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One-pot synthesis of 4-alkynyl-1-aza-9,10-anthraquinones from 2-acylethynyl-3-amino-1,4-naphthoquinones

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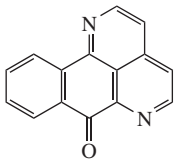
Cyclization of 2-(3-oxoalk-1-ynyl)-3-amino-1,4-naphthoquinones under the action of hydrogen bromide followed by Sonogashira cross-coupling of the thus formed 4-bromo substituted azaanthraquinone with terminal acetylenes represent the one-pot synthesis of 4-alk-1-ynyl-1-aza-9,10-anthraquinones.

A number of natural compounds have a 1-aza-9,10-anthraquinone (benzo[*g*]quinoline-5,10-dione) nucleus in their structure. These substances exhibit antitumor, fungicidal and antibacterial activities.[1–8] For example, alkaloid sampangine **1** and its derivatives are effective against fungi and mycobacteria which are AIDS-related opportunistic infection pathogens.[5] Also, these compounds unlike certain chemical fungicides, efficiently prevent various plant diseases.[3]



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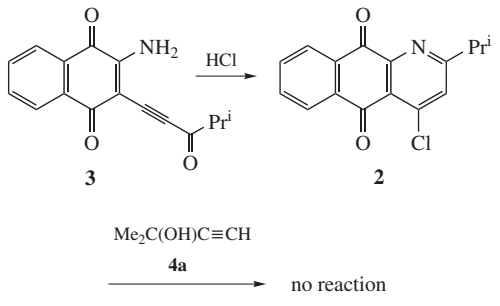
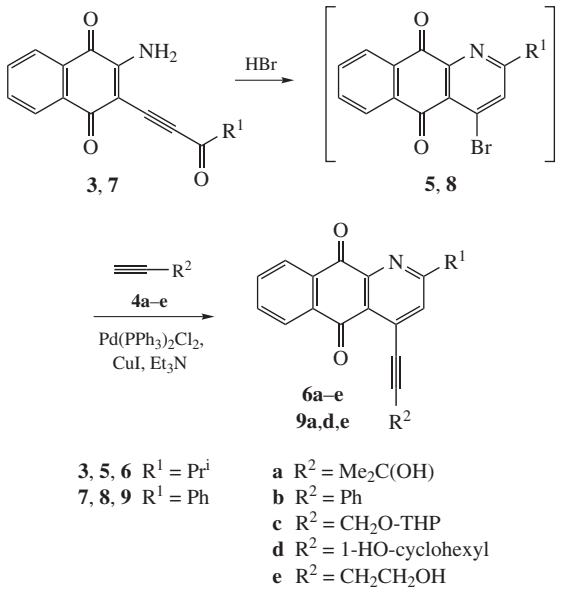
In view of the aforesaid, previously unknown 4-alk-1-ynylbenzo[*g*]quinoline-5,10-diones seem to be of interest. Herein, we report the new one-pot synthesis of such compounds from available 3-amino-2-(3-oxoalk-1-ynyl)-1,4-naphthoquinones.[9,10]

Earlier we have elaborated a convenient method for the synthesis of 4-chloro- and 4-bromoquinolines from *o*-(3-oxoalk-1-ynyl)anilines.[11] It is a cascade process including addition of hydrogen halide to the ketoacetylenic amine, *Z*,*E*-isomerization of the adduct, and intramolecular condensation. We successfully used this method for the preparation of 4-chloro-2-isopropylbenzo[*g*]quinoline-5,10-dione **2** by the cyclization of 3-amino-2-(3-oxo-4-methylpentynyl)-1,4-naphthoquinone **3** that has both reactive substituents in the quinone moiety rather than in an aromatic ring (Scheme 1).[12]

Aryl halides (reactivity: ArI > ArBr > ArCl) are known to react with terminal acetylenes in the presence of Pd,Cu-catalysts



Scheme 1



Scheme 2

and bases yielding alkynylarenes.[13] Aryl chlorides react with terminal acetylenes in the case when the chlorine atom is activated by electron-withdrawing substituents or/and heteroatomic units of the ring.[14,15] Nevertheless, attempted coupling of chloroazaanthraquinone **2** with 2-methylbut-3-yn-2-ol **4a** failed.

