Acta Poloniae Pharmaceutica – Drug Research, Vol. 65 No. 6 pp. 749–751, 2008 ISSN 0001-6837
Polish Pharmaceutical Society

AN APPROACH FOR SYNTHESIS OF TROPINONE ANALOGUE N-SUBSTITUTED WITH TRIAZINE RING

BEATA KOLESIŃSKA* and ZBIGNIEW J. KAMIŃSKI

Institute of Organic Chemistry, Technical University of Łódź, 116 Żeromskiego St., 90-924 Łódź, Poland

Key words: 2-chloro-4,6-dimethoxy-1,3,5-triazine, 2,4-dichloro-6-methoxy-1,3,5-triazine, alkylation, dealkylation, substitution, alkyl halide, tropinone.

Tropane alkaloids have received much attention because many of them reveal remarkable biological activity (1-5). Compounds with tropinone structure or related 8-azabicyclo[3.2.1]octane skeletons have attracted considerable attention in medicinal chemistry because of their influence on neurotransmitters. They are of interest as analogues of cocaine and other physiologically active compounds and are considered as candidates for drug development, for example, for treatment of cocaine addiction, neurodegenerative diseases such as Alzheimer (6, 7) and Parkinson, etc. Several new tropinone analogues were prepared for the treatment of obstructive lung diseases (8), structure-activity studies (9, 10) inhibition of dopamine uptake (11) binding as ligand of nicotinic acetylcholine receptor (12) etc. There were also identified and prepared other pharmaceutically interesting alkaloids with tropane fragment incorporated into more complex structure (13, 14).

Due to their unique structural feature, the synthesis of tropane skeleton was a challenge and involved long sequence of reactions until pioneering synthesis of R. Robinson (15). Recently, a variety of new synthetic approaches to this class of bicyclic nitrogen heterocycles has been developed, based mainly on cycloaddition, transition metal catalyzed reactions, tandem domino reactions and others (16-22).

An alternative approach, very efficient in the search for the new derivatives, involved modification of tropane skeleton (23). The modifications were based on aldol type condensation (24, 25), modification of carbonyl group (26, 27), annulation (28), Wittig type reaction (29) and others. The often used modification pathway starts with N-demethylation of tropinone (30-32). Herein we attempted to use our new N-dealkylation procedure based on quaternization of tertiary amines after treatment with 2-chloro-4,6-disubstituted-1,3,5-triazine (33). It has been expected that this approach would be useful for the preparation of hybrid combining in one structure the tropane fragment, topoisomerase inhibitors based on aminotriazine and additional reactive center ready for incorporation of nitrogen mustards (NM) fragment used as antineoplastic agents. It is anticipated that the presence of all these pharmacophores would be benefical for improving therapeutic index of the hybrid structure.

EXPERIMENTAL

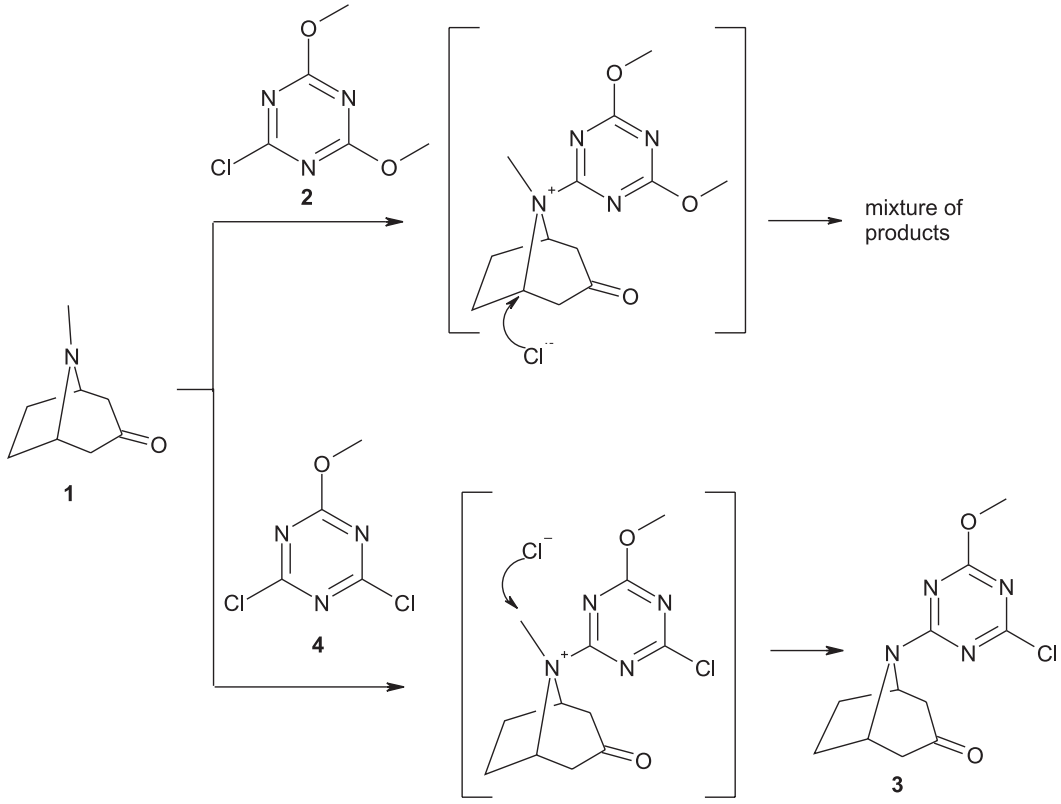
Reaction of tropinone (1) with 2-chloro-4,6-dimethoxy-1,3,5-triazine (2)

