Benzylfuran in the synthesis of benzo-annelated heterocycles

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Authors′ data on the synthesis of benzo-annelated heterocycles from benzylfurans upon reactions proceeding either with retention or with opening of the furan ring are surveyed.

Key words: furan, benzylfuran, annelated heterocycles.

Owing to diverse chemical reactivity, furan derivatives are widely used in the synthesis of various classes of compounds, which is reflected in a number of reviews. In particular, data on the synthesis of 1,4-dicarbonyl compounds and cyclopentenones from furans have been summarized,[1] examples of synthetic application of oxidation[2] and cycloaddition[3] of furan derivatives have been generalized, and the use of furans in asymmetric synthesis has been considered.[4] The Akhmatovich reaction[5] and its aza analog[6,7] have found wide use in the synthesis of natural products. Data on the transformation of furans into other heterocycles are described systematically in a review.[8]

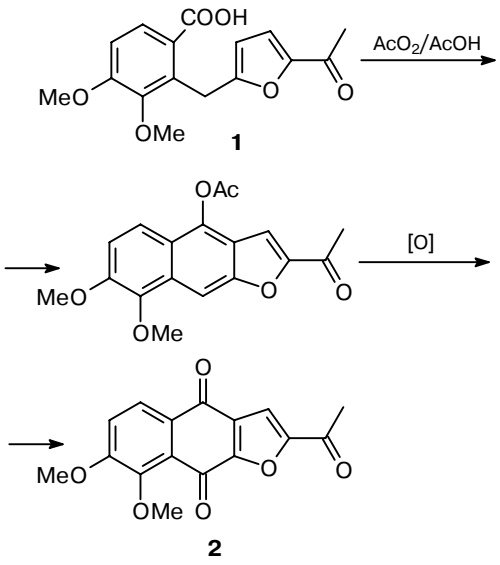
The present review is devoted to the application of benzylfurans in the synthesis of benzoannelated heterocycles; it is mainly based on authors′ studies because only a few examples of investigations along this line can be found in the literature.

The reactions of benzylfurans resulting in the formation of fused heterocycles can be divided into two types, namely, reactions with retention of the furan ring and those with ring opening.

Reactions with retention of the furan ring

The transformation of α-benzylfurans into benzoannelated heterocycles with retention of the furan nucleus occurs upon an attack by the *ortho*-substituent in the aromatic ring on the β-position of the furan ring, which gives rise to a new ring between the furan and aromatic rings. Thus the 2-(*o*-carboxybenzyl)furan derivative **1** undergoes intramolecular benzoylation to the β-position of the furan ring (Scheme 1)[9] to give 7,8-dimethoxy-2-acetylfuronaphthoquinone (**2**) exhibiting a cytotoxic activity.

Scheme 1



We found that ultraviolet irradiation or storage in the light of solutions of (2-nitrophenyl)difurylmethanes **3** results in furoquinoline derivatives **4** (Scheme 2).[10]

An interesting rearrangement was discovered in a study of chemical properties of (2-isothiocyanoaryl)difurylmethanes **5**.[11,12] We found that on treatment with perchloric acid in dioxane, compounds **5** are converted into 4*H*-benzothiazine derivatives **6** (Scheme 3).

In this case, the *ortho*-substituent attacks the α-position of the furan ring; this is followed by stabilization of the furanium cation through cleavage of the $C-C_{Fur}$ bond. We described similar $C-C_{Fur}$ bond cleavage reactions in relation to other substrates.[13—15] The subsequent attack by the S atom on the carbenium center results in cyclization to give compounds **6**.

