# Unexpected Transformations of Aziridino-phosphazenes Built on *ortho*-Phenylene Scaffolds

**Marta Marin-Luna, Javier Diaz-Moreno, Angel Vidal and Mateo Alajarin**

Departamento de Química Orgánica, Universidad de Murcia, Facultad de Química, Regional Campus of International Excellence "*Campus Mare Nostrum*", Espinardo, 30100, Murcia, Spain.

e-mail: martamarin@um.es

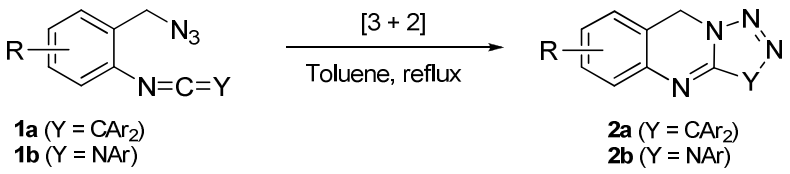
**Abstract:** A Staudinger imination reaction of alkyl 3-(*o*-azidophenyl)aziridino-2-carboxylates with trimethyl phosphine promotes an intramolecular aza-Wittig reaction between the non-isolated putative phosphazenes and the carbonyl group of the ester function. A further hydrolytic treatment of the resulting iminoesters led ultimately to 3-amino-2-quinolones via a molecular reorganization at the aziridino fragment.

**Keywords**: aziridine, heterocumulenes, [3+2] cycloaddition, aza-Wittig reaction

## INTRODUCTION

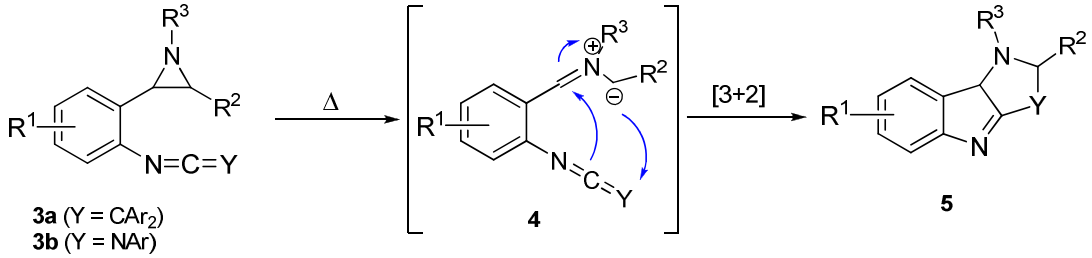
It is well known that heterocumulene functions of the type X=C=Y are prone to participate in pericyclic processes, mainly in cycloaddition reactions. In a wide variety of such reactions, the heterocumulenic function usually acts as a two-atom component through the participation of one of its two cumulated double bonds.[1]

During the course of our studies on the reactivity of heterocumulenes we have recently reported that *N*-aryl ketenimines and carbodiimides substituted at the *ortho* position by an azidomethyl function **1** transformed into triazolo[5,1-*b*]quinazolines **2a** and tetrazolo[5,1-*b*]quinazolines **2b** when them toluene solutions were heated at reflux temperature for short periods of time. We interpreted these transformations as occurring by an intramolecular [3+2] cycloaddition reaction between the azido group, which acts as the three-atom component, and the C=Y cumulated bond of the heterocumulene function (Y = $CAr_2$ for ketenimines; Y = N-Ar for carbodiimides; Scheme 1).[2] Further dinitrogen extrusion from these [3+2] cycloadducts provided indoloquinazolines and 2-aminoquinazolines.




***Scheme 1***. Intramolecular [3+2] cycloaddition of azidomethyl-heterocumulenes **1**

Within this frame of research we reasoned that [3+2] cycloaddition reactions could occur in structurally related ketenimines **3a** and carbodiimides **3b** in which the azido function of heterocumulenes **1** is replaced by an aziridine ring. Thus, the heterocumulenes **3** could thermally undergo the ring opening of the three-membered heterocycle affording zwitterionic intermediates type **4** which would then experiment the desired intramolecular [3+2] cycloaddition, potentially yielding new examples of [*b*]-fused indoles **5**. (Scheme 2)




***Scheme 2***. Planned intramolecular [3+2] cycloaddition of aziridino-heterocumules **3**

With this aim, we next faced with the preparation of aziridino-heterocumulenes type **3** built on *ortho*-phenylene scaffolds. In our view, these new ketenimines and carbodiimides should be easily accessible via the respective phosphazene derivatives by aza-Wittig reactions with ketenes and isocyanates. To this end, 2- or 3-(*o*-azidophenyl)aziridines were the logical starting materials, desirably substituted by electron-withdrawing groups at the vicinal carbon atom of the aziridine (e.g., $R^2$ = COOR) with the aim of promoting the ring opening step by stabilizing the rising negative charge at the zwitterion **4**.

