

HETEROCYCLES, Vol. 78, No. 3, 2009, pp. 635 - 644. © The Japan Institute of Heterocyclic Chemistry
 Received, 9th September, 2008, Accepted, 30th October, 2008, Published online, 31st October, 2008
 DOI: 10.3987/COM-08-11544

EFFICIENT SYNTHESSES OF 1-AZATRICYCLIC RING SYSTEMS FROM ANTHRANYLAMIDE

Daniele Muroi, Mauro Mucedda, and Antonio Saba*

Department of Chemistry, University of Sassari, Via Vienna 2, 07100 Sassari,
 Italy, saba@uniss.it

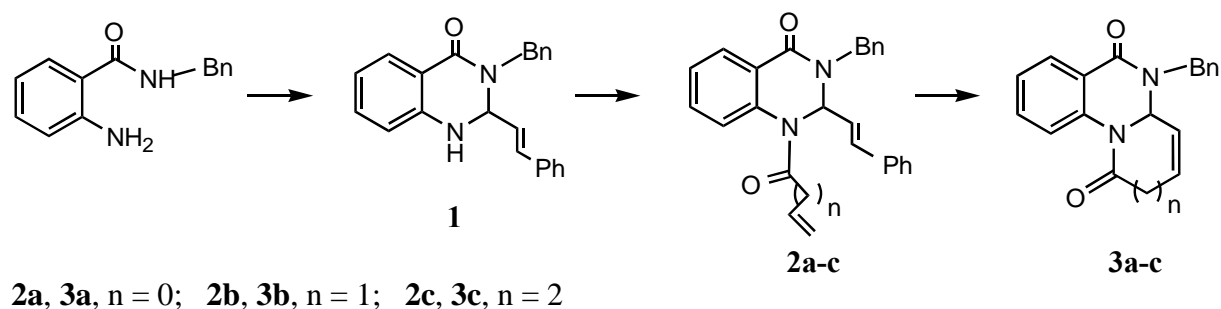
Abstract - Concise syntheses of novel tricyclic quinazolinone and pyrrolo-benzoazacyclononenone alkaloids in two and three steps (two pots), starting from 3-styrylquinazolinone, by utilizing RCM and cascade spiro-to fused protocols, respectively, were reported.

INTRODUCTION

As part of the ongoing efforts devoted to optimize synthetic protocols to prepare 1-azacyclic alkaloids by using simple reagents and concise procedures, as cascade cyclization processes,¹ or ring closing metathesis (RCM),² herein we describe a synthetic approach to the family of tricyclic quinazolinone and medium sized azacyclic systems by utilizing both these procedures, even starting from N-benzyl-anthranylamide, easily available and convenient material.

Tricyclic systems which possess the 4(3*H*)quinazoline moiety³ are encountered in medicinal chemistry for their interesting pharmacological activities as respiratory stimulant, bronchodilator⁴ or antihistaminic and sedative-hypnotic activity.⁵

For such purpose, construction of five- six- and seven-membered rings by RCM of quinazolinone derivatives, bearing two unsaturated pendants properly situated, has been planned (Scheme 1).



Scheme 1

RESULT AND DISCUSSION

Acylation of racemic 3-styryl-2-benzyl-quinazolinone **1**, prepared from *N*-benzyl-anthranilamide,⁶ with acryloyl, ω -butenoyl and ω -pentenoyl chlorides, in the presence of pyridine or triethylamine, afforded the quinazolinone dienes **2a**, **2b** and **2c**.

The N-acyl in the place of N-alkyl derivatives choice was due to knowledge that the Grubb's RCM catalytic protocol may present difficulties in metathesizing compounds containing amino groups, whose nitrogen lone pair generally tends to coordinate the metal centre, poisoning and deactivating of ruthenium catalyst.

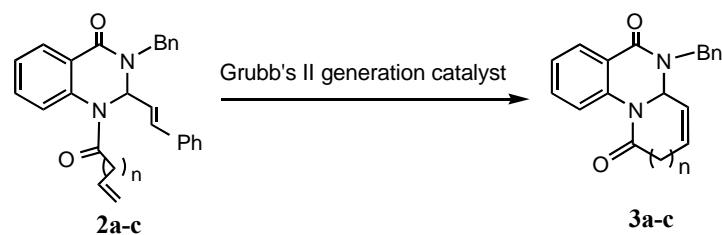
In order to prevent this inconvenience, conversion of the amine into carbamate, sulfonamide or amide functions have been carried out.⁷ However, increasing examples of successful metathesized amine compounds are reported.⁸

With the desired diene compounds in hand, we studied with accuracy the RCM reaction in order to field optimum conditions. After surveying several catalysts, the Grubb's second generation one (Grubb's II), was chosen, being better its efficiency. Then the catalytic intramolecular cyclizations were performed in different reaction conditions and the results are summarized in Table 1.