To the vigorously stirred solution of CDMT (**2**) (0.350 g, 2 mmol) in dichloromethane (5 mL) tropinone (**1**) (0.28 g, 2 mmol) was added. The mixture was gently boiled under reflux for 24 h. The solution was cooled to room temperature, washed with 1 M aqueous $KHSO_4$ and water, dried with $MgSO_4$ and evaporated. The mixture of products was obtained according to TLC, HPLC and NMR.

Reaction of tropinone (1) with 2,4-dichloro-6-methoxy-1,3,5-triazine (4). Synthesis of 8-(4-chloro-6-methoxy-1,3,5-triazin-2-yl)-8-aza-bicyclo[3.2.1]octan-3-one (3)

The vigorously stirred solution of 2,4-dichloro-6-methoxy-1,3,5-triazine (**4**) (0.18 g, 1 mmol) and tropinone (**1**) (0.28 g, 2 mmol) in dichloromethane (5 mL) was gently boiled under reflux for 24 h. The solution was cooled to room temperature, washed

* Corresponding author: dr. inż. Beata Kolesińska, e-mail: beata.kolesinska@p.lodz.pl



Scheme 1. Reaction of tropinone (**1**) with 2-chloro-4,6-dimethoxy-1,3,5-triazine (**2**) and 2,4-dichloro-6-methoxy-1,3,5-triazine (**4**).

with 1 M aqueous $KHSO_4$ and water, dried with $MgSO_4$ and evaporated. The crude residue was poured on silicagel column and eluted with dichloromethane. Fraction with spot $R_f = 0.17$ (TLC, dichloromethane) was collected and after evaporation yielded 8-(4-chloro-6-methoxy-1,3,5-triazin-2-yl)-8-aza-bicyclo[3.2.1]octan-3-one (**3**) (0.17 g, 64%); m.p. = 194-196°C.

^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.83 (2H, AB system, J_1 = 10 Hz, J_2 = 6.5 Hz); 2.16-2.22 (2H, m); 2.46 (2H, d, J = 16 Hz); 2.70 (2H, AB system, J_1 = 16 Hz, J_2 = 4.5 Hz); 4.00 (3H, s); 5.02-5.06 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 28.51; 48.34; 52.70; 55.26; 147.69; 163.22; 171.38; 206.81. IR (film/NaCl) (ν, cm^{-1}): 2960, 1710, 1580, 1495, 1455, 1390, 1360, 1285, 1260, 1220, 1195, 1045, 995, 950. Analysis: Calcd. for $C_{11}H_{13}ClN_4O_2$: C 49.17%; H 4.88%; N 20.85%; Cl 13.19%. Found: C 49.37%; H 4.89%; N 20.55%; Cl 13.15%.

RESULTS AND DISCUSSION

It was found that quaternary N-triazinylammonium chlorides are formed from broad range tertiary amines and 2-chloro-4,6-disubstituted-1,3,5-triazines (**2**). In most of the cases quaternization reaction proceeded quickly under mild condition allowing isolation of appropriate intermediate quaternary salts. Amines, with spacious substituents on nitrogen atom reacted with **2** less readily giving under more vigorous conditions appropriate quaternary ammonium chlorides, which subsequently decomposed to alkyl chlorides and appropriate 2-(dialkylamino)-4,6-dimethoxy-1,3,5-triazines, respectively. For tertiary amines with different substituents on the nitrogen atom the strongly diversified reactivity of N-alkyl groups has been observed. It has been found that the most prone to substitution were the groups affording the most reactive halides (benzyl ~ allyl > methyl > alkyl), but substitution involving the phenyl group never was detected. Moreover, the substituted alkyl groups were not susceptible to rearrangement and thus, no formation of rearranged haloalkanes was observed.

It has been found that this procedure with sterically constrained bicyclic system of tropinone **1** proceeded less favorably than in the case of typical tertiary amines. Reaction of **1** with **2** yielded, as

expected, strongly polar intermediate product detected by TLC method, however, the subsequent decomposition gave a mixture of ring opening and *N*-demethylated nortropane products, according to the ^{1}H-NMR studies.