## EXPERIMENTAL

### *Preparation of 3-(o-azidophenyl)aziridine 11 (Ar = 4-t-Bu-$C_6H_4$)*

To a solution of dibromo derivative **10** (3 mmol) in ethanol (10 mL) 4-*t*-butylbenzylamine (12 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 4 days. Then, the reaction was quenched with water (150 mL). The aqueous phase was extracted with dichloromethane (3 x 75 mL) and the combined organic phases were dried over magnesium sulfate. Then, the solvent was

removed under reduced pressure and the residue was purified by silica gel column chromatography using a mixture of hexanes/diethyl ether (4:1,v/v) as eluent.

*cis*-3-(*o*-Azidophenyl)aziridine **11:** yield 56%; yellow prims, mp 63-65 ºC; IR (nujol) ν 2114 (vs), 1715 (vs) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.99 (3H, t, $J$ = 6.8 Hz), 1.32 (9H, s), 2.69 (1H, d, $J$ = 6.8 Hz), 3.12 (1H, d, $J$ = 6.8 Hz), 3.61 (1H, d, $J$ = 13.6 Hz), 3.90-4.05 (3H, m), 7.07-7.11 (2H, m), 7.25-7.30 (1H, m), 7.36 (4H, s), 7.55-7.57 (1H, m); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 13.9, 31.3, 34.4 (s), 44.1, 45.2, 60.6, 63.1, 117.3, 124.3, 125.3, 126.5 (s), 127.7, 128.5, 130.2, 134.5 (s), 138.4 (s), 150.1 (s), 168.1 (s); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{27}N_4O_2$ $[M + H]^+$: 379.2129; found: 379.2194.

***Preparation of the aziridino-dihydroquinolone 15 (Ar = 4-t-Bu-$C_6H_4$)***

To a solution of *cis*-3-(*o*-azidophenyl)aziridine **11** (0.6 mmol) in anhydrous toluene (10 mL) trimethylphosphine (0.6 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 1 h. Then, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using first a mixture of hexanes/diethyl ether (7:3,v/v) and then ethyl acetate as eluents.

Aziridino-dihydroquinolone **15:** yield 67%; colorless prisms, mp 159-160 ºC; IR (nujol) ν 3283 (m), 1670 (vs), 1591 (vs) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.31 (9H, s), 2.81 (1H, dd, $J$ = 6.0, 1.6 Hz), 3.09 (1H, d, $J$ = 6.0 Hz), 3.65 (1H, d, $J$ = 13.6 Hz), 3.94 (1H, d, $J$ = 13.6 Hz), 6.86 (1H, d, $J$ = 7.6 Hz), 7.03 (1H, td, $J$ = 7.6, 1.2 Hz), 7.23 (1H, td, $J$ = 7.6, 1.6 Hz), 7.24-7.28 (2H, m), 7.33-7.39 (3H, m), 9.20 (1H, s); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 31.3, 34.4 (s), 42.3, 44.1, 62.8, 116.0, 120.7 (s), 122.9, 125.4, 127.4, 128.7, 134.5 (s), 136.1 (s), 150.2 (s), 168.4 (s); HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{23}N_2O$ $[M + H]^+$: 307.1805; found: 307.1793.