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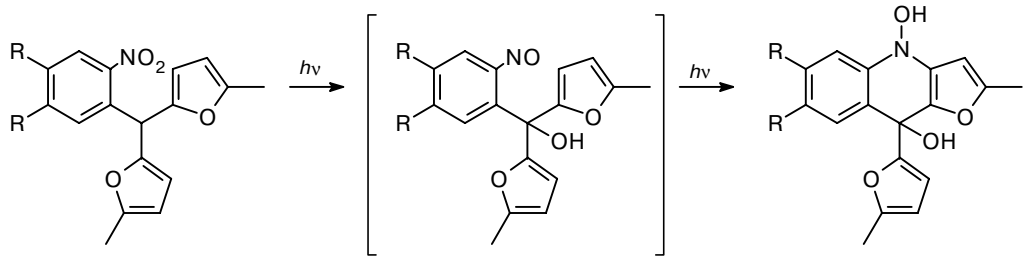
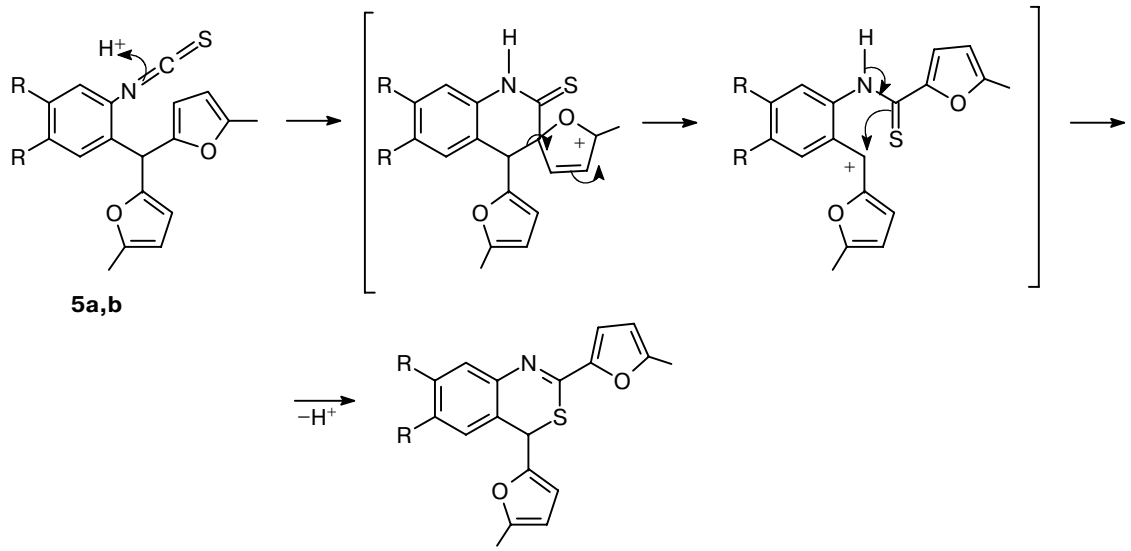
Scheme 2



3a,b **4a,b**

R = H (**a**), OMe (**b**)

Scheme 3



5a,b **6a,b**

R = H (**a**), OMe (**b**)

Reactions with furan ring opening

The other type of reaction, *i.e.*, syntheses of heterocycles from benzylfurans with opening of the furan ring, presents much greater interest. This is due both to the diversity of mechanisms of transformation of benzylfurans and to the diversity of reaction products.

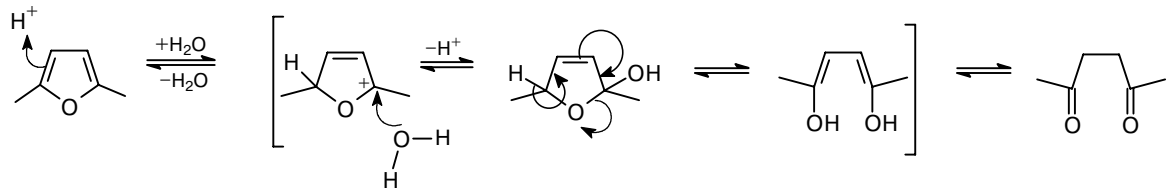
All the available examples of synthesis of heterocycles from benzylfurans accompanied by opening of the furan ring can be divided into two groups: syntheses of oxygen-containing heterocycles (in particular, benzofurans) and nitrogen-containing heterocycles.

Synthesis of benzofuran derivatives

Hydrolytic cleavage of the furan ring, resulting most often in 1,4-dicarbonyl compounds formation, was discovered by Marckwald[16] in 1887, and still occupies a worthy place in the synthetic organic chemistry.[1] This reaction starts with protonation at the α-position of the furan ring and involves a nucleophilic attack of a water molecule on the furanium ion thus formed (Scheme 4).

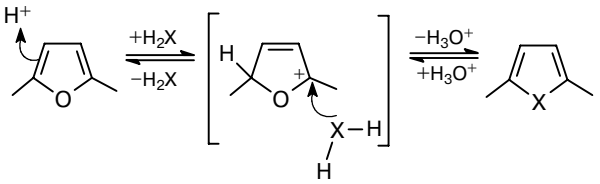
Replacement of the nucleophile in this scheme afford in the formation of new heterocycles. For example, new recyclization of furans into thiophenes has been

Scheme 4



discovered[17,18]; it was found that in alcoholic solutions, a variety of furan derivatives are converted into the corresponding thiophenes on treatment with hydrogen sulfide in the presence of acids (Scheme 5).[8] Later, this reaction has been used to prepare selenophenes.[19]