Therefore, we applied the above method to prepare more reactive 4-bromo-2-isopropylbenzo[*g*]quinoline-5,10-dione **5** (Scheme 2). As one should expect, the reaction of compound **3** with hydrogen bromide under the conditions of the reaction with hydrogen chloride[10] afforded the desired bromide **5**. According to TLC and ^{1}H NMR data, it was contaminated with some by-products. However, we failed to obtain compound **5** analytically pure probably because of its instability.[10] Therefore, we performed the synthesis of 2-isopropyl-4-(3-hydroxy-3-methylbutynyl)-benzo[*g*]quinoline-5,10-dione **6a** without isolation of the intermediate **5**. Amino ketone **3** was cyclized with hydrogen bromide in anhydrous chloroform at 20 °C for 7–9 h. After removal of the solvent by an argon flow or *in vacuo*, pyridine, Et_3N and other components of Sonogashira process[13] were added to the residue containing supposedly hydrobromide of compound **5** (protonated at the pyridine site). The cross-coupling was carried out at 40 °C. 2-Isopropyl-4-phenylethynylbenzo[*g*]quinoline-5,10-dione **6b** was synthesized under the same conditions (Table 1, entries 1, 2).

Table 1 4-Alkynyl-1-aza-9,10-anthraquinones prepared.

Entry	Product	R^1	R^2	Yield (%)	Mp/°C
1	**6a**	Pr^i	$Me_2C(OH)$	49	157–158
2	**6b**	Pr^i	Ph	49	146–147
3	**6c**	Pr^i	CH_2O-THP	40	83.5–84.5
4	**6d**	Pr^i	1-hydroxycyclohexyl	53	188–189
5	**6e**	Pr^i	CH_2CH_2OH	47	145–146
6	**9a**	Ph	$Me_2C(OH)$	67	169–170
7	**9d**	Ph	1-hydroxycyclohexyl	50	176–177
8	**9e**	Ph	CH_2CH_2OH	41	183–184

Unfortunately, this procedure had some disadvantages: the use of different solvents at the cyclization and cross-coupling steps and unexpected need in introducing additional portions of the catalyst and terminal acetylene to stimulate the reaction. These drawbacks were avoided in a modified procedure, when both steps were carried out in dioxane, the cross-coupling being performed at 40–50 °C and being complete within 40–100 min.† The method makes it possible to prepare various 4-acetylenic derivatives of both 2-alkyl- and 2-arylsubstituted benzo[*g*]-quinoline-5,10-diones (Scheme 2, Table 1, entries 3–8).

The structure of the synthesized compounds was confirmed by elemental analysis, ^{1}H NMR and IR spectra.‡ ^{1}H NMR spectra of azaanthraquinones **6**, **9** are similar to that of cleistopholine (4-methylbenzo[*g*]quinoline-5,10-dione).[5] At the same time, the replacement of an acetylenic group for methyl and introducing isopropyl or phenyl substituent to the 2-position result in a downfield shift of the signal of H^3 proton from 7.41 to 7.57–7.72 or to 8.09–8.12 ppm, respectively. It is noteworthy that the chemical shifts of *ortho*-protons of phenyl group depend on its position in the molecule and increase as follows: phenylethynyl < < phenyl at the 2-position of pyridine ring < benzoyl (ketone **7**).

Thus, we have developed a convenient one-pot procedure for the synthesis of 4-alkynyl-1-aza-9,10-anthraquinones from 2-acylethynyl-3-amino-1,4-naphthoquinones. The products are perspective key intermediates for the preparation of analogues of natural bioactive compounds.

References

1 (*a*) A. P. Krapcho and M. Ellis, *Arkivoc*, 2000, **1**, part 1, 43; (*b*) www.arkat-usa.org.
2 F. Bracher, *Liebigs Ann. Chem*., 1989, 87.
3 D. E. Wedge and D. G. Nagle, *US Patent 6844353*, 2005.
4 R. Hargreaves, C. L. David, L. Whitesell and E. B. Skibo, *Bioorg. Med. Chem. Lett*., 2003, **13**, 3075.
5 J. R. Peterson, J. K. Zjawiony, S. Liu, C. D. Hufford, A. M. Clark and R. D. Rogers, *J. Med. Chem.*, 1992, **35**, 4069.
6 Ch. Patarapanich and J. M. Cassady, *J. Nat. Prod.*, 1999, **62**, 1390.
7 S. Mekideche and L. Desaubry, *Tetrahedron Lett*., 2008, **40**, 5268.
8 L. Bingjing, W. Lin, Ch. Guangying, H. Changri and W. Jing, *Molecules*, 2010, **15**, 6349.
9 M. S. Shvartsberg, E. A. Kolodina, N. I. Lebedeva and L. G. Fedenok, *Tetrahedron Lett*., 2009, **50**, 6769.
10 M. S. Shvartsberg, E. A. Kolodina, N. I. Lebedeva and L. G. Fedenok, *Izv. Akad. Nauk, Ser. Khim.*, 2012, 580 (in Russian).
11 M. S. Shvartsberg and E. A. Kolodina, *Mendeleev Commun.*, 2008, **18**, 109.
12 E. A. Kolodina, N. I. Lebedeva and M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2381 (*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 2466).
13 R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874.
14 C. E. Castro, R. Holden, V. K. Honwad, A. Malte and S. Moje, *J. Am. Chem. Soc*., 1969, **21**, 6464.
15 N. Sato, A. Nayakawa and R. Takeuchi, *Heterocycl. Chem.*, 1990, **27**, 503.

