^+, for ^{81}Br], 294 (2) [M^+, for ^{79}Br], 215 (25) [$M^+ - Br$], 129 (100). $C_{10}H_7BrN_4S$ (295.16): calcd. C 40.69, H 2.39, N 18.98; found C 40.82, H 2.33, N 18.87.

Preparation of Amine 13: A mixture of bromide **12** (2 g, 6.78 mmol) and potassium phthalimide (1.47 g, 8.13 mmol) in dry DMF (10 mL) was heated at 80 °C for 12 h, with vigorous stirring. The cooled mixture was poured into ice/water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting residue was purified by column chromatography [silica gel, hexanes/EtOAc (7:3, v/v)] to yield 4-azido-2-phenyl-5-(phthalimidomethyl)thiazole (1.59 g, 65%). Hydrazine hydrate (7.5 equiv.) was added to a solution of the 4-azido-2-phenyl-5-(phthalimidomethyl)thiazole (1.6 g, 4.43 mmol) in a mixture of THF (40 mL) and EtOH (6 mL), and the reaction mixture was stirred for 16 h at room temperature and 1.5 h at 50 °C. After cooling, the mixture was filtered, the solid was washed with THF (10 mL), and the solvent was removed from the filtrate. The resulting material was purified by column chromatography [silica gel, Et_2O/MeOH (1:1, v/v)] to yield amine **13** (0.81 g, 79%) as yellow prisms. M.p. 95−97 °C (Et_2O). IR (neat): $\tilde{\nu}$ = 3373 (NH_2), 3310 (NH_2), 2144 (N_3) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.72 (br. s, 2 H), 3.87 (s, 2 H), 7.39−7.43 (m, 3 H), 7.86−7.89 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 36.8, 122.5 (s), 125.9, 129.0, 130.3, 133.2 (s), 143.8 (s), 164.6 (s) ppm. MS (70 eV, EI): *m/z* (%) = 231 (21) [M^+], 203 (20) [$M^+ - N_2$], 121 (100). $C_{10}H_9N_5S$ (231.28): calcd. C 51.93, H 3.92, N 30.28; found C 51.79, H 3.98, N 30.14.

General Procedure for the Preparation of the 2,5,5-Triphenyl-5,8-dihydro-6*H*-azeto[1,2-*a*][1,3]thiazolo[4,5-*d*]pyrimidines 16: Trimethylphosphane (1 mmol, 1 mL of a 1 M toluene solution) was added to a solution of the corresponding aldimine **14** (1 mmol) in dry toluene (10 mL) and the reaction mixture was stirred at room temperature until the evolution of nitrogen ceased (30 min). A solution of diphenyl ketene (0.19 g, 1 mmol) in the same solvent (5 mL) was then added. The reaction mixture was stirred at room temperature for 15 min and was then heated at reflux temperature for 1 h. The solvent was removed under reduced pressure and the resulting material was chromatographed on a silica gel column, with hexanes/EtOAc as eluent.

Compound 16a: 0.28 g, 51%. M.p. 161−163 °C (CH_2Cl_2/Et_2O). IR (nujol): $\tilde{\nu}$ = 1653 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.69 (d, *J* = 11.2 Hz, 1 H), 4.78 (d, *J* = 11.2 Hz, 1 H), 5.57 (s, 1 H), 7.01−7.06 (m, 5 H), 7.19−7.42 (m, 10 H), 7.78−7.81 (m, 2 H), 7.99−8.02 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 43.0, 69.4 (s), 72.9, 106.1 (s), 122.7 (s), 126.2, 127.0, 127.5, 127.6, 128.1, 128.8, 128.9, 129.5, 130.0, 131.7, 133.5 (s), 133.6 (s), 137.6 (s), 141.4 (s), 155.2 (s), 164.6 (s), 165.2 (s) ppm. MS (70 eV, EI): *m/z* (%) = 549 (45) [M^+, for ^{81}Br], 548 (28), 547

(57) [M^+, for ^{79}Br], 167 (100). $C_{31}H_{22}BrN_3S$ (548.50): calcd. C 67.88, H 4.04, N 7.66; found C 68.03, H 3.92, N 7.80.