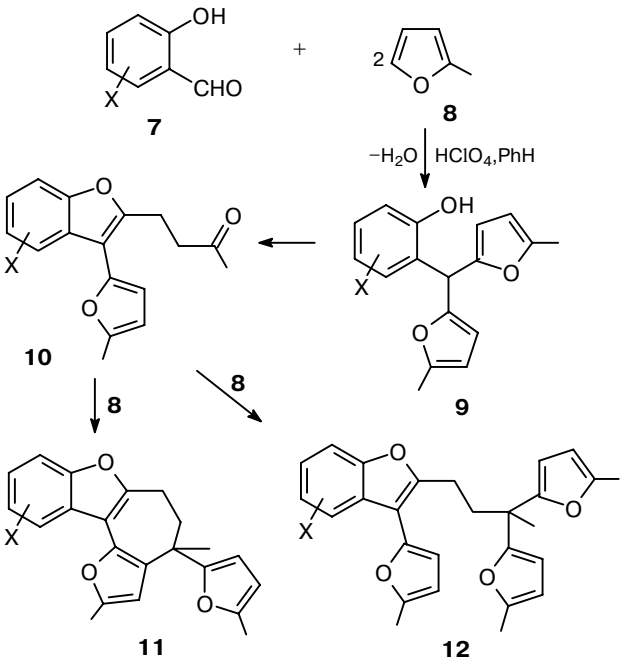
Scheme 5



X = S, Se

A similar reaction is also possible in the case of an intramolecular attack by a nucleophile. We found that the reaction of salicylaldehydes **7** with 2-methylfuran (**8**) in benzene catalyzed by perchloric acid gives, besides the expected product **9**, benzofuran derivatives **10—12**, (Scheme 6).[20,21]

Scheme 6



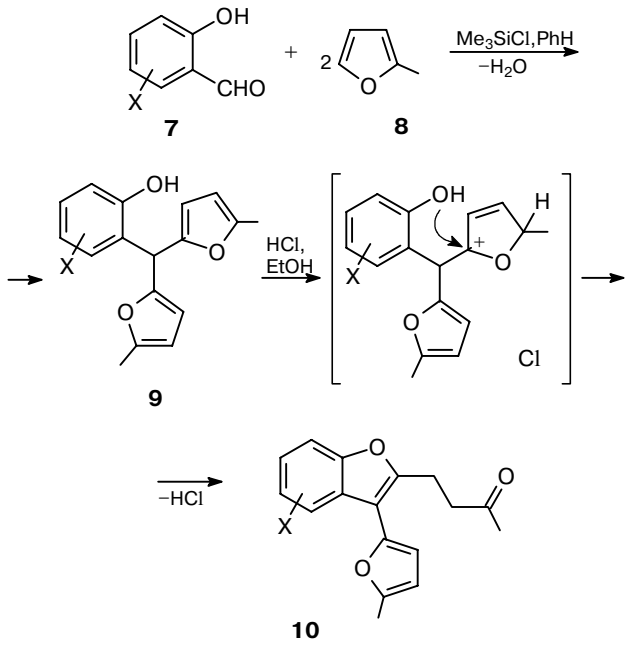
X = H, CH_3, OCH_3, Br, Cl, I, NO_2

This reaction has been of no preparative value because it is difficult to isolate the final products from the reaction mixture. Therefore, an attempt was undertaken to develop conditions of selective synthesis of compounds **9** and **10**.

It was found that chlorotrimethylsilane is a selective catalyst in the synthesis of (2-hydroxyaryl)difurylmethanes.[22] With this catalyst, resinification during the reaction can be reduced and the reaction can be stopped at the first step, *i.e.*, when compounds **9** have been formed (Scheme 7).

The second step of the reaction, *i.e.*, transformation of compounds **9** into benzofuran **10** in a high yield, was accomplished in HCl-saturated ethanol.[23] The mechanism suggested for this reaction includes protonation of the furan ring followed by a nucleophilic attack of the furanium cation by the phenol hydroxy group (Scheme 7).

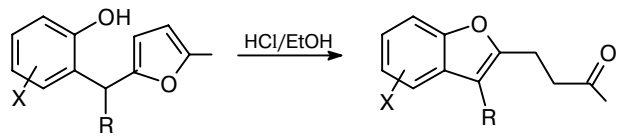
Scheme 7



X = H, Me, OMe, Br, Cl, I, NO_2

Similar conditions have been used to prepare a series of benzofuran derivatives containing various alkyl or aryl substituents in position 3 (Scheme 8).[24]

Scheme 8



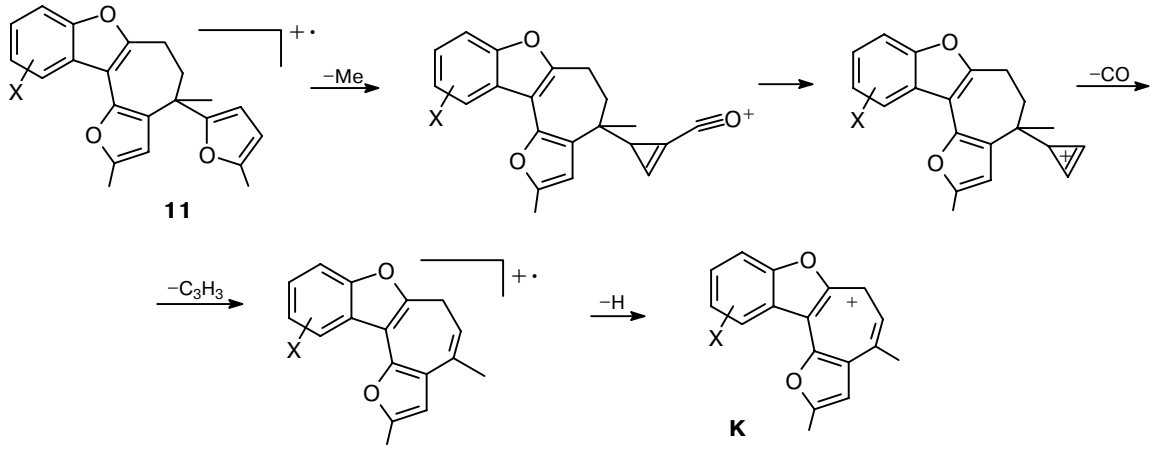
R = Alk, Ar; X = H, Me

We found that ketones **10** can also be prepared directly by the reaction between salicylaldehydes[7] and 2-methylfuran[8] in ethanol saturated with HCl.[23]