By refluxing of compound **2a** in CH₂Cl₂, CH₂ClCH₂Cl and PhMe solutions for 2 days in the presence of 5 mol% of Grubb's II catalyst, no traces of the desired tricyclic alkaloid were observed. This failure could be ascribed to a strain opposed to the construction of a five membered-ring on the pre-existing six-membered one. This is probably due to the particular rigidity of the latter, concomitant with that of the amidic alkene pendant. By refluxing a CH₂ClCH₂Cl solution of **2b** for 1.5 h, in the presence of Grubb's II catalyst (5 mol%), the conversion was complete and the target alkaloid **3b** was obtained as the sole product in excellent yield. Changing the reaction conditions, both conversion and yield decrease (Entries 4 and 6).

In the case of diene compound **2c** (Entry 8) a 71/29 mixture of the target azepino quinazolinone **3c** and the undesired **3b** was obtained. The formation of the latter compound is probably due to the terminal double bond isomerization of substrate **2c** preceding the intramolecular cyclization step. Anyhow, the homologous compounds **3c** and **3b** were easily separated by flash chromatography (light petroleum ether/ethyl acetate 7:3). Aiming to minimize this isomerization, the reaction of **2c** has been performed in the same solvent at milder conditions (40 °C, Entry 9). In this case, as in boiling CH₂Cl₂ solution (Entry 7), the exclusive formation of **3c** is compromised by a very low conversion.

It is noteworthy that better results were obtained in CH₂ClCH₂Cl than in CH₂Cl₂ solution, generally employed in the RCM reactions; this suggests that suitable temperatures are required in the process. Moreover, 1,2-dichloroethane has been shown to be more effective than toluene, at a given reaction temperature.

Table 1. Optimization of Ring-Closing Metathesis

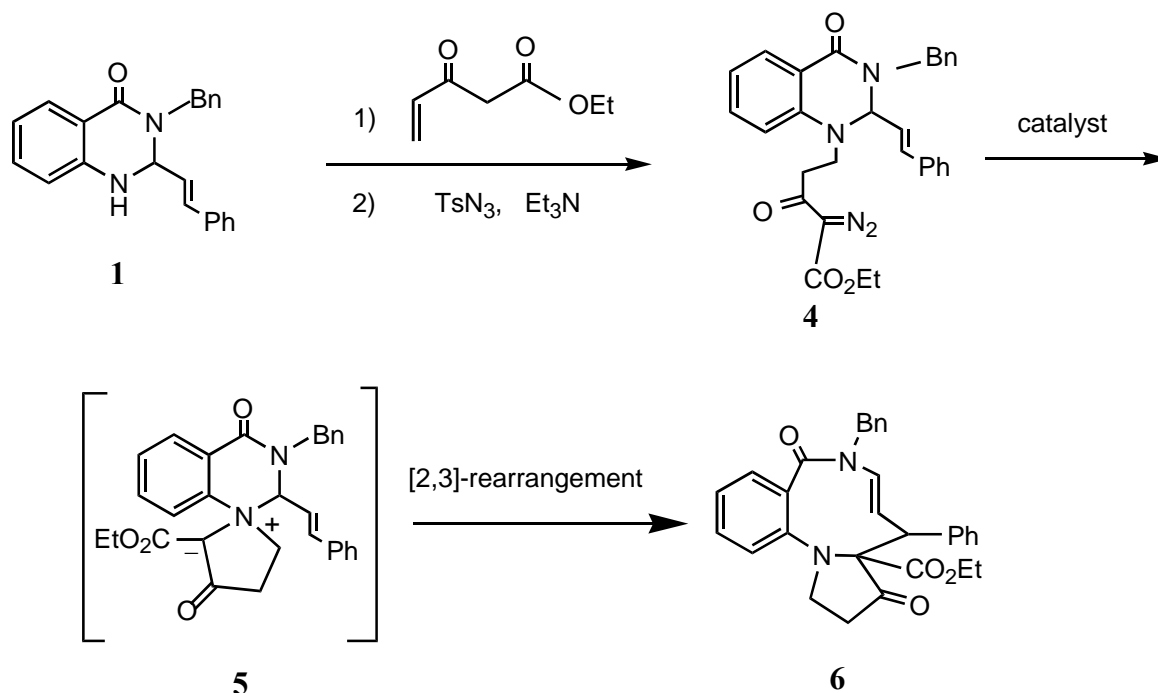
Entry	Substrate ^(a)	n	Solvent	T (°C)	Time	Yield(%) ^(b)	Product
1	2a	0	CH ₂ Cl ₂	reflux	2 d	0(0)	3a
2	2a	0	CH ₂ ClCH ₂ Cl	reflux	2 d	0(0)	3a
3	2a	0	toluene	80	2 d	0(0)	3a
4	2b	1	CH ₂ Cl ₂	reflux	2 h	93(46)	3b
5	2b	1	CH ₂ ClCH ₂ Cl	reflux	1.5 h	96(100)	3b
6	2b	1	toluene	80	50'	92(74)	3b
7	2c	2	CH ₂ Cl ₂	reflux	3.5 h	91(15)	3c
8	2c	2	CH ₂ ClCH ₂ Cl	reflux	18'	71(100)	3c+3b
9	2c	2	CH ₂ ClCH ₂ Cl	40	3.5 h	92(10)	3c
10	2c	2	toluene	80	3.5 h	82(40)	3c+3b