Compound 16b: 0.32 g, 64%. M.p. 153−155 °C (CH_2Cl_2/Et_2O). IR (nujol): $\tilde{\nu}$ = 1655 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.68 (d, *J* = 11.4 Hz, 1 H), 4.79 (d, *J* = 11.4 Hz, 1 H), 5.59 (s, 1 H), 7.00−7.43 (m, 15 H), 7.78−7.82 (m, 2 H), 7.98−8.03 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 42.9, 69.3 (s), 72.7, 106.0 (s), 126.1, 127.0, 127.5, 127.6, 128.0, 128.1, 128.7, 128.8, 128.9, 129.1, 130.0, 133.0 (s), 133.5 (s), 134.5 (s), 137.6 (s), 141.3 (s), 155.1 (s), 164.6 (s), 165.2 (s) ppm. MS (70 eV, EI): *m*/*z* (%) = 505 (65) [M^+, for ^{37}Cl], 504 (66), 503 (100) [M^+, for ^{35}Cl]. $C_{31}H_{22}ClN_3S$ (504.05): calcd. C 73.87, H 4.40, N 8.34; found C 73.71, H 4.51, N 8.22.

Acknowledgments

This work was supported by the MCYT and FEDER (Project BQU2001-0010), Fundación Séneca-CARM (Project PI-1/00749/FS/01), and Acedesa (a division of Takasago). R.-A. O. thanks the Spanish Ministerio de Educación, Cultura y Deporte for a fellowship.

[1] L. Ghosez, J. Marchand-Brynaert, in *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming); Pergamon Press: Oxford, U. K. **1991**; Vol 5, pp 108−113.
[2] A. Dondoni, *Heterocycles* **1980**, *14*, 1547−1566.
[3] M. Alajarín, A. Vidal, F. Tovar, *Targets Heterocycl. Syst.* **2000**, *4*, 293−326.
[4] B. Arnold, M. Regitz, *Angew. Chem.* **1979**, *91*, 337. B. Arnold, M. Regitz, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 320.
[5] A. Van Camp, D. Goossens, M. Moya-Portuguez, J. Marchand-Brynaert, L. Ghosez, *Tetrahedron Lett.* **1980**, *21*, 3081−3084.
[6] M. Alajarín, P. Molina, A. Vidal, *Tetrahedron Lett.* **1996**, *37*, 8945−8948.
[7] M. Alajarín, P. Molina, A. Vidal, F. Tovar, *Tetrahedron* **1997**, *53*, 13449−13472.
[8] M. Alajarín, A. Vidal, F. Tovar, A. Arrieta, B. Lecea, F. P. Cossío, *Chem. Eur. J.* **1999**, *5*, 1106−1117.
[9] F. P. Cossío, A. Arrieta, B. Lecea, M. Alajarín, A. Vidal, F. Tovar, *J. Org. Chem.* **2000**, *65*, 3633−3643.
[10] M. Alajarín, A. Vidal, F. Tovar, M. C. Ramírez de Arellano, F. P. Cossío, A. Arrieta, B. Lecea, *J. Org. Chem.* **2000**, *65*, 7512−7515.
[11] T. Sakai, I. Kawabata, T. Kishimoto, T. Ema, M. Utaka, *J. Org. Chem.* **1997**, *62*, 4906−4907.
[12] O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba, S. Terashima, *Tetrahedron Lett.* **1992**, *33*, 3483−3486.
[13] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635−646.
[14] E. Breitmaier, W. Voelter, *Carbon-13 NMR Spectroscopy*, 3rd ed., VCH, New York, **1987**, p. 143.
[15] A. K. Bose, J. C. Kapur, J. L. Fahey, M. S. Manhas, *J. Org. Chem.* **1973**, *38*, 3437−3438.
[16] A. K. Bose, J. C. Kapur, M. S. Manhas, *Synthesis* **1974**, 891−894.
[17] A. K. Bose, M. S. Manhas, J. M. Van der Veen, S. G. Amin, I. F. Fernández, K. Gala, R. Gruska, J. C. Kapur, M. S. Khajavi, J. Kreder, L. Mukkavilli, B. Ram, M. Sugiura, J. E. Vincent, *Tetrahedron* **1981**, *37*, 2321−2334.
[18] S. D. Sharma, U. Mehra, *Tetrahedron Lett.* **1984**, *25*, 1849−1852.
[19] S. D. Sharma, U. Mehra, V. Kaur, *Indian J. Chem. Sect. B* **1986**, *25B*, 1061−1064.
[20] S. D. Sharma, V. Kaur, P. Bhutani, J. P. S. Khurana, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2246−2250.
[21] D. Bormann, *Chem. Ber.* **1970**, *103*, 1797−1804.
[22] M. M. Campbell, B. P. Connarty, *Heterocycles* **1982**, *19*, 1853−1854.
[23] P. Molina, A. Arques, M. V. Vinader, J. Becher, K. Brondum, *J. Org. Chem.* **1988**, *53*, 4654−4663.
[24] E. C. Taylor, A. McKillop, G. H. Hawks, *Org. Synth.* **1973**, *52*, 36−38.
[25] H. Pracejus, G. Wallura, *J. Prakt. Chem.* **1962**, *19*, 33−36.

Received July 31, 2002
[O02442]