In a study of mass-spectrometric fragmentation of compound **11**, the formation of stable cation **K** upon the well-known stepwise destruction of the furan ring was established (Scheme 9)[21].

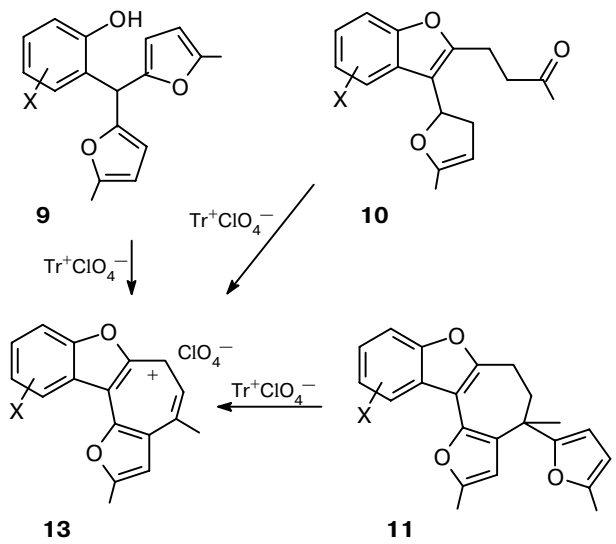
It has also been shown[25] that benzo[*b*]furo[2,3-*h*]-1-oxaazulenium salts **13** (analogs of cation **K**) can be

Scheme 9



synthesized on a preparative scale by treatment of (2-hydroxyaryl)difurylmethanes **9**, benzofurans **10**, or tetracyclic compounds **11** with trityl perchlorate (Scheme 10).

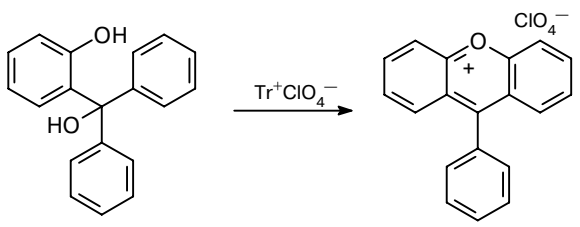
Scheme 10



X = H, CH_3, OCH_3, Br, Cl, I, NO_2

The formation of salts **13** from compound **9** was somewhat unexpected because treatment of their analog, 2-hydroxytriphenylmethanol, with trityl perchlorate affords 9-phenylxanthylium perchlorate[26] due to the nucleophilic attack by the hydroxyl O atom on the *ortho*-position of the unsubstituted benzene ring (Scheme 11).

Scheme 11



Meanwhile, in the case of compound **9**, salts **13** are formed *via* the rearrangement (Scheme 12) of the (2-hydroxyaryl)difurylcarbenium ions formed in the first step.

Later,[27] it has been found that on refluxing benzofurans **10** with an equimolar amount of perchloric acid in dioxane, intramolecular cyclization takes place followed by disproportionation of the cycloheptatriene derivative **14** formed; finally, perchlorates **13** and compounds **15** can be isolated from the reaction mixture (Scheme 13).

In addition, perchlorates **13** can be prepared directly from salicylaldehydes **7** and 2-methylfuran (**8**) by refluxing in dioxane with perchloric acid.[27]

Thus, we found that the use of more or less hard acids as catalysts allows one to prepare selectively any of the three products (**9**, **10**, or **13**) directly by the reaction of salicylaldehydes and silvane.

