Regioselectivity Change in the Reaction of Naphthalene and 2-Naphthyl Ethers with 1,3,5-Triazines Depending on Reagent Quantities

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Abstract: A new method for the synthesis of 4*H*-benzo[*de*]isoquinolin-4-ones has been developed, based on the reaction of 2-naphthyl ethers with an equimolar quantity of 1,3,5-triazines in polyphosphoric acid. With a 2.5 molar excess of 1,3,5-triazines in polyphosphoric acid, the products of 1,6-diacylation (diformylation) are formed. Isoquino[6′,5′,4′:10,5,6]anthra[2,1,9-*def*]isoquinoline is formed upon reaction of a 1.5 molar excess of 1,3,5-triazine with naphthalene in polyphosphoric acid at 130–140 °C.

Key words: 1,3,5-triazines, polyphosphoric acid, naphthalenes, acylation, 4*H*-benzo[*de*]isoquinolin-4-ones, isoquino[6′,5′,4′:10,5,6]anthra[2,1,9-*def*]isoquinoline

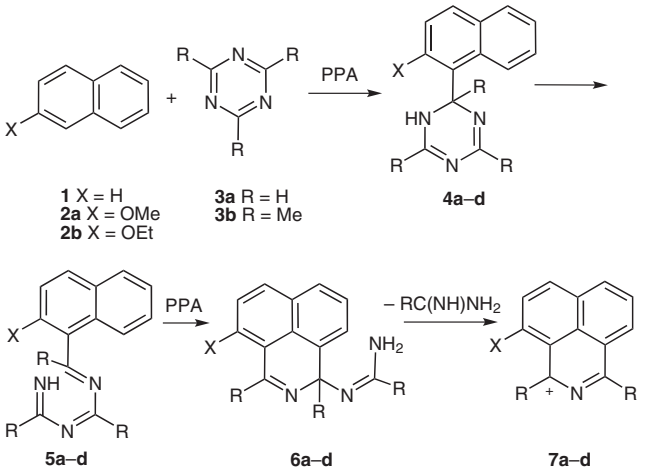
The monoacylation of naphthalene derivatives has already become a very well studied classic reaction. In contrast, there are few examples of the diacylation and diformylation of naphthalene derivatives.[1]

It is well known that 1,3,5-triazine can undergo ring cleavage upon treatment with nucleophilic reagents and serve as a formyl group precursor. This property has been extensively used in organic synthesis.[2] Thus, formamidines,[2a] perimidines,[2b] benzimidazoles,[2b] benzothiazoles,[2b] benzoxazoles,[2b] purines,[2b] pyridines,[2c,d] pyrimidines[2c,e,f] and 1,6-naphthyridines[2g–i] have been obtained utilizing different nucleophiles in reactions with 1,3,5-triazine (**3a**).

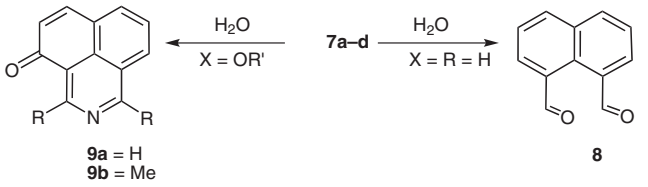
Recently, we have reported the new reagent system of 1,3,5-triazines in polyphosphoric acid and have proved its effectiveness for the acylation and formylation of perimidine[3a,b] and substituted naphthalenes,[3c] and the *peri*-annelation of carbocyclic[3d] and pyridine rings.[3e] In the present paper we suggest methods for pyridine ring annelation to naphthalenes and regioselective 1,6-diacylation (diformylation) of 2-naphthyl ethers.

On the basis of our previous work,[3] we propose that in the case of the reaction of 1,3,5-triazines with naphthalene and its monosubstituted derivatives, an intermediate **4** is formed, which is opened as for azanaphthalenes and in the series of subsequent transformations gives off the cation **7** (Scheme 1).

The behavior of cations **7a–d** depends on the nature of X. As a result of hydrolysis, dicarbonyl compounds (e.g., **8**) or 4*H*-benzo[*de*]isoquinolin-4-ones **9a**,**b** (if X = OR′) may be formed (Scheme 2).