***Preparation of the 3-amino-2-quinolone 16 (Ar = 4-t-Bu-$C_6H_4$)***

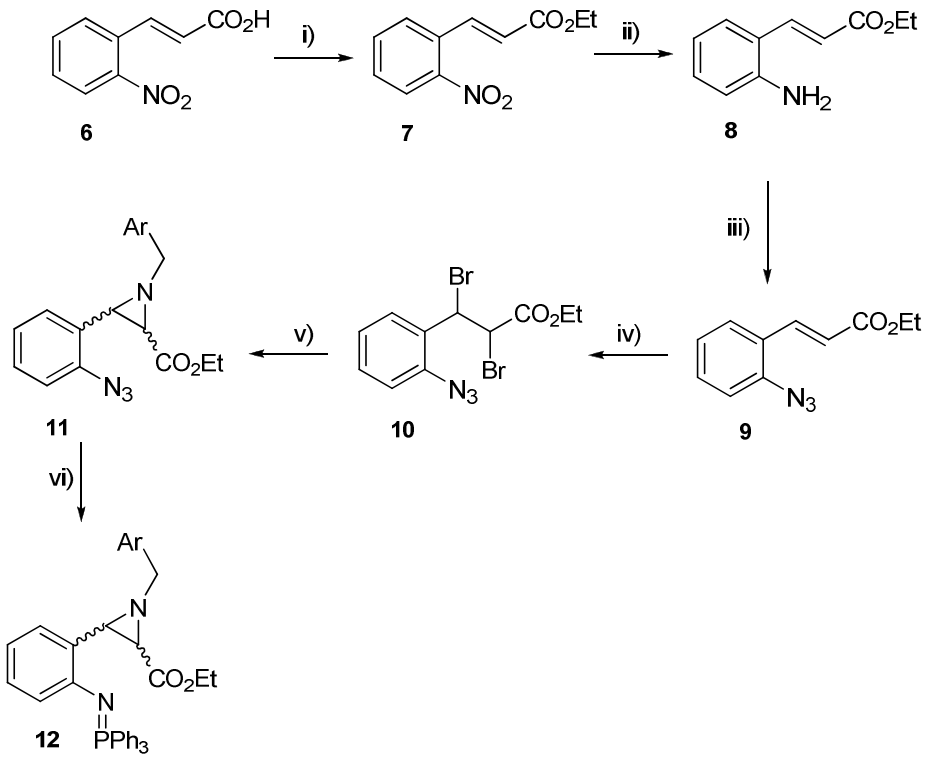
To a suspension of silica gel (0.5 g) in dichloromethane (15 mL) aziridino-dihydroquinolone **15** (0.25 mmol) and 3-4 drops of water were added. The resulting mixture was stirred at room temperature for 48 h. Then, the solution was filtered and the silica gel was washed with dichloromethane (30 mL) and ethyl acetate (30 mL). The solvent was removed under reduced pressure. Finally, the crude product was purified by

silica gel column chromatography using a mixture of hexanes/ethyl acetate (1:1,v/v) as eluent.

3-Amino-2-quinolone **16**: yield 73%; colorless prisms, mp 225-226 ºC; IR (nujol) ν 3405 (s), 1648 (vs) $cm^{-1}$; $^{1}H$ NMR (DMSO-$d_6$, 300 MHz) δ: 1.19 (9H, s ), 4.30 (2H, d, *J* = 6.3 Hz ), 6.23 (1H, t, *J* = 6.3 Hz), 6.41 (1H, s), 6.96 (1H, td, *J* = 7.8, 1.5 Hz), 7.06 (1H, td, *J* = 7.2, 1.5 Hz), 7.15 (1H, d, *J* = 7.5 Hz), 7.22-7.30 (5H, m), 11.81 (1H, s); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ: 31.1, 34.1 (s), 45.3, 103.1, 114.5, 121.8 (s), 121.9, 123.9, 124.4, 125.1, 126.8, 131.4 (s), 136.0, 137.3 (s), 149.1 (s), 157.9 (s). HRMS (ESI): *m/z*: calcd for $C_{20}H_{23}N_2O$ $[M + H]^+$: 307.1805; found: 307.1816.