^(a)Catalyst: 2.2 mol%. ^(b)Isolated yield after column chromatography based on recovered starting material. Conversion in brackets.

Due to combination of two or more distinct reactions into a single transformation, cascade or tandem processes are powerful methods for constructing complex structures starting from relatively simple materials. In this field, intramolecular cyclizations based on metallo carbenoids generated by transition metal catalyzed decomposition of diazo compounds⁹ and leading to ammonium ylides, which spontaneously undergo sigmatropic [1,2]- or [2,3]-rearrangements, has gained significant importance in organic synthesis and has become a versatile strategy for the synthesis of nitrogen heterocycles.¹⁰

For this purpose, utilization of the same styryl quinazolinone **1** as the starting material, was planned (Scheme 2). In this case, the initiation of cascade process is based upon catalytic decomposition of **4**. Generation of metallo carbenoid species with intramolecular attack to the amine nitrogen is expected to produce the spirocyclic ylide **5**. This intermediate could rearrange with [2,3]-shift,¹¹ across the pendant unsaturated group, leading to the nine-membered pyrrolo azacycle **6** with three carbons expansion of the heterocycle ring moiety. Nevertheless, the presence of a conjugative styryl function, situated on the putative migrating carbon, could activate the ylide Stevens [1,2]-rearrangement,¹² consequently, formation of the pyrrolo benzodiazepine **7** would not be avoided, in principle (Figure 1).

Effectively, decompositions of the corresponding diazo quinazolinones, bearing the carbon migrating atom activated by an ester group, afforded the Stevens [1,2]-shift products in acceptable total yields and complete stereoselectivity, as recently reported by our group.^{1c}



Scheme 2

The cyclization precursor **4** was conveniently prepared by two steps one pot conjugate addition of **1** to ethyl 3-keto-pent-4-enoate,¹³ followed by diazo-transfer reaction with tosyl azide.

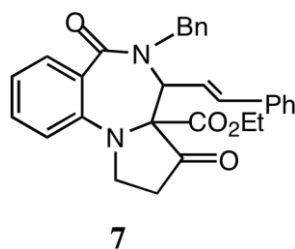


Figure 1

Two transition metal catalysts were studied. The Cu(acac)₂ catalyzed diazo-decomposition of **4**, carried out in refluxing toluene, gave mixtures of the expected pyrrolo benzoazacyclononenone **6** and the pyrrolobenzodiazepinone **7**, in 81/19 ratio (NMR spectrometry). The same reaction, performed by using Rh₂(OAc)₄ in refluxing toluene, afforded mixtures of **6** and **7** in 54/46 ratio, respectively. In both cases the decompositions gave quantitative overall yields, in spite of preceding data demonstrating the copper-

based catalysis to be more effective for generation of ammonium ylides.¹⁴

Olefin geometry of **6** has been assigned on the base of spectroscopic data.¹⁵ No traces of the intermediate ylide **5** was observed: at the employed reaction conditions it was impossible its isolation or spectroscopic detection.