Scheme 1 Mechanism of the reaction of 1,3,5-triazines **3a**,**b** with naphthalene derivatives



Scheme 2 Hydrolysis of cations **7a–d**

Indeed, reaction of naphthalene (**1**) with 1,3,5-triazine (**3a**) in polyphosphoric acid[4] (reagent ratio 1:1.5, at 65–70 °C for 3 h, then at 100–110 °C for 2 h), followed by quenching of the reaction mixture with water, leads to naphthalene-1,8-dicarbaldehyde (**8**) in 31% yield[5] (Scheme 2; Table 1, entry 1). A byproduct, isoquino[6′,5′,4′:10,5,6]anthra[2,1,9-*def*]isoquinoline (**10**), is formed in ~6% yield. It is likely that compound **10** is formed by the mechanism shown in Scheme 3. Thus, sequential heating of naphthalene (**1**) with 1,3,5-triazine (**3a**) at 65–70 °C for 3 hours, then at 130–140 °C for 6 hours, leads to the formation of **10** in 27% yield (Table 1, entry 2).

In the case of the 2-naphthyl ethers **2a**,**b**, reaction with an equimolar quantity of 1,3,5-triazine (**3a**) in polyphosphoric acid at 110–115 °C leads to the formation of 4*H*-benzo[*de*]isoquinolin-4-one (**9a**) in 36–64% yield

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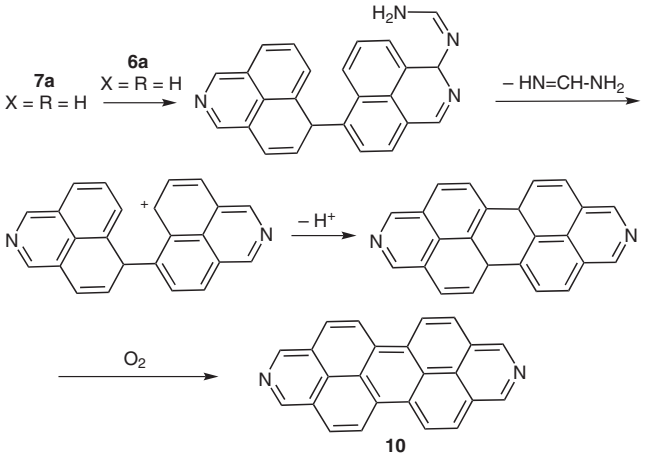
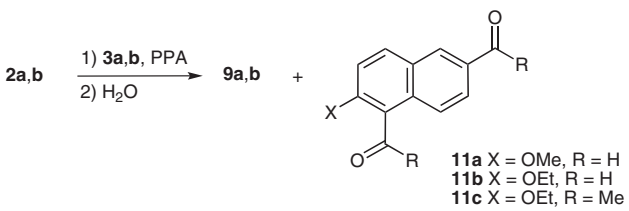


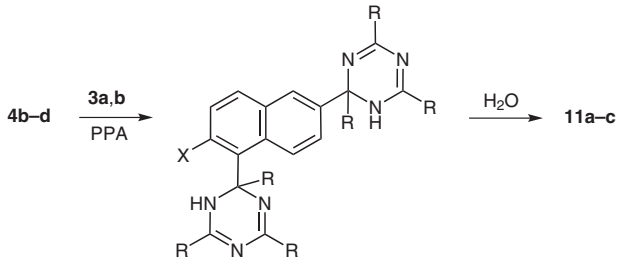
Scheme 3 Mechanism of the formation of isoquino[6′,5′,4′:10,5,6]anthra[2,1,9-*def*]isoquinoline (**10**)



Scheme 4 Reaction of 2-naphthyl ethers **2a**,**b** with 1,3,5-triazines **3a**,**b**

(Scheme 2). 1,6-Diacylation (diformylation) products **11a**,**b** are formed as byproducts (Scheme 4).

Probably, the formation of compounds **11a**–**c** occurs as a result of the reaction of intermediates **4b**–**d** with triazines **3a**,**b** (Scheme 5). Therefore, the formation of compound **11** would be stimulated by excess triazine **3**, and the formation of **9** would be the result of higher temperature.



Scheme 5 Mechanism of the formation of compounds **11a**–**c**

Accordingly, we were able to increase the yield of the 4*H*-benzo[*de*]isoquinolin-4-ones **9** up to 67–89% by heating 2-naphthyl ethers **2** with a 1.1 molar excess of triazines **3** in polyphosphoric acid at 40–45 °C for one hour, then at 100–115 °C for three hours (Table 1, entries 3, 5 and 7). Compounds **11** were obtained in 68–91% yield by the reaction of compounds **2** with a 2.5 molar excess of triazines **3** at 75–80 °C for five hours (Table 1, entries 4, 6 and 8).

In conclusion, the advantages of the described methods for 1,6-diacylation (diformylation) and [*cd*]pyridine cycle *peri*-annelation include reagent availability, experimental simplicity and applicability to the synthesis of a broad range of naphthalene derivatives.