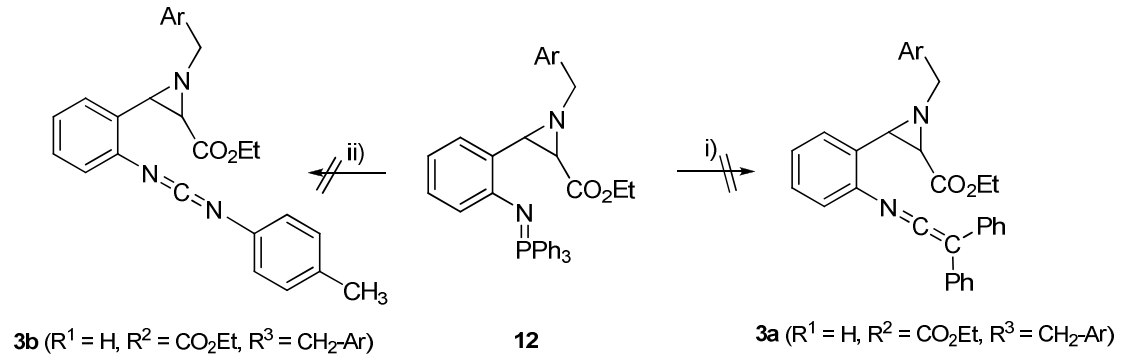
## RESULTS AND DISCUSSION

For the synthesis of the targeted heterocumulenes **3** ($R^1$ = H, $R^2$ = $CO_2Et$, $R^3$ = $CH_2$-Ar) first we attempted the preparation of the phosphazene precursors **12**. Thus, the synthetic route started by the preparation of the unsaturated ester **7** by acid-catalyzed esterification of carboxylic acid **6**. Next, the reduction of the nitro group of **7** with iron led to the aniline **8**, which was converted into the *o*-azidocinnamate **9** by sequential treatment with sodium nitrite and sodium azide. Addition of bromine to the C=C bond of **9** yielded the dibromo derivative **10** and its subsequent reaction with a range of benzylamines provided the aziridines **11**. Fortunately, we were able to resolve the mixture of *cis/trans* isomers of **11** during the purification step through silica gel column chromatography. Finally, the azides **11** transformed into phosphazenes **12** *via* a Staudinger imination reaction with triphenylphosphine. (Scheme 3)




***Scheme 3***. Preparation of the phosphazenes **12**. *Reagents and conditions*: i) cat. $H_2SO_4$, EtOH, reflux, 48 h; ii) Fe, AcOH, EtOH, reflux, 4.5 h; iii) $NaNO_2$, AcOH, HCl, 0 ºC, 1 h and then $NaN_3$, AcOH, HCl, 0 ºC, 4 h; iv) $Br_2$, $CHCl_3$, 0 ºC, 12 h; v) R-$C_6H_4$-$CH_2NH_2$, EtOH, r.t., 4 d; vi) $PPh_3$, $Et_2O$, r.t., 16 h.

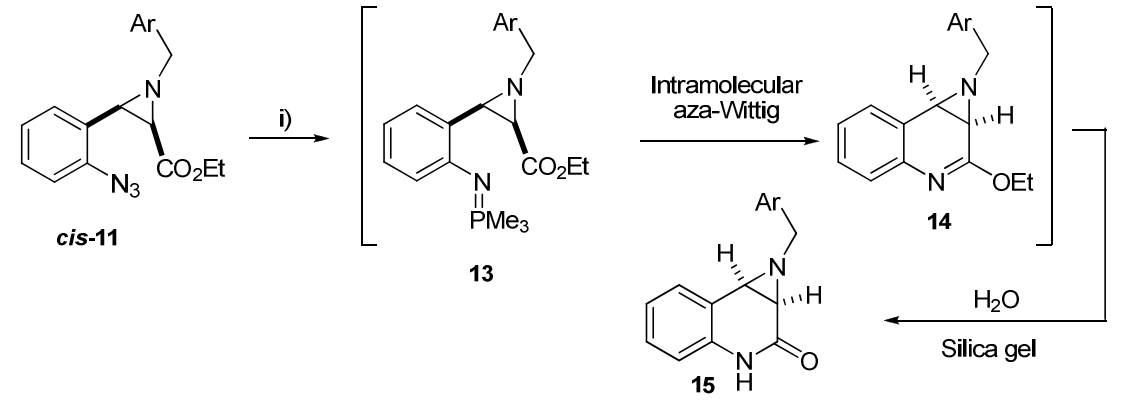
With phosphazenes **12** in our hands we next addressed the preparation of ketenimines **3a** ($R^1$ = H, $R^2$ = $CO_2Et$, $R^3$ = $CH_2$-Ar). Thus diphenylketene was added to toluene solutions of different phosphazenes **12** and the resulting reaction mixtures were stirred at room temperature for several hours. Unfortunely, in all the cases the starting phosphazenes **12** were recovered unchanged whereas the ketene seems to polymerize. On the other hand, with the aim of preparing carbodiimides **3b** ($R^1$ = H, $R^2$ = $CO_2Et$, $R^3$ = -$CH_2$-Ar), we carried out the reaction of phosphazenes **12** with *p*-tolylisocyanate in toluene solution at room temperature. The results of these experiments were also negative, obtaining complex reaction mixtures. (Scheme 4)




***Scheme 4***. Unsuccessful reactions of phosphazenes **12** with ketenes and isocyanates. *Reagents and conditions*: i) $Ph_2C=C=O$, toluene, r.t., 3 h; ii) 4-$CH_3$-$C_6H_4$-N=C=O, toluene, r.t., 3 h.