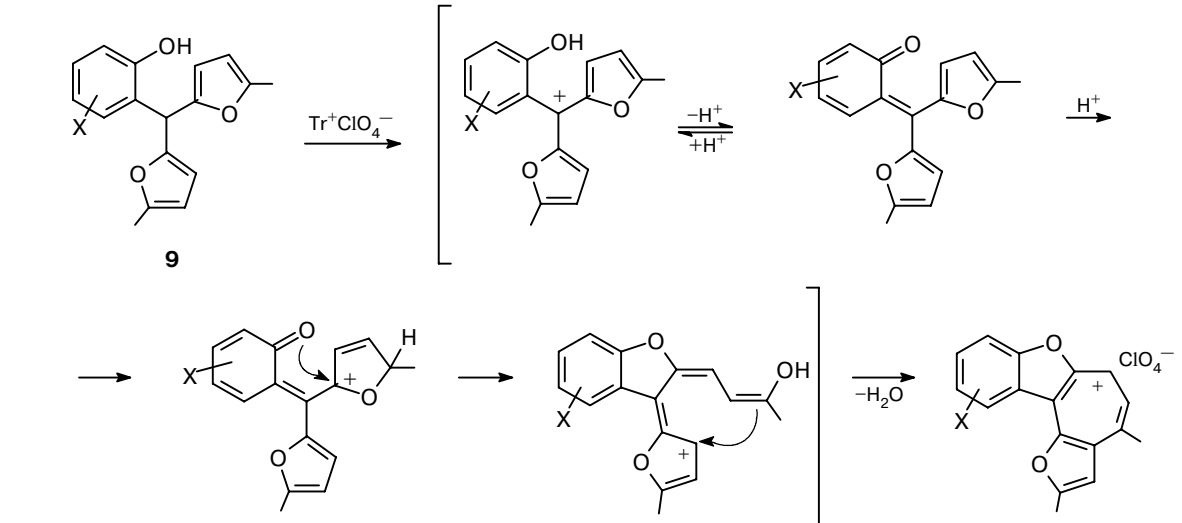
Synthesis of nitrogen-containing heterocycles

An interesting route of the synthetic application of benzylfurans is the preparation of nitrogen-containing heterocycles.

It has been reported that deoxygenation of (2-nitrophenyl)difurylmethanes (**16**) by triethyl phosphite yielded carbazole derivatives **17**. It was suggested that the reaction passes through a furoaziridine structure, whose destruction results in the formation of the corresponding indole derivatives, which undergo a series of consecutive transformations to give compounds **17** (Scheme 14).[28,29]

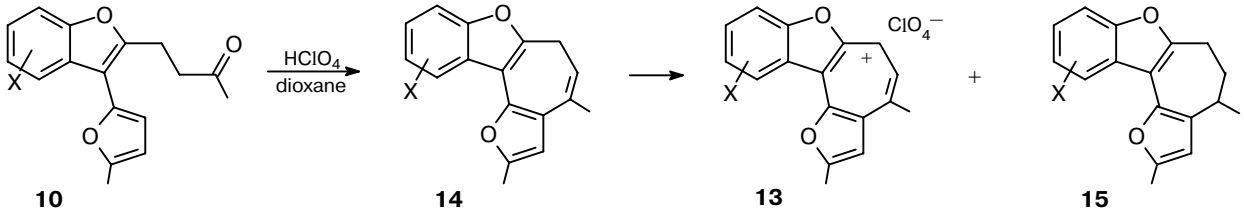
It should be noted that a similar reaction for (2-nitrophenyl)dipyrrolylmethane **18** has been reported[29] to follow a different route, namely, to give compound **19** (Scheme 15).

Scheme 12



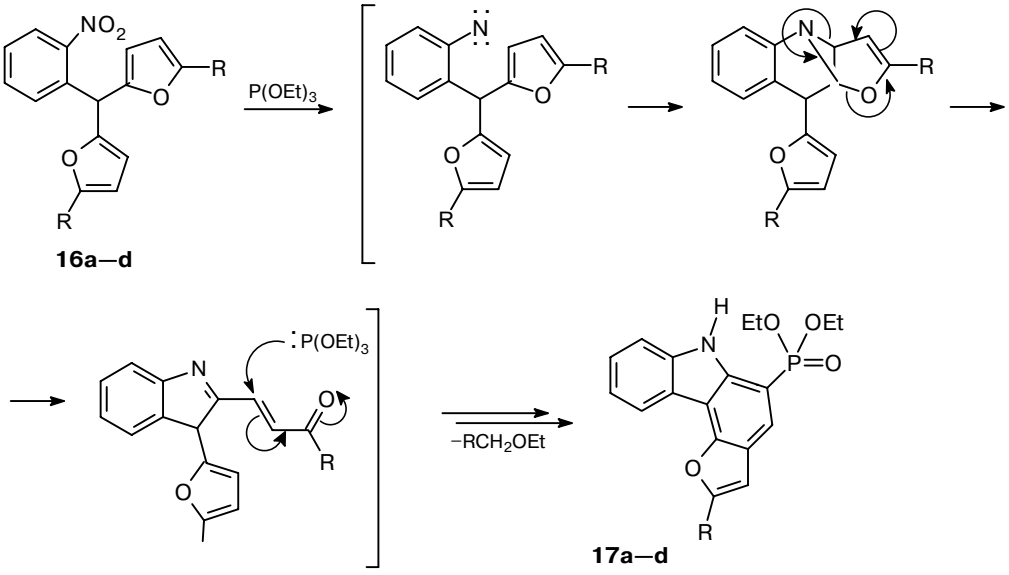
X = H, CH_3, OCH_3, Br, Cl, I, NO_2

Scheme 13



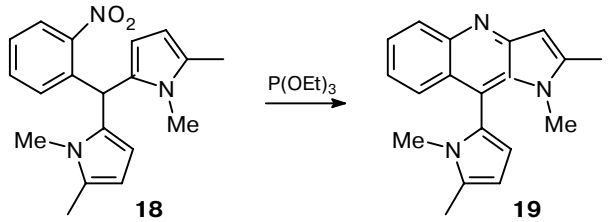
X = H, CH_3, OCH_3, Br, Cl, I, NO_2

Scheme 14



16, **17**: R = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**)