Table 1 Reaction Conditions

Entry	R	X	Ratio (**1**:**3** or **2**:**3**)	Temp (°C), time (h)	Product: yield (%)	Product: yield (%)
1	H	H	1:1.5	65–70, 3; then 100–110, 2	**8**: 31	**10**: 6
2	H	H	1:1.5	65–70, 3; then 130–140, 6		**10**: 27
3	H	OMe	1:1.1	40–45, 1; then 100–110, 3	**9a**: 87	**11a**: 9
4	H	OMe	1:2.5	75–80, 5	**9a**: 8	**11a**: 88
5	H	OEt	1:1.1	40–45, 1; then 100–110, 3	**9a**: 89	**11b**: 7
6	H	OEt	1:2.5	75–80, 5	**9a**: 7	**11b**: 91
7	Me	OEt	1:1.1	40–45, 1; then 110–115, 3	**9b**: 67	**11c**: 11
8	Me	OEt	1:2.5	75–80, 5	**9b**: 6	**11c**: 68

Preparative column chromatography was performed on SDS flash silica gel (35–70 mesh). Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (2–400 mbar) with a bath temperature of up to 60 °C. Thin-layer chromatography (TLC) was performed on Silufol UV-254 silica gel plates. In general, the course of reactions was followed by TLC. NMR spectra were obtained on a Bruker AM-300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C) using CF_3CO_2D, $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are expressed in ppm downfield from TMS, which was used as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer. Mass spectra were recorded on a Varian CH 7 spectrometer. Melting points of small samples were obtained after recrystallization; solvents are given in parentheses. Microanalyses were carried out on a CHN-1 Elemental Analyzer. 2,4,6-Trimethyl-1,3,5-triazine (**3b**) was obtained by a known procedure.[6] Other chemicals used in this study were commercially available.

Naphthalene-1,8-dicarbaldehyde (8)

A mixture of naphthalene (**1**; 0.128 g, 1 mmol) and 1,3,5-triazine (**3a**; 0.12 g, 1.5 mmol) in PPA (3–4 g) was stirred at 65–70 °C for 3 h and then at 100–110 °C for 2 h. The reaction mixture was poured into cold H_2O (30 mL) with intense stirring. The resulting mixture was extracted with EtOAc (3 × 50 mL). The solution was concentrated under reduced pressure; compound **8** was purified by flash chromatography on silica gel (EtOAc); yield: 0.057 g (31%); mp 139–141 °C (H_2O) (Lit.[5] 140–141 °C). For spectroscopic data, see Ref.[1d]

4*H*-Benzo[*de*]isoquinolin-4-ones 9a,b

A mixture of the 2-naphthyl ether **2a** or **2b** (1 mmol) and the corresponding 1,3,5-triazine **3a**,**b** (1.1 mmol) in PPA (3–4 g) was stirred at 40–45 °C for 1 h and then at 100–110 °C for 3 h. The reaction mixture was poured into cold H_2O (30 mL) with intense stirring. The resulting mixture was extracted with EtOAc (3 × 50 mL); compounds **11** were extracted. The aqueous layer was basified with ammonia to pH 8–9 and, after cooling, the precipitated crystals or oil was extracted with EtOAc (3 × 50 mL). The solution was concen-

trated under reduced presssure, and the residue was purified by crystallization.

4*H*-Benzo[*de*]isoquinolin-4-one (9a)
Yield: 0.158 g (87%) from **2a** with **3a**; yield: 0.161 g (89%) from **2b** with **3a**; yellow crystals; mp 169–171 °C (EtOAc; with sublimation).

IR (KBr): 1654 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.71 (d, *J* = 9.9 Hz, 1 H, H-5), 7.87 (dd, *J* = 7.3, 8.0 Hz, 1 H, H-8), 8.07 (d, *J* = 9.9 Hz, 1 H, H-6), 8.22 (dd, *J* = 7.3, 0.8 Hz, 1 H, H-7), 8.40 (dd, *J* = 8.0, 0.8 Hz, 1 H, H-9), 9.31 (s, 1 H, H-1), 9.71 (s, 1 H, H-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 96.60, 128.84, 129.28, 130.38, 131.27, 135.01, 135.63, 136.91, 137.41, 141.77, 145.96, 191.12.

MS (EI): *m*/*z* (%) = 181 (100) [M$^+$], 153 (98), 126 (32).

Anal. Calcd for $C_{12}H_7NO$: C, 79.55; H, 3.89; N, 7.73. Found: C, 79.68; H, 3.82; N, 7.65.

