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Concise synthesis of fused polycyclic quinolines

Elisabetta Rossi,[a,*] Giorgio Abbiati,[a] Antonio Arcadi[b] and Fabio Marinelli[b]

[a]*Istituto di Chimica Organica, Facoltà di Farmacia, Università degli Studi di Milano, Via Venezian, 21, I-20133 Milan, Italy*
[b]*Dipartimento di Chimica, Ingegneria Chimica e Materiali, Facoltà di Scienze, Università de L'Aquila, Via Vetoio, Coppito due, 67100 L'Aquila, Italy*

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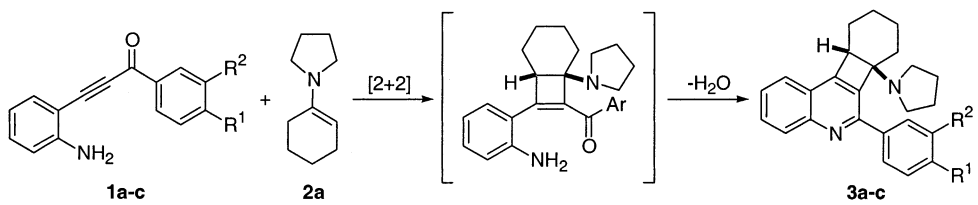
Abstract—β-(2-Aminophenyl)-α,β-ynones react with enamines of cyclic ketones by domino [2+2]cycloaddition/annelation reaction giving rise to bicyclo[4.2.0]-octane[7,8-*c*]-2-aryl quinolines or to *c*-fused quinolines. The reactivity of ynones towards acyclic enamines and thermal rearrangement of tetracyclic to the corresponding tricyclic derivatives are also described.

The [2+2]cycloadditions of enamines with electrophilic acetylenes in apolar solvents are well documented and represent an important strategy for the synthesis of cyclobutene derivatives.[1] Moreover, thermal rearrangement of this type of cyclobutenes is a useful method for ring enlargement with two carbon atoms and has been widely used in the synthesis of medium-sized carbo- and heterocycles,[1a,1b,1d,2] azulenes,[3] azuleno[1,2-*b*]azulenes,[4] C-19-diterpene alkaloids,[5] and several natural products.[6] However, while the behavior in these reactions of acetylene mono- and dicarboxylates as well as methyl propiolate has received great attention both from the theoretical and applied point of view, less attention has been paid to the cycloaddition reactions with α,β-ynones and related compounds. To date, only few reports dealing with these latter reactions have appeared in the literature. For example, the 1,4-diphenyl-2-butyne-1,4-dione reacts with enamines of cyclic ketones to give, as expected, bicyclic cyclobutenes or monocyclic 1,3-dienes.[1b] Instead, no cycloaddition between 3-pentyn-2-one and [2-(6,6-dimethylcyclohex-1-enyl)vinyl]-dimethylamine was observed to take place upon heating and at a pressure of up to 7 kbar.[7]

Recently, in connection with our ongoing interest in the synthesis of heterocyclic compounds from alkynes,[8] we reported the synthesis of a polycyclic fused quinoline ring through a domino cycloaddition/annelation reaction of a β-(2-aminophenyl)-α,β-ynone with 1-(cyclohexen-1-yl)pyrrolidine.[9] So, with the aim to develop and to define the scope and limitation of this synthetic methodology, we extended our study to the reactivity of



	R_1	R_2	Yield (%)
3a	Cl	H	56
3b	H	CF_3	58
3c	COMe	H	52

Scheme 1.

Keywords: [2+2]cycloadditions; tandem reactions; polycyclic quinolines.
* Corresponding author. Fax: 00390270638473; e-mail: elisabetta.rossi@unimi.it

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β-(2-aminoaryl)-α,β-ynones towards enamines derived from cyclic ketones and from aldehydes.

When β-(2-aminophenyl)-α,β-ynones **1a–c** were treated in toluene under reflux for 4–6 h with 3 equiv. of 1-(cyclohexen-1-yl)pyrrolidine **2a**, the 1-(1′-pyrrolidino)bicyclo[4.2.0]octane[7,8-*c*]-2-arylquinolines **3a–c**[10] were isolated in moderate yields (Scheme 1).

The structures of **3a–c** were assigned on the basis of analytical and spectral data. In particular, ^{1}H NMR, Apt, COSY and HETCOR experiments performed at 300 MHz are in agreement with the presence of a C_{sp^3}-H group, coupled to an adjacent C_{sp^3}-H_2, and of seven quaternary C_{sp2} which is incompatible with an isomeric ring enlargement product (Fig. 1, structure B, $n=1$). Moreover, NOESY experiment confirmed the assigned regio- and stereochemistry showing diagnostic NOE effects between C_{sp^3}-H and pyrrolidine nucleus and between C_{sp^3}-H and the aromatic hydrogen at C-5 on the quinoline nucleus.