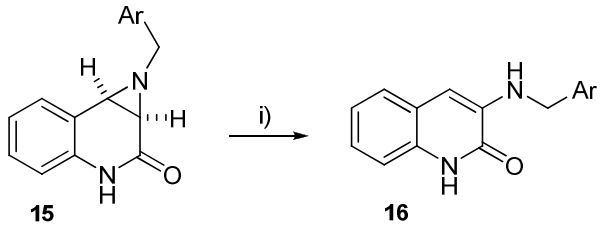
In search of more promising results in attempting the preparation of heterocumulenes **3**, we made a structural modification of the phosphazene precursors **12**. We reasoned that trimethylphosphazenes **13**, clearly more reactive than them triphenyl partners **12**, could successfully react with ketenes and isocyanates. However, rather unexpectedly, when we carried out the Staudinger imination reactions of azides ***cis*-11** with trimethylphosphine the reactions products were not the expected phosphazenes **13** but instead we isolated the aziridino-dihydroquinolones **15**.

The formation of species **15** is explained by the occurrence of an intramolecular aza-Wittig reaction between the phosphazene fragment of **13**, which is formed in the first reaction step, with the carbonyl group of the ester affording the iminoester function of the aziridino-dihydroquinolines **14**. Finally, compounds **14** transformed into **15** by a hydrolysis reaction, presumably catalyzed by the silica gel used in the purification step by column chromatography. (Scheme 5)




***Scheme 5***. Preparation of aziridino-dihydroquinolones **15**. *Reagents and conditions*: i) $PMe_3$, toluene, r.t., 1 h.

In the course of these experiences we noted that compounds **15** slowly transformed into another species when kept in solution and in the presence of silica gel. Thus, when dichloromethane solutions of aziridino-dihydroquinolones **15** were stirred at room temperature for two days in the presence of a small amount of silica gel, it converted into the 3-amino-2-quinolones **16** in good yields. (Scheme 6)




***Scheme 6***. Preparation of 3-amino-2-quinolones **16**. *Reagents and conditions*: i) Silica gel, wet dichloromethane, r.t., 48 h

Globally considered, the conversion of **15** into **16** is just the isomerization of the aziridino fragment into an enamino grouping with a concomitant 1,2-C-to-N hydrogen atom migration. This transformation might be tentatively interpreted as a sequence of two more simple chemical events: the hydrolytic ring opening of the aziridine ring at the distal C-N bond, initiated by the protonation at its N atom, followed by a dehydration step along the 3,4 C-C bond of the dihydroquinolone ring system. The recovery of aromaticity at the nitrogenated six-membered ring of **16** would positively contribute to the occurrence of these **15** → **16** transformations.

## CONCLUSIONS

In this communication we have summarized the results obtained in our attempts to prepare, via aza-Wittig reactions of phosphazenes, aziridino-heterocumulenes capable of undergoing intramolecular [3+2] cycloadditions. In this context we have shown the unexpected transformations of trimethylphosphazenes **13** into 3-amino-2-quinolones **16** by a sequence of three reaction steps: the intramolecular aza-Wittig reaction between the phosphazene and ester functions, followed by the hydrolysis of the so formed iminoester grouping and a final isomerization of the aziridine ring to an enamine fragment.

## ACKNOWLEDGEMENTS

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## REFERENCES

[1] For some leading references see: (a) Cossio, F. P.; Arrieta, A.; Lecea, B.; Alajarin, M.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2000**, *65*, 3633. (b) Alajarin, M.; Marin-Luna, M.; Vidal, A. *Eur. J. Org. Chem.* **2012**, 5637, and references cited therein.

[2] Alajarin, M.; Bonillo, B.; Ortin, M-M. ; Orenes, R-A.; Vidal, A. *Org. Biomol. Chem.* **2011**, *9*, 6741.