CONCLUSIONS

This work reports very concise and convenient syntheses of novel tricyclic quinazolinone in two steps and pyrrolo benzoazacyclononenone alkaloids in three steps two pots, starting from a simple material as 3-styryl quinazolinone, by utilizing the RCM and cascade spiro-to fused protocols, respectively.

Of particular significance, both these procedures utilizes no additional reagents beyond a catalyst and the other product from the reaction is a volatile olefin (RCM) or nitrogen (cascade).

The efficacy of the tandem ylide formation/rearrangement reaction suggests a valid approach to the medium sized azacycloalkene system containing natural products.¹⁶

It is noteworthy that amino esters, conformationally constrained analogues to natural amino acids, can be recognized into both the diazepinone and azacyclononenone frames, consequently it could be of interesting synthetic tool.¹⁷

Moreover, larger cycle amino ester as **6** could prove useful in peptide mimic design.¹⁸

Finally, the presence of a carbon-carbon double bond make the alkaloids **3** and **6** further functionalizable. Biological evaluations and structure-activity relationship (SAR) will be reported in due course.

EXPERIMENTAL

General

¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on a Varian VXR-300 spectrometer with TMS as internal standard. Infrared (IR) spectra were performed on a FT/IR-480plus JASCO spectrophotometer. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use.

(E)-1-Acryloyl-3-benzyl-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one **2a**.

A CH₂Cl₂ (0.5 mL) solution of acryloyl chloride (0.68 mL, 8 mmol) was added dropwise to a solution of *(E)*-3-benzyl-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one **1** (1.3 g, 3.8 mmol), and TEA (1.6 mL, 11.4 mmol) in CH₂Cl₂ (25 mL) and stirred at 0 °C under nitrogen atmosphere. After the addition was complete, the solution was stirred at rt for 21 h. The solvent was evaporated and the residue gave, after flash chromatography (light petroleum ether/EtOAc 8:2), the quinazolinone diene **2a** (0.8 g, 53%), yellow crystals, mp 56-58 °C. ¹H NMR (CDCl₃): δ 4.24 (AB system, 1H), 5.38 (AB system, 1H), 5.77 (t, 1H,

J=5.7 Hz), 5.98 (dd, 1H, J=15.9, 6.0 Hz), 6.47-6.62 (m, 3H), 7.10-7.47 (m, 13H), 7.44 (t, 1H, J=7.8, Hz), 8.14 (d, 1H, J=6.6 Hz). ^{13}C NMR (CDCl_3): δ 48.2, 67.2, 122.0, 122.7, 123.3, 125.8, 126.5, 127.6, 127.7, 127.9, 128.2, 128.3, 128.6, 130.3, 132.2, 134.0, 134.9, 136.0, 136.6, 161.5, 163.6. IR (nujol): 3028, 2924, 1668, 1649, 1467, 1376, 1318, 1222, 1159, 1105, 1077, 1028, 965, 924 cm^{-1} . Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_2$: C, 79.16; H, 5.62; N, 7.10%. Found: C, 78.93; H, 5.65; N, 7.07%.

(E)-3-Benzyl-1-but-3-enoyl-2-styryl-2,3-dihydroquinazolin-4(1H)-one 2b.

A CH_2Cl_2 (1 mL) solution of 3-butenoyl chloride (0.35 g, 3.4 mmol) was added dropwise to a solution of (E)-3-benzyl-2-styryl-2,3-dihydroquinazolin-4(1H)-one **1** (1.06 g, 3.1 mmol), DMAP (0.04 g, 0.31 mmol) and pyridine (0.53 mL, 6.6 mmol) in CH_2Cl_2 (15 mL) and stirred at 0 °C under nitrogen atmosphere. After the addition was complete, the solution was stirred at rt for 6 h. The solvent was evaporated and the residue gave, after flash chromatography (light petroleum ether/EtOAc 7:3), the quinazolinone diene **2b** (0.83 g, 65%), amorphous yellow solid. ^1H NMR (CDCl_3): δ 2.96-3.41 (m, 2H), 4.20 (AB system, 1H), 4.99-5.0 (m, 1H), 5.13 (d, 1H, J=7.2 Hz), 5.39 (AB system, 1H), 5.78-5.96 (m, 2H), 6.45 (d, 1H, J=15.6 Hz), 7.19-7.35 (m, 13H), 7.49 (dt, 1H, J=7.8, 2.1 Hz), 8.14 (d, 1H, J=6.9 Hz). ^{13}C NMR (CDCl_3): δ 38.9, 48.2, 67.2, 118.6, 122.1, 123.4, 123.7, 126.4, 126.6, 126.8, 128.2, 128.3, 128.4, 128.5, 128.7, 130.4, 132.1, 132.3, 133.9, 134.9, 136.2, 137.2, 161.4, 169.2. IR (Nujol): 3028, 2923, 1679, 1651, 1604, 1470, 1448, 1375, 1256, 1202, 1160, 1077, 1028, 966, 922, 757 cm^{-1} . Anal. Calcd for $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_2$: C, 79.39; H, 5.92; N, 6.86%. Found: C, 79.28; H, 5.94; N, 6.90%.