Scheme 15



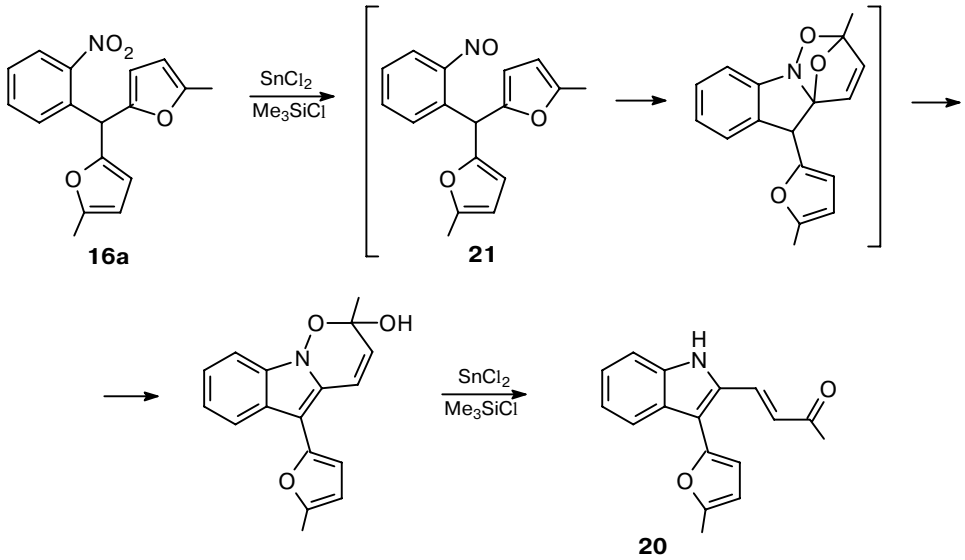
18 **19**

Later, we succeeded in isolating indole derivatives that were suggested as intermediates in the synthesis of carbazoles, reported previously.[29] Upon the reduction of (2-nitrophenyl)difurylmethane **16a** by $SnCl_2$ in the presence of Me_3SiCl, indole **20** was formed as the only reaction product, instead of the corresponding (2-aminophenyl)difurylmethane.[30] Further studies[12,31] showed that nitroso compound **21** is the key intermediate of this reaction and that cycloaddition of the nitroso group on of furan ring is the key step (Scheme 16).

These results account for the fact that a similar reaction for compound **22** does not give indole derivative **23** but yields the corresponding amine **24** (Scheme 17). Evidently, inactivation of the nitroso group as a dienophile due to the electron-donating effect of the methoxy group is significant in this case.

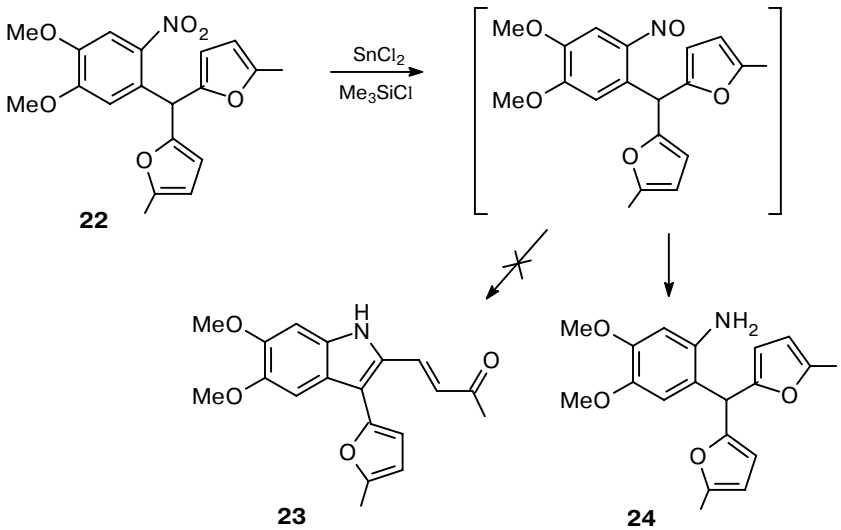
(2-Acetylaminoaryl)difurylmethanes **25**, like (2-hydroxyaryl)difurylmethanes,[25] are converted into tetracyclic salts **26** on treatment with trityl perchlorate (Scheme 18).[31]