1,3-Dimethyl-4*H*-benzo[*de*]isoquinolin-4-one (9b)
Yield: 0.14 g (67%) from **2b** with **3b**; yellow crystals; mp 186–188 °C (EtOAc; with sublimation).

IR (KBr): 1656 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.01 (s, 3 H, 1-Me), 3.03 (s, 3 H, 3-Me), 6.66 (d, *J* = 9.9 Hz, 1 H, H-5), 7.79 (dd, *J* = 7.3, 8.4 Hz, 1 H, H-8), 7.96 (d, *J* = 9.9 Hz, 1 H, H-6), 8.15 (dd, *J* = 7.3, 0.8 Hz, 1 H, H-7), 8.48 (dd, *J* = 8.4, 0.8 Hz, 1 H, H-9).

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.52; H, 5.22; N, 6.61.

Isoquino[6′,5′,4′:10,5,6]anthra[2,1,9-*def*]isoquinoline (10)
A mixture of naphthalene (**1**; 0.128 g, 1 mmol) and 1,3,5-triazine (**3a**; 0.12 g, 1.5 mmol) in PPA (3–4 g) was stirred at 65–70 °C for 3 h and then at 130–140 °C for 6 h. The reaction mixture was poured into cold H_2O (30 mL) with intense stirring. The resulting mixture was basified with ammonia to pH 8–9 and, after cooling, the precipitated crystals or oil was extracted with EtOAc (3 × 50 mL). The solution was concentrated under reduced pressure, and the residue was purified by crystallization from pyridine.

Yield: 0.044 g (27%); yellow crystals; mp 326–328 °C (Lit.[7] 326–328 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 9.5 Hz, 4 H, H-4/7/11/14), 9.22 (d, *J* = 9.5 Hz, 4 H, H-5/6/12/13), 9.61 (s, 4 H, H-1/3/8/10).

^{13}C NMR (75 MHz, CF_3CO_2D): δ = 123.72, 128.23, 129.68, 130.21, 130.99, 132.61, 136.24.

MS (EI): *m*/*z* (%) = 328 (100) [M$^+$].

Anal. Calcd for $C_{24}H_{12}N_2$: C, 87.79; H, 3.68; N, 8.53. Found: C, 87.94; H, 3.59; N, 8.47.

1,6-Dicarbonyl Compounds 11; General Procedure
A mixture of the 2-naphthyl ether **2a** or **2b** (1 mmol) and the corresponding 1,3,5-triazine **3a**,**b** (2.5 mmol) in PPA (3–4 g) was stirred at 75–80 °C for 5 h. The reaction mixture was poured into cold H_2O (30 mL) with intense stirring. After cooling, the precipitate was collected by filtration and purified by crystallization.

2-Methoxynaphthalene-1,6-dicarbaldehyde (11a)
Yield: 0.188 g (88%) from **2a** with **3a**; light yellow crystals; mp 158–159 °C (EtOH).

IR (KBr): 1691, 1682 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (s, 3 H, Me), 7.36 (d, *J* = 9.1 Hz, 1 H, H-3), 8.01 (dd, *J* = 9.1, 1.8 Hz, 1 H, H-7), 8.16 (d, *J* = 9.1 Hz, 1 H, H-4), 8.20 (d, *J* = 1.8 Hz, 1 H, H-5), 9.31 (d, *J* = 9.1 Hz, 1 H, H-8), 10.07 (s, 1 H, 6-CHO), 10.81 (s, 1 H, 1-CHO).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.57, 113.53, 116.65, 125.72, 127.03, 127.49, 132.60, 133.49, 134.98, 138.71, 165.53, 191.45, 191.61.

Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.01; H, 4.64.

2-Ethoxynaphthalene-1,6-dicarbaldehyde (11b)
Yield: 0.207 g (91%) from **2b** with **3a**; light yellow crystals; mp 147–148 °C (EtOH).

IR (KBr): 1690, 1681 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (t, *J* = 6.9 Hz, 3 H, *Me*CH_2), 4.34 (q, *J* = 6.9 Hz, 2 H, MeC*H*$_2$), 7.36 (d, *J* = 9.1 Hz, 1 H, H-3), 8.05 (dd, *J* = 9.1, 1.8 Hz, 1 H, H-7), 8.19 (d, *J* = 9.1 Hz, 1 H, H-4), 8.25 (d, *J* = 1.8 Hz, 1 H, H-5), 9.37 (d, *J* = 9.1 Hz, 1 H, H-8), 10.11 (s, 1 H, 6-CHO), 10.90 (s, 1 H, 1-CHO).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.42, 65.32, 115.44, 124.46, 124.89, 126.12, 127.00, 132.12, 133.91, 134.14, 139.11, 165.01, 190.93, 191.67.