(E)-3-Benzyl-1-pent-4-enoyl-2-styryl-2,3-dihydroquinazolin-4(1H)-one 2c.

To a solution of (E)-3-benzyl-2-styryl-2,3-dihydroquinazolin-4(1H)-one **1** (1.43 g, 4.2 mmol), DMAP (0.05 g, 0.42 mmol) and pyridine (0.72 mL, 9.0 mmol) in CH_2Cl_2 (30 mL) a CH_2Cl_2 (1 mL) solution of 4-pentenoyl chloride (0.51 g, 4.6 mmol) was added dropwise and stirred at 0 °C under nitrogen atmosphere. After the addition was complete, the solution was stirred at rt for 21 h. The solvent was evaporated and the residue gave, after flash chromatography (light petroleum ether/EtOAc 7:3), the quinazolinone diene **2c** (1.05 g, 60%), amorphous yellow solid. ^1H NMR (CDCl_3): δ 2.25-2.54 (m, 4H), 4.14 (AB system, 1H), 4.89-4.96 (m, 2H), 5.43 (AB system, 1H), 5.60-5.72 (m, 1H), 5.93 (dd, 1H, J=15.9, 2.1 Hz), 6.47 (d, 1H, J=15.9 Hz), 7.09-7.34 (m, 13H), 7.49 (t, 1H, J=7.5 Hz), 8.14 (d, 1H, J=7.5 Hz). ^{13}C NMR (CDCl_3): δ 28.9, 32.9, 66.8, 115.5, 122.1, 123.3, 123.7, 125.8, 126.0, 126.5, 127.7, 128.1, 128.2, 128.3, 128.4, 128.6, 132.2, 133.7, 134.9, 136.1, 136.2, 137.1, 161.6, 170.5. IR (CHBr_3): 3019, 2923, 1668, 1648, 1604, 1471, 1447, 1378, 1312, 1206, 1143, 1077, 1028, 965, 918, 756, 693 cm^{-1} . Anal. Calcd for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_2$: C, 79.59; H, 6.20; N, 6.82%. Found: C, 79.78; H, 6.17; N, 6.85%.

General procedure for the RCM reaction

A solution of substrate (2.5 mmol) in 5 mL of dry degassed toluene was added dropwise to a solution of 2.2 mol% of catalyst in 5 mL of the same solvent; afterward the mixture was refluxed under argon. The solvent was evaporated and the residue was submitted to flash chromatography (light petroleum ether/EtOAc 7:3).

5-Benzyl-4a,5-dihydro-2H-pyrido[1,2a]quinazoline-1,6-dione 3b: white crystals, mp 122-124 °C. Yield 96%. ¹H NMR (CDCl₃): δ 2.87 (AB system, 1H), 3.20 (AB system, 1H), 4.74 (AB system, 1H), 5.09 (AB system, 1H), 5.72-5.84 (m, 1 H), 5.82 (AB system, 1H), 6.07 (AB system, 1H), 7.13-7.34 (m, 5H), 7.38 (dt, 1H, J=7.5, 1.5 Hz), 7.57 (dt, 1H, J=7.5, 0.9 Hz), 7.83 (d, 1H, J=8.1 Hz), 8.18 (dd, 1H, J=6.3, 1.5 Hz). ¹³C NMR (CDCl₃): 32.4, 45.8, 69.2, 117.9, 123.7, 123.8, 126.1, 126.5, 127.2, 128.5, 128.7, 128.8, 132.2, 137.9, 139.7, 164.0, 165.5. IR (CHBr₃): 2924, 1674, 1652, 1603, 1479, 1465, 1446, 1374, 1331, 1296, 1027, 975, 921, 888, 850, 795, 729, 693, 654. Anal. Calcd for C₁₉H₁₆N₂O₂: C, 74.98; H, 5.30; N, 9.20%. Found: C, 74.79; H, 5.27; N, 9.24%.