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† *General procedure for the synthesis of alkynylazaanthraquinones* **6**, **9**. A solution of HBr (~0.7 g) was prepared by the saturation of anhydrous dioxane (12 ml) with gaseous HBr. A part of the solution (~5 ml, 3–4 mmol of HBr) was added dropwise to ketone **3** or **7** in dioxane (7 ml) and stirred at room temperature for 7–9 h. During this period the solution of HBr (~5 ml) was additionally introduced into the reaction mixture portionwise. After the completion of the cyclization (TLC control) Et_3N (6 ml), terminal acetylene **4** (1 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg) and CuI (10 mg) were added under argon and stirred at 45–50 °C for 40–100 min (TLC control). The product was isolated in usual way and purified by flash chromatography on silica gel in toluene and crystallization from toluene–hexane or other solvents.

‡ The ^{1}H NMR and IR spectra were recorded using Bruker DPX200 and Bruker Vector 22 spectrometers, respectively.

Crucial 3-amino-2-benzoylethynyl-1,4-naphthoquinone **7** was synthesized from 3-acetylamino-2-bromo-1,4-naphthoquinone analogously to ketone **3**;[10] mp 204.5–206 °C (CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.21, 6.53 (both br. s, 2H, NH_2), 7.45–7.65 (m, 3H, *m*-H_{Ph}, *p*-H_{Ph}), 7.65–7.90 (m, 2H, 6-H, 7-H), 8.05–8.30 (m, 2H, 5-H, 8-H), 8.30–8.50 (m, 2H, *o*-H_{Ph}). IR ($CHCl_3$, ν/cm^{-1}): 1605, 1629, 1684 (C=O), 2179 (C≡C), 3375, 3420, 3488 (NH_2).

Typical spectra of acetylenic derivatives of benzo[*g*]quinoline-5,10-diones are given below.

6a: ^{1}H NMR ($CDCl_3$) δ: 1.38 (d, 6H, Me, *J* 6.9 Hz), 1.73 (s, 6H, Me_2CO), 2.50 (br. s, 1H, OH), 3.34 (sept., 1H, CH, *J* 6.9 Hz), 7.58 (s, 1H, 3-H), 7.70–7.85 (m, 2H, 7-H, 8-H), 8.20–8.40 (m, 2H, 6-H, 9-H). IR ($CHCl_3$, ν/cm^{-1}): 1673, 1688 (C=O), 2222 (C≡C), 3529 (OH).

6b: ^{1}H NMR ($CDCl_3$) δ: 1.42 (d, 6H, Me, *J* 7.0 Hz), 3.38 (sept., 1H, CH, *J* 7.0 Hz), 7.40–7.50 (m, 3H, *m*-H_{Ph}, *p*-H_{Ph}), 7.72 (s, 1H, 3-H), 7.70–7.90 (m, 4H, 7-H, 8-H, *o*-H_{Ph}), 8.30–8.40 (m, 2H, 6-H, 9-H). IR ($CHCl_3$, ν/cm^{-1}): 1674, 1688 (C=O), 2209 (C≡C).

6c: ^{1}H NMR ($CDCl_3$) δ: 1.39 (d, 6H, Me, *J* 7.0 Hz), 1.50–2.00 [m, 6H, $(CH_2)_3$], 3.34 (sept., 1H, CH, *J* 7.0 Hz), 3.55–3.70, 3.85–4.05 (2m, 2H, CH_2O), 4.69 (s, 2H, $C{\equiv}CCH_2$), 5.05–5.15 (m, 1H, O–CH–O), 7.63 (s, 1H, 3-H), 7.75–7.85 (m, 2H, 7-H, 8-H), 8.25–8.40 (m, 2H, 6-H, 9-H). IR ($CHCl_3$, ν/cm^{-1}): 1675, 1688 (C=O), 2227(C≡C).

9a: ^{1}H NMR ($CDCl_3$) δ: 1.65 (s, 6H, Me), 7.40–7.60 (m, 3H, *m*-H_{Ph}, *p*-H_{Ph}), 7.70–7.90 (m, 2H, 7-H, 8-H), 8.09 (s, 1H, 3-H), 8.15–8.45 (m, 4H, 6-H, 9-H, *o*-H_{Ph}). IR ($CHCl_3$, ν/cm^{-1}): 1673, 1689 (C=O), 2221 (C≡C), 3530 (OH).