A pure *N*-demethylated product **3** was, however, obtained by reacting tropinone with more reactive 2,4-dichloro-6-methoxy-1,3,5-triazine (**4).** After isolation by column chromatography, monosubstituted triazine **3** was obtained with 64% yield. The strong downfield shift of signal of H-C-N-triazine fragment in ^{1}H-NMR spectrum from 3.450 ppm observed for the substrate to 5.043 ppm in the product was previously noticed and reported as very characteristic for introduction of triazine ring.

It has to be added that the prepared hybrid structure bearing triazine and tropane fragment was ready for further modification by the treatment of the reactive chlorine substituent in the triazine ring with variety of nucleophiles. This opens the new path leading to hybrides with three pharmacophores in one molecule.

REFERENCES

1. Gadzikowska M., Grynkiewicz G.: Acta Pol. Pharm. Drug Res. 59, 149 (2002).
2. Humphrey A.J., O'Hagan D.: Nat. Prod. Reports 18, 494 (2001).
3. Christen, P.: Bioact. Nat. Prod. (Part C) 22, 717 (2000).
4. Isomura S., Hoffman T.Z., Wirsching P., Janda K.D.: J. Am. Chem. Soc. 124, 3661 (2002).
5. Singh S.: Chem. Rev. 100, 925 (2000).
6. Hernandez A.S., Thaler A., Castells J., Rapoport H.: J. Org. Chem. 61, 314 (1996).
7. Piccardi R., Renaud P.: Eur. J. Org. Chem. 28, 4752 (2007).
8. Tsyskovskaia I., Kandil M., Beaumier Y.: Synth. Commun. 37, 439 (2007).
9. Gong P.K., Blough B.E., Brieaddy L.E., Huang X., Kuhar M.J., Navarro H.A., Carroll F.I: J. Med. Chem. 50, 3686 (2007).
10. Zou M-F., Cao J., Kopajtic T., Desai R.I., Katz J.L., Newman A.H.: J. Med. Chem. 49, 6391 (2006).
11. Simoni D., Rossi M., Bertolasi V., et al.: J. Med. Chem. 48, 3337 (2005).
12. Zhang S., Izenwasser S., Wade D., Cheng J., Liu Y., Xu L., Trudell M.L.: J. Heterocycl. Chem. 44, 1425 (2007).
13. Baylis A.M., Davies M.P.H., Thomas E.J.: Org. Biomol. Chem. 5, 3139 (2007).
14. Sastraruji T., Jatisatienr A., Pyne S.G., Ung A.T., Lie W., Williams M.C.: J. Nat. Prod. 68, 1763 (2005).
15. Robinson, R.: J. Chem. Soc. 762 (1917).
16. Reddy R.P., Davies H.M.L.: J. Am. Chem. Soc. 129, 10312 (2007).
17. Mikami K., Ohmura H.: Chem. Commun. 2626 (2002).
18. Deng S.X., Huang D.W., Landry D.W.: Tetrahedron Lett. 42, 6259 (2001).
19. Isomura S., Hoffman T.Z., Wirsching P., Janda K.D.: J. Am. Chem. Soc. 124, 3661 (2002).
20. Gong L., Hogg J.H., Collier J., Wilhelm R.S., Soderberg C.: Bioorg. Med. Chem. Lett. 17, 3597 (2003).
21. Nussbaumer P., Geyl D., Horvath A., Lehr P., Wolff B., Billich A.: Bioorg. Med. Chem. Lett. 13, 3673 (2003).
22. Cramer N., Laschat S., Baro A., Frey W.: Synlett 2175 (2003).
23. Willand N., Folléas B., Boutillon C., Verbraeken L., Gesquière J.C., Tartar A., Deprez B.: Tetrahedron Lett. 48, 5007 (2007).
24. Majewski M., Ulaczyk-Lesanko A., Fan W.: Can. J. Chem. 84, 257 (2006).
25. Zheng G., Dwoskin L., Crooks P.: Synth. Commun. 34, 1931 (2004).
26. Audouze K., Nielsen E., Ostergaard O.G.M., et al.: J. Med. Chem. 49, 3159 (2006).
27. Li, A., Kindelin P.J., Klumpp D.A.: Org. Lett. 8, 1233 (2006).
28. Harling J.D., Harrington F.P., Thompson M.: Synth. Commun. 31, 787 (2001).
29. Zhang Y., Joseph D.B., Bowen W.D., et al.: J. Med. Chem. 44, 3937 (2001).
30. Gilbert A.M., Stack G.P., Nilakantan R., et al.: Bioorg. Med. Chem. Lett. 14, 515 (2004).
31. Berdini V., Cesta M.C., Curti R., et al.: Tetrahedron 58, 5669 (2002).
32. Gong L., Hogg J.H., Collier J., Wilhelm R.S., Soderberg C.: Bioorg. Med. Chem. Lett. 13, 3597 (2003).
33. Kolesińska B., Kamiński Z.J.: Pol. J. Chem. in press (2008).
34. Kamiński Z.J., Kolesińska B., Markowicz S.W., Pokrzeptowicz K.: Pol. J. Chem. 73, 1965 (1999).