(Z)-6-Benzyl-6,6a,9,10-tetrahydroazepino[1,2a]quinazoline-5,11-dione 3c: white crystals, 48-50 °C. Yield 71%. ¹H NMR (CDCl₃): δ 2.50-2.62 (m, 3H), 3.05-3.18 (m, 1H), 4.05 (AB system, 1H), 5.61 (AB system, 1H), 5.70-5.79 (m, 1H), 5.88 (ddd, 1H, J=11.1, 4.5, 2.1 Hz), 6.24 (dd, 1H, J=4.2, 2.1 Hz), 7.19 (dt, 1H, J=7.2, 1.2 Hz), 7.24-7.42 (m, 5H), 7.48 (dt, 1H, J=7.5, 1.5 Hz), 8.13 (dd, 1H, J=7.8, 1.5 Hz), 8.31 (d, 1H, J=8.4 Hz). ¹³C NMR (CDCl₃): 25.7, 36.2, 47.6, 66.0, 118.3, 119.2, 123.9, 127.9, 128.1, 128.6, 129.0, 129.5, 133.1, 133.5, 135.6, 138.1, 161.0, 172.8. IR (CHBr₃): 1679, 1655, 1601, 1479, 1460, 1428, 1391, 1376, 1296, 1264, 1197, 873, 754, 654. Anal. Calcd for C₂₀H₁₈N₂O₂: C, 81.15; H, 5.92; N, 8.23%. Found: C, 79.88; H, 5.89; N, 8.19%.

(E)-Ethyl 5-(3-benzyl-4-oxo-2-styryl-3,4-dihydroquinazolin-1(2H)-yl)-2-diazo-3-oxopentanoate 4.

A solution of (*E*)-3-benzyl-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one **1** (0.60 g, 1.76 mmol), and 3-oxopent-4-enoic acid ethyl ester (0.50 g, 3.52 mmol), in MeCN (15 mL) was stirred at rt for 7 days. The solvent was evaporated and a solution of tosyl azide (0.52 g, 2.6 mmol) and TEA (0.37 mL, 2.6 mmol) in CH₂Cl₂ (15 mL) were added dropwise at 0 °C. After the addition was complete, the solution was stirred at rt overnight. The solvent was evaporated and the residue gave, after flash chromatography (light petroleum ether/EtOAc 7:3), the diazo compound **4a** (0.53 g, 61%) as a yellow oil. ¹H NMR: δ 1.27 (t, 3H, J=8.0 Hz), 3.02 (AB system, 1H), 3.20 (AB system, 1H), 3.46-3.56 (m, 2H), 3.90 (AB system, 1H), 4.21 (q, 2H, J=8.0 Hz), 5.05 (d, 1H, J=8.4 Hz), 5.55 (AB system, 1H), 6.21 (dd, 1H, J=15.6, 8.4 Hz), 6.51 (d, 1H, J=15.6 Hz), 6.70 (d, 1H, J=8.4 Hz), 6.87 (t, 1H, J=7.5 Hz), 7.22-7.35 (m, 11H), 8.04 (dd, 1H,

$J=7.8, 1.5$ Hz). ^{13}C NMR (CDCl_3): δ 14.2, 38.5, 42.6, 46.7, 61.5, 75.6, 111.9, 116.6, 118.3, 122.7, 126.8, 127.4, 128.4, 128.6, 129.4, 133.8, 135.4, 136.8, 145.4, 160.9, 162.5, 190.3. IR (neat): 3028, 2980, 2136, 1714, 1650, 1604, 1492, 1454, 1372, 1306, 1251, 1218, 1163, 1132, 1098, 1048, 1028, 992, 912, 746, 695 cm^{-1} . Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_4$: C, 70.85; H, 5.55; N, 11.02%. Found: C, 71.01; H, 5.51; N, 10.99%.

General procedure for the diazo-decomposition

To a refluxing solution of catalyst (Rh_2OAc_4 , 2.6 mg, 3 mol% or $\text{Cu}(\text{acac})_2$, 2.6 mg, 5 mol%) in 6 mL of dry toluene, a solution of diazo compound (0.2 mmol) in 5 mL of dry toluene was added dropwise over 30 min. After stirring for 30 min at reflux, the mixture was cooled, and after evaporation of the solvent, purified by flash chromatography (light petroleum ether/ EtOAc 7:3).