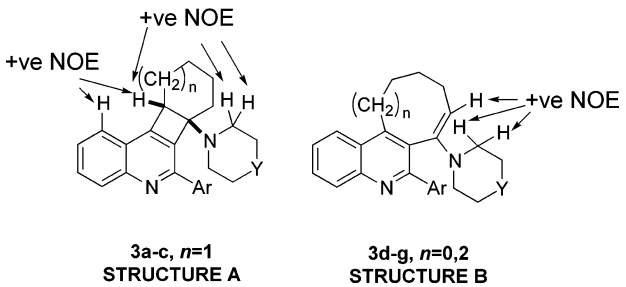
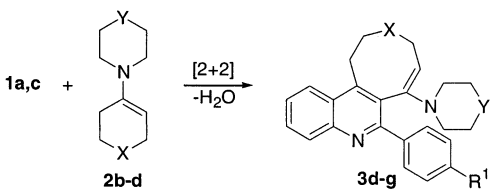


Figure 1.

When β-(2-aminophenyl)-α,β-ynones **1a**,**c** were treated under standard conditions with 1-(cyclopenten-1-yl)pyrrolidine **2b** and 1-(cyclopenten-1-yl)morpholine **2c** or 1-(cyclohepten-1-yl)pyrrolidine **2d**, the corresponding *c*-fused quinolines **3d–g**[11] were isolated in moderate yields (Scheme 2).



	X	Y
2b	-	-
2c	-	O
2d	$(CH_2)_2$	-

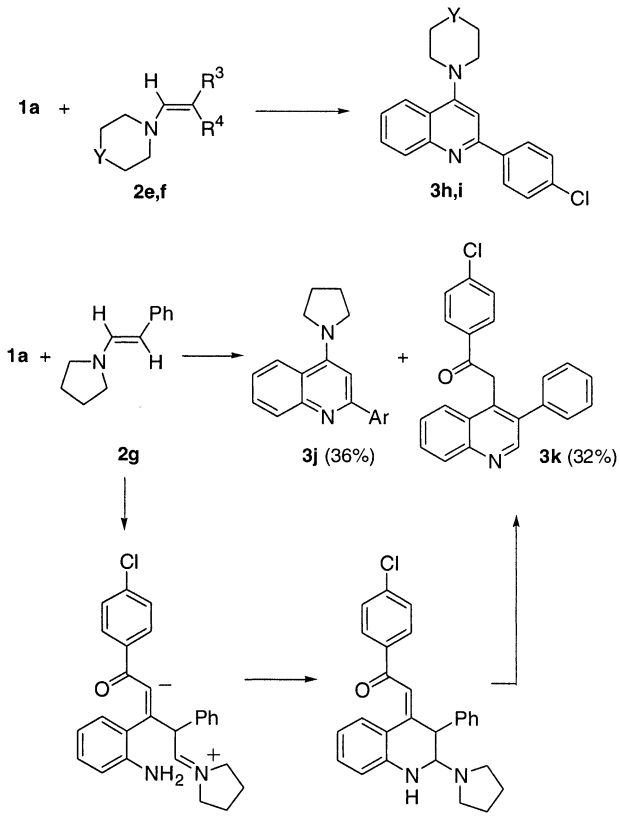
	R_1	X	Y	Yield (%)
3d from **1a** and **2b**	Cl	-	-	58
3e from **1c** and **2b**	COMe	-	-	55
3f from **1a** and **2c**	Cl	-	O	52
3g from **1a** and **2d**	Cl	$(CH_2)_2$	-	45

Scheme 2.

Combined mono-(^{1}H NMR, Apt) and bidimensional (COSY, HETCOR, NOESY) experiments, performed at 300 MHz, allowed the complete assignment of each resonance of derivatives **3d–g**. In particular, compounds **3d–g** showed for the olefinic proton a double doublet at near 5 ppm which gave positive NOE interactions with the methylenic protons of the cyclic amine but not with the aromatic protons of the quinoline ring, (Fig. 1, structure B).

The reactivity of α,β-ynones **1** was then tested with enamines derived from aldehydes (Scheme 3). β,β-Disubstituted enamines **2e**,**f** failed to give cycloaddition reactions with **1a**, and 4-aminoquinolines **3h**,**i** were isolated after prolonged reaction times (24 h).