Scheme 16



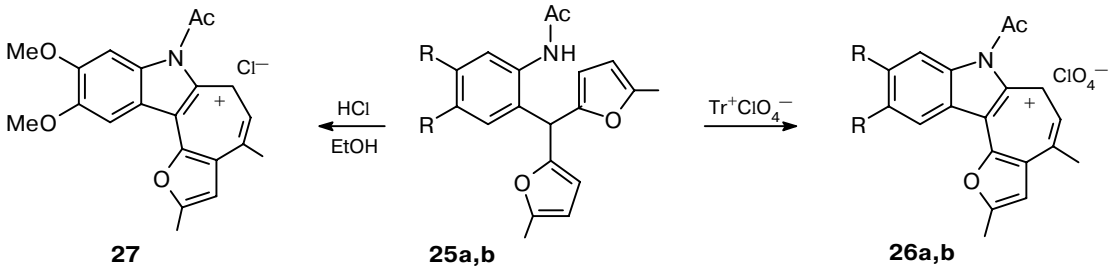
16a **21** **20**

Scheme 17



22 **23** **24**

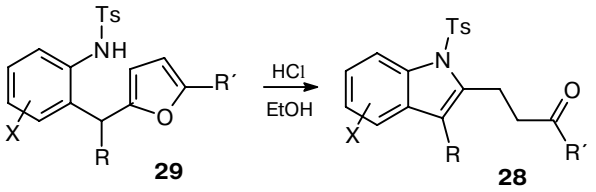
Scheme 18



25, 26: R = H (**a**), OMe (**b**)

However, the attempt to synthesize indole ketones, similarly to their oxygen analogs, by refluxing compounds **25** in ethanol saturated with HCl gas was unsuccessful; in the case of compound **25b**, salt **27** was isolated.

Scheme 19

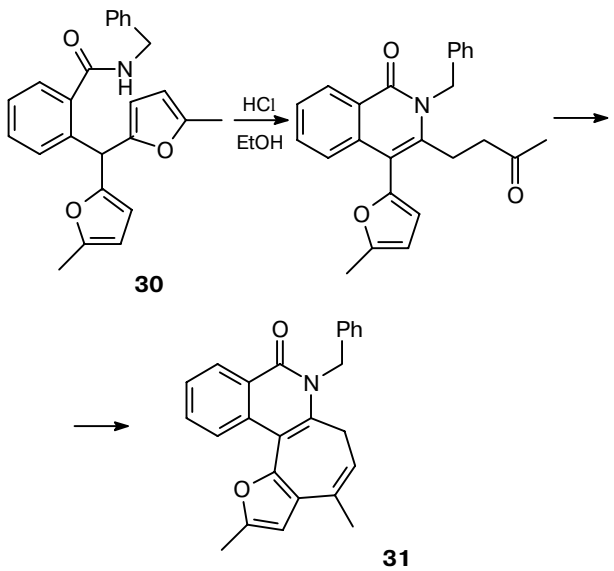


28, 29: R = Alk, Ar; R′ = Me, Et

Later, we prepared indole ketones **28** from benzylfuran derivatives **29** under conditions of hydrolytic cleavage of the furan ring using a tosyl protection (Scheme 19).[32,33]

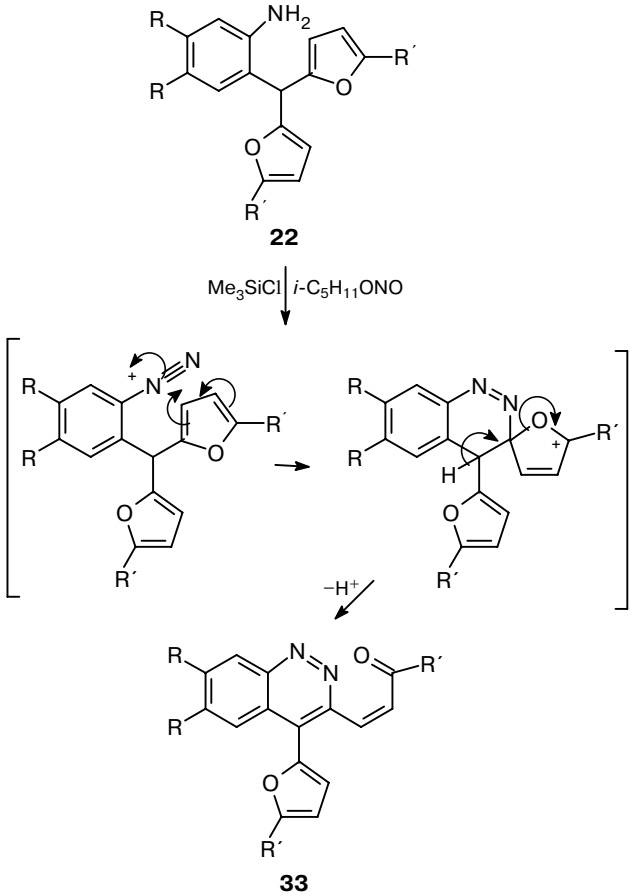
We found[34,35] that recyclization of amide **30** carried out under standard conditions (refluxing in ethanol saturated with HCl) does not stop at the step of ketone formation but proceeds further as intramolecular cyclization giving rise to tetracyclic compound **31** with an isoquinolone fragment (Scheme 20).