(E)-Ethyl 4-benzyl-5,15-dioxo-1-phenyl-4,5,13,14,15,15a-hexahydro-1H-benzo[b]-1H-pyrrolo [1,2*i*] [1,5]diazonine-15a-carboxylate 6: (yield 74.9%), white crystals, mp 45-47 °C. ^1H NMR (CDCl_3): δ 1.15 (t, 3H, $J=7.2$ Hz), 2.50-2.62 (m, 1H), 2.72-2.82 (m, 1H), 3.81 (q, 1H, $J=7.2$ Hz), 3.94-4.17 (m, 3H), 4.28 (AB system, 1H), 4.97 (d, 1H, $J=7.4$ Hz), 5.51 (dd, 1H, $J=15.9, 7.4$), 5.60 (AB system, 1H), 5.92 (d, 1H, $J=15.9$ Hz), 6.94-6.99 (m, 3H), 7.15-7.39 (m, 9H), 7.47 (dt, 1H, $J=7.4, 1.8$ Hz), 8.47 (dd, 1H, $J=7.4, 1.8$ Hz). ^{13}C NMR (CDCl_3): δ 14.1, 34.1, 43.6, 55.5, 64.4, 78.9, 113.3, 118.6, 119.3, 122.7, 127.1, 126.6, 127.4, 128.0, 128.3, 128.4, 129.2, 132.8, 134.7, 135.8, 137.2, 142.9, 165.7, 167.1, 204.0. IR (CHBr_3): 3413, 2256, 1769, 1733, 1614, 1492, 1478, 1451, 1372, 1291, 1227, 749, 692 cm^{-1} . Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_4$: C, 74.98; H, 5.87; N, 5.83%. Found: C, 74.73; H, 5.83; N, 5.86%.

(Z)-Ethyl 5-benzyl-3,6-dioxo-4-styryl-2,3,5,6-tetrahydro-1H-4H-benzo[f]pyrrolo[1,2-*a*][1,4]-diazepine-3a-carboxylate 7: (yield 21.1%), white crystals, mp 108-110 °C. ^1H NMR (CDCl_3): δ 0.98 (t, 3H, $J=7.2$ Hz), 2.61-2.72 (m, 2H), 3.55 (dt, 1H, $J=8.4, 2.4$ Hz), 3.80-3.98 (m, 3H), 4.25 (AB system, 1H), 4.85 (d, 1H, $J=9.3$ Hz), 5.35 (AB system, 1H), 5.58 (dd, 1H, $J=15.9, 9.3$ Hz), 5.69 (d, 1H, $J=15.9$ Hz), 6.78-6.81 (m, 2H), 7.13-7.36 (m, 9H), 7.44 (dd, 1H, $J=7.8, 1.5$ Hz), 7.53 (dt, 1H, $J=7.8, 1.5$ Hz), 7.76 (dd, 1H, $J=7.8, 1.5$ Hz). ^{13}C NMR (CDCl_3): δ 14.01, 14.04, 35.51, 43.27, 52.61, 61.16, 61.96, 77.20, 83.66, 121.47, 123.15, 124.27, 126.39, 127.63, 128.05, 128.39, 128.41, 129.41, 130.64, 131.50, 131.96, 135.70, 135.83, 137.25, 143.11, 166.53, 169.92, 203.28. IR (CHBr_3): 2969, 1764, 1733, 1624, 1466, 1364, 1298, 1227, 1201, 1143, 1052, 965, 763, 693, 654 cm^{-1} . Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_4$: C, 74.98; H, 5.87; N, 5.83%. Found: C, 74.82; H, 5.84; N, 5.87.

ACKNOWLEDGEMENTS

The Authors are thankful to Fondazione Banco di Sardegna for financial support.