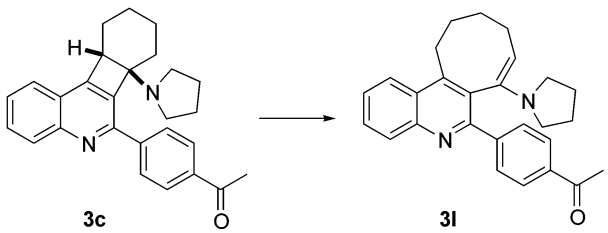
Very likely, compounds **3h**,**i** were formed by domino Michael addition/annelation reaction of piperidine or morpholine, which might be generated by the slow hydrolysis of the starting enamines. Finally, β-monosubstituted enamine **2g** reacts with **1a** giving rise, beside the 4-amino derivative **3j**, to a new 3,4-disubstituted quinoline **3k** probably through a nucleophilic attack/intramolecular annelation/isomerization/elimination cascade reaction (Scheme 3).



	R^3	R^4	Y		Y	Yield (%)
2e	Me	Ph	O	**3h**	O	52
2f	Me	Me	CH_2	**3i**	CH_2	76
2g	Ph	H	-			

Scheme 3.

Thus, ynones **1** react with cyclohexanone enamine by domino [2+2]cycloaddition/annelation reaction giving rise to stable tetracyclic quinoline derivatives **3a–c**, whereas, in the cycloaddition reactions performed with cyclopentanone and cycloheptanone enamines, the polyfused primary adducts thermally rearrange to the corresponding *c*-fused tricyclic quinolines **3d–g**. On the basis of semiempirical AM1 calculations the enthalpies of formation for the compounds of structure B ($n=0$–2) are 96–108 kJ mol^{-1} lower than that of the corresponding compounds of structure A ($n=0$–2). Probably, the activation energy for ring enlargement of **3a–c** is higher compared with that of the adducts derived from the reaction of cyclopentanone and cycloheptanone enamines. This hypothesis was confirmed by heating under reflux in xylene pure **3c**. Under these conditions **3c** was quantitatively converted into the thermodynamically favored tricyclic quinoline **3l** (Scheme 4).



Scheme 4.

The lack of reactivity of enamines **2e–g** towards cycloaddition could be attributed to electronic effects. As it is well known,[12] the reactivity of an enamine double bond is related to the resonance interaction between the nitrogen lone-pair electrons (n) and the alkene π-system (π) and results from decreased s-character for nitrogen orbital. For the enamines derived from medium-sized heterocyclic amines the decrease in s-character for a nitrogen orbital is greater for the enamines of cyclic ketones and lower in enamines derived from acyclic ketones and aldehydes.

In conclusion, the reactions of ynones **1** with cyclic enamines allow the preparation of new tri- and tetracyclic quinoline derivatives through domino [2+2]cycloaddition/annelation reactions. Interestingly, ynone **1a** reacts with the β-monosubstituted enamine **2g** giving rise by intramolecular cyclization to 3,4-disubstituted quinoline **3k**. Further work is in progress in order to evaluate the scope and limitations of this synthetic approach.