MS (EI): *m*/*z* (%) = 228 (54) [M$^+$], 199 (87), 171 (43), 144 (36), 115 (100).

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.79; H, 5.24.

1,6-Diacetyl-2-ethoxynaphthalene (11c)
Yield: 0.173 g (68%) from **2b** with **3b**; light yellow crystals; mp 172–173 °C (EtOH).

IR (KBr): 1736, 1678 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (t, *J* = 6.9 Hz, 3 H, *Me*CH_2), 2.69 (s, 3 H, 6-COMe), 3.07 (s, 3 H, 1-COMe), 4.18 (q, *J* = 6.9 Hz, 2 H, MeC*H*$_2$), 7.09 (d, *J* = 9.1 Hz, 1 H, H-3), 7.73 (d, *J* = 8.8 Hz, 1 H, H-8), 7.86 (d, *J* = 9.1 Hz, 1 H, H-4), 7.99 (dd, *J* = 8.8, 1.8 Hz, 1 H, H-7), 8.38 (d, *J* = 1.8 Hz, 1 H, H-5).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.11; H, 6.23.

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References

(1) For reviews, see: (a) Pozharskii, A. F. *Russ. Chem. Rev. (Engl. Transl.)* **2003**, *72*, 447. (b) See also: Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671. (c) Tanaka, M.; Souma, U. *J. Chem. Soc., Chem. Commun.* **1991**, 1551. (d) Mutsuo, T.; Masahiro, F.; Hisanori, A.; Yoshie, S. *J. Org. Chem.* **1993**, *58*, 3213. (e) Gorelik, A. M.; Reznichenko, A. V.; Andronova, N. A.; Lyk'yanetz, E. A. *Zh. Org. Khim.* **1983**, *19*, 199.

(2) (a) Hinkel, L. E.; Ayling, E. E.; Beynon, J. H. *J. Chem. Soc.* **1935**, 674. (b) Grundmann, E. J.; Kreutzberger, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 6559. (c) Gromov, S. P.; Yashunskii, D. V.; Sagitullin, R. S.; Bundel, Y. u. G. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1992**, *9*, 1054. (d) Bilbao, E. R.; Alvarado, M.; Masaguer, C. F.; Ravina, E. *Tetrahedron Lett.* **2002**, *43*, 3551. (e) Moehrle, H.; Pycior, M. *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327*, 533. (f) Schaper, W. *Synthesis* **1985**, 861. (g) Balogh, M.; Hermecz, I.; Naray-Szabo, G.; Simon, K.; Meszaros, Z. *J. Chem. Soc., Perkin Trans. 1* **1986**, 753. (h) Balogh, M.; Hermecz, I.; Simon, K.; Pusztay, L. *J. Heterocycl. Chem.* **1989**, *26*, 1755. (i) Kleinschroth, J.; Mannhardt, K.; Hartenstein, J.; Satzinger, G. *Synthesis* **1986**, 859. (j) Aksenov, A. V.; Aksenova, I. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2009**, *45*, 130.

(3) (a) Aksenov, A. V.; Borovlev, I. V.; Lyahovnenko, A. S.; Aksenova, I. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2007**, *43*, 527. (b) Aksenov, A. V.; Borovlev, I. V.; Lyahovnenko, A. S.; Aksenova, I. V. *Russ. J. Org. Chem. (Engl. Transl.)* **2007**, *43*, 1579. (c) Aksenov, A. V.; Aksenova, I. V.; Zamorkin, A. A.; Borovlev, I. V. *Russ. J. Org. Chem. (Engl. Transl.)* **2008**, *44*, 151. (d) Aksenov, A. V.; Lyahovnenko, A. S.; Aksenova, I. V.; Nadein, O. N. *Tetrahedron Lett.* **2008**, *49*, 1808. (e) Aksenov, A. V.; Borovlev, I. V.; Aksenova, I. V.; Kovalev, D. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2007**, *43*, 1353.

(4) Polyphosphoric acid containing 86% P_2O_5 was used; preparation according to: Uhlig, F. *Angew. Chem.* **1954**, *66*, 435.

(5) Stille, J. K.; Foster, R. T. *J. Org. Chem.* **1963**, *28*, 2703.

(6) Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 2778.

(7) Stang, P. J.; Cao, D. H.; Saito, S.; Arif, A. M. *J. Am. Chem. Soc.* **1995**, *117*, 6273.