REFERENCES AND NOTES

1. (a) A. Saba, *Tetrahedron Lett.*, 2003, **44**, 2895; (b) D. Muroi, A. Saba, and N. Culeddu, *Tetrahedron: Asymmetry*, 2004, **15**, 2609; (c) D. Muroi, A. Saba, and N. Culeddu, *Tetrahedron*, 2006, **62**, 1459; (d) D. Muroi, A. Saba, and N. Culeddu, *Heterocycles*, 2006, **68**, 47; (e) M. Mucedda, D. Muroi, A. Saba, and C. Manassero, *Tetrahedron*, 2007, **63**, 12232.
2. D. Muroi, M. Mucedda, and A. Saba, *Tetrahedron Lett.*, 2008, **49**, 2373.
3. For a review on quinazoline alkaloids, see: (a) J. P. Michael, *Nat. Prod. Rep.*, 2000, **17**, 603; (b) S. John, 'Supplements to the Second Edition of Rodd's Chemistry of Carbon Compounds', Vol. IV I/J, ed. by M. F. Ansell, Elsevier Inc., Amsterdam, 1995, pp. 223-240.
4. S. John, 'The Alkaloids, Chemistry and Pharmacology', Vol. 29, ed. by A. Brossi, Academic Press, Inc., New York, 1986, pp. 99-140.
5. (a) V. Alagarsamy, V. R. Solomon, and M. Murugan, *Bioorg. Med. Chem.*, 2007, **15**, 4009; (b) A. S. Shawali, H. M. Hassaneen, and N. K. Shurrab, *Heterocycles*, 2008, **75**, 1479; (c) J. J. Wade, *U. S. Patent*, No. 4,528,288 (*Chem. Abstr.*, 1986, 104, 5889); (d) W. R. West July, *Eur. Patent*, No. 34,529 (*Chem. Abstr.*, 1982, **96**, 20114).
6. T. A. Kilroe Smith and H. Stephen, *Tetrahedron*, 1957, **1**, 38.
7. (a) R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446; (b) R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117.
8. P. Compain, *Adv. Synth. Catal.*, 2007, **349**, 1829. In this review examples are reported in which successful RCM reactions are performed utilizing substrates containing secondary and tertiary amines.
9. A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223.
10. For general reviews of the Stevens rearrangement, see: (a) I. E. Markò, 'The Stevens and related rearrangements', ed. by B. M. Trost and I. Fleming, Wiley, Inc., Oxford, 1991, p. 913; (b) F. G. West and G. S. Clark, 'Nitrogen, Oxygen and Sulfur Ylide Chemistry', ed. by J. S. Clark, Oxford University Press, Inc., Oxford, 2002; (c) For a recent review of the Stevens rearrangement of ammonium ylides, see: J. A. Vanecko, H. Wan, and F. G. West, *Tetrahedron*, 2006, **62**, 1043; (d) For a review of ammonium ylides generated by diazo compounds, see: M. P. Doyle, M. A. McKervey, and T. Ye, 'Modern Catalytic Methods for Organic Synthesis with Diazo Compounds', John Wiley and Sons, Inc., New York, NY, 1997.
11. For some examples of [2,3]-rearrangement of allylic ammonium ylides, see: (a) J. S. Clark and M. D. Middleton, *Org. Lett.*, 2002, **4**, 765; (b) E. Roberts, J. P. Sancon, J. B. Sweeney, and J. A. Workman, *Org. Lett.*, 2003, **5**, 4775; (c) C.-Y. Zhou, W.-Y. Yu, P. W. Chan, and C.-M. Che, *J. Org. Chem.*, 2004, **69**, 7072.

12. (a) J. A. Vanecko and F. G. West, [Org. Lett., 2002, 4, 2813](#); (b) A. Padwa, L. S. Beall, C. K. Eidell, and K. J. Worsencroft, [J. Org. Chem., 2001, 66, 2414](#); (c) F. G. West, K. W. Glaeske, and B. N. Naidu, [Synthesis, 1993, 977](#).
13. R. Zibuck and J. M. Streiber, [J. Org. Chem., 1989, 54, 4717](#).
14. The copper-based catalysis has been demonstrated to be more effective: a) F. G. West, B. N. Naidu, and R. W. Tester, [J. Org. Chem., 1994, 59, 6892](#); (b) see ref. 1 (e).
15. Coupling constants were found by ^1H 300 MHz NMR to be 15.9 Hz.
16. For the use of spirocyclic ammonium ylide rearrangements to prepare medium-sized azacycles, see: (a) D. L. Wright, R. M. Weekly, R. Groff, and M. McMills, [Tetrahedron Lett., 1996, 37, 2165](#); (b) J. S. Clark, P. B. Hodgson, M. D. Goldsmith, A. J. Blake, P. A. Cooke, and L. J. Street, [J. Chem. Soc., Perkin Trans. 1, 2001, 3325](#).
17. (a) F. G. West and B. N. Naidu, [J. Org. Chem., 1994, 59, 6051](#); (b) C. Cativiela and M. D. Diaz-de-Villegas, [Tetrahedron: Asymmetry, 1998, 9, 3517](#); (c) S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, and W. D. Lubell, [Tetrahedron, 1997, 53, 12789](#); (d) see ref. 11 (a).
18. A. Giannis and T. Kolter, [Angew. Chem., Int. Ed. Engl., 1993, 32, 1244](#).