References

1. (a) Cook, A. G. In *Enamines: Synthesis, Structure, and Reactions*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 7, pp. 384–388; (b) Kaupp, G.; Pogodda, U.; Atfah, A.; Meier, H.; Vierengel, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 768–770; (c) Hongo, H.; Nakano, H.; Okuyama, Y. *Heterocycles* **1995**, *40*, 831–836; (d) Tunoglu, N.; Uludag, N. *Org. Prep. Proced. Int.* **1997**, *29*, 541–547.
2. (a) Reinhoudt, D. N.; Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Harkema, S.; van Hummel, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1341–1350; (b) Vieilles-cazes, C.; Coen, S.; Ragonnet, B.; Roggero, J. P. *Heterocycles* **1985**, *23*, 927–930; (c) Vos, G. J. M.; Benders, P. H.; Reinhoudt, D. N.; Egberink, R. J. M.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1986**, *51*, 2004–2011; (d) Matsunaga, H.; Sonoda, M.; Tomioka, Y.; Yamazaki, M. *Chem. Pharm. Bull.* **1986**, *34*, 396–400; (e) Takahata, H.; Anazawa, A.; Moriyama, K.; Yamazaki, T. *Chem. Lett.* **1986**, 5–6; (f) Tsuge, O.; Hatta, T.; Takahashi, Y.; Maeda, H.; Kakahi, A. *Heterocycles* **1998**, *47*, 665–670.
3. Bengtson, G.; Keyaniyan, S.; De Meijere, A. *Chem. Ber.* **1986**, *119*, 3607–3630.
4. Kuroda, S.; Hirooka, S.; Iwaki, H.; Ikeda, M.; Takeshi, N.; Ogisu, M.; Yasunami, M.; Takase, K. *Chem. Lett.* **1986**, 2039–2042.
5. Van Beek, G.; Van der Baan, J. L.; Klumpp, G. W.; Bickelhaupt, F. *Tetrahedron* **1986**, *42*, 5111–5122.
6. (a) Yoshii, E.; Kimoto, S. *Chem. Pharm. Bull.* **1969**, *17*, 629–632; (b) Stork, G.; Macdonald, T. L. *J. Am. Chem. Soc.* **1975**, *97*, 1264–1265; (c) Fex, T.; Froborg, J.; Magnusson, G.; Thorén, S. *J. Org. Chem.* **1976**, *41*, 3518–3520; (d) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728–6733; (e) Larson, E. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 521–525.
7. Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844–4848.
8. See, for example: (a) Arcadi, A.; Rossi, E. *Tetrahedron*, **1998**, *54*, 15253–15272; (b) Arcadi, A.; Attanasi, O. A.; Guidi, B.; Rossi, E.; Santeusanio, S. *Eur. J. Org. Chem.* **1999**, 3117–3126.
9. Arcadi, A.; Rossi, E.; Marinelli, F. *Tetrahedron* **1999**, *55*, 13233–13250.
10. 1(1′-Pyrrolidino)bicyclo[4.2.0]-octane[7,8-*c*]-2-(4-chlorophenyl)quinoline **3a**. Mp 139–141°C; IR cm^{-1}: 3062, 2963, 1622, 1590, 1571, 1261, 1091, 1020, 799; ^{1}H NMR ($CDCl_3$): δ 1.04 (m, 2H, 3′a, 4′a), 1.43 (m, 2H, 3′b, 4′b), 1.80 (m, 4H, N-CH_2-CH_2), 2.05 (m, 2H, 2′a, 5′a), 2.35 (m, 2H, 2′b, 5′b), 2.59 (m, 2H, CH_2N), 2.90 (m, 2H, CH_2N), 4.09 (dd, 1H, H6′, $J=2.9$, 4.7), 7.45 (d, 2H, H3″, H5″, $J=8.8$), 7.50 (m, 1H, H6), 7.76 (m, 1H, H5), 7.85 (m, 1H, H7), 8.18 (d, 1H, H8, $J=8.8$), 8.64 (d, 2H, H2″, H6″, $J=8.8$); ^{13}C NMR ($CDCl_3$): δ 18.90 and 19.53 (C3′/C4′), 24.40 (2C, N-C-C), 25.49 (C2′/C5′), 29.88 (C2′/C5′), 40.98 (C6′), 47.94 (2C, N-C), 70.11 (C1′), 123.08 (C7), 124.69 (quat. C), 126.78 (C6), 129.34 (C2″, C6″ and C5), 130.50 (C3″ and C5″), 131.41 (C8), 136.08, 136.31, 148.27, 151.83 and 153.34 (quat. C).
11. 6-(4-Chlorophenyl)-7-pyrrolidin-1-yl-10,11-dihydro-9*H*-cycloepta[*c*]quinoline **3d**. Mp 132–133°C; IR cm^{-1}: 3050, 2916, 1610, 1550, 1535, 1262, 775; ^{1}H NMR ($CDCl_3$): δ 1.40 (m, 4H, N-CH_2-CH_2), 1.78 (m, 1H, 9a), 2.13 (m, 3H, 9b, 11a, 11b), 2.53 (m, 2H, CH_2N), 2.75 (m, 2H, CH_2N), 2.80 (m, 1H, 10a), 3.45 (dd, 1H, 10b, $J=4.8$, 12.8), 4.92 (t, 1H, H8, $J=7.6$), 7.35 (d, 2H, H3′, H5′, $J=8.4$), 7.58 (t, 1H, H2/H3, $J=8.3$), 7.72

(t, 1H, H2/H3, $J=8.4$), 7.78 (d, 2H, H2′, H6′, $J=8.4$), 8.16 (d, 2H, H1, H4, $J=8.6$); ^{13}C NMR ($CDCl_3$): δ 23.25 (C9), 24.94 (2C, N-C-C), 25.98 (C10), 34.97 (C11), 48.03 (2C, N-C), 98.53 (C8), 124.22 (C1), 126.83 (C2/C3), 127.73 (2C, C3′, C5′), 129.50 (C2/C3), 130.13 (2C, C2′, C6′), 130.64 (C4), 126.52, 129.32, 134.26, 140.41, 144.57, 147.50, 148.19, 156.06 (quat. C).

12. Cook, A. G. In *Enamines*: *Synthesis*, *Structure*, *and Reaction*, 2nd ed.; Cook, A. G. Ed.; Marcel Dekker: New York, 1988; Chapter 1, pp. 1–27.