Scheme 20



The reactions of diazonium salts with furan derivatives are known to proceed ambiguously giving diverse products depending on the conditions. In particular, a diazonium salt can not only attack a furan compound into α-[36] or β-position[37,38] as an electrophile but can also act as a dienophile.[36,39] Therefore, it has been of

Scheme 21



R = R = H, OMe, OCH_2O, OCH_2CH_2O; R′ = Me, Et

interest to study diazotization of (2-aminoaryl)difurylmethanes. An unsuccessful attempt of diazotization of (2-aminophenyl)difurylmethanes by $NaNO_2$ in the presence of mineral acids is documented.[29] We found that diazotization of amines **32** with isoamyl nitrite in the presence of Me_3SiCl in acetonitrile with ice-bath cooling smoothly gives cinnoline derivatives **33** (Scheme 21).[40,41]

The key step of this reaction is the electrophilic attack by the diazonium group on the α-position of the furan ring, resulting in further ring opening with retention of the *cis*-configuration of the alkenone fragment.

Conclusion

The examples considered in the review demonstrate the potential of *ortho*-substituted benzylfurans in the synthesis of benzo-annelated heterocycles. Benzylfurans hold great promise as convenient versatile synthons, which can find use in the preparation of various compounds, including natural products.

References

1. G. Piancatelli, M. D´Auria, and F. D´Onofrio, *Synthesis,* 1994, 867.
2. P. Merino, S. Franco, F. L. Merchan, and T. Tejero, in *Recent Research Development in Synthetic Organic Chemistry*, Ed. S. G. Pandalai, Transworld Research Network, Trivandum, India, 2000, **3**, 65.
3. C. O. Kappe, S. S. Murphree, and A. Padwa, *Tetrahedron,* 1997, **53**, 14179.
4. J. Jurczak, E. Kobrzycka, and J. Raczko, *Pol. J. Chem.*, 1999, **73**, 29.
5. M. P. Georgiadis, K. F. Albizati, and T. M. Georgiadis, *Org. Prep. Proced. Int.*, 1982, **24**, 95.
6. M. A. Ciufolini, C. Y. W. Hermann, Q. Dong, T. Simizu, S. Swaminathan, and N. Xi, *Synlett,* 1998, 105.
7. W.-S. Zhou, Z.-H. Lu, Y.-M. Xu, L.-X. Liao, and Z.-M. Wang, *Tetrahedron*, 1999, **55**, 11959.
8. T. I. Gubina and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, 1995, 1034 [*Chem. Heterocycl. Compd.*, 1995, **31**, 900 (Engl. Transl.)].
9. C. L. Zani, A. B. de Oliveira, and V. Snieckus, *Tetrahedron Lett.*, 1987, **28**, 6561.
10. A. V Butin, T. A. Stroganova, V. T. Abaev, and V. G. Kul'nevich, *Khim. Geterotsikl. Soedin.*, 1998, 1250 [*Chem. Heterocycl. Compd.*, 1998, **34**, 1073 (Engl. Transl.)].
11. V. T. Abaev and A. V. Butin, *Proc. 12th Symp. on Chemistry of Heterocyclic Compounds and 6th Blue Danube Symp. on Heterocyclic Chemistry* (*Brno, Czech Republic, 1996*), Brno, 1996, 1.
12. A. V. Butin, V. T. Abaev, T. A. Stroganova, and A. V. Gutnov, *Molecules*, 1997, **2**, 62.
13. A. V. Butin, T. A. Stroganova, and V. G. Kul'nevich, *Khim. Geterotsikl. Soedin.*, 1996, 175 [*Chem. Heterocycl. Compd.*, 1996, **32**, 153 (Engl. Transl.)].
14. A. V. Butin, T. A. Stroganova, and V. G. Kul´nevich, *Khim. Geterotsikl. Soedin.*, 1996, 738 [*Chem. Heterocycl. Compd.*, 1996, **32**, 631 (Engl. Transl.)].
15. T. A. Stroganova, A. V. Butin, L. N. Sorotskaya, and V. G. Kul´nevich, *Arkivoc*, 2000, **1**, 641.
16. W. Marckwald, *Ber. Deutsch. Chem. Ges.*, 1887, **20**, 2811.
17. USSR Pat. 595961; *Byul. Izobret.*, 1980, 347 (in Russian).
18. V. G. Kharchenko, I. A. Markushina, and T. I. Gubina, *Zh. Org. Khim.*, 1982, **18**, 394 [*J. Org. Chem. USSR*, 1982, **18**, 343 (Engl. Transl.)].
19. USSR Pat. 929642 SSSR; *Byul. Izobret.*, 1982, 100 (in Russian).
20. A. V. Butin, V. E. Zavodnik, and V. G. Kul'nevich, *Khim. Geterotsikl. Soedin.*, 1992, 997 [*Chem. Heterocycl. Compd.*, 1992, **28**, 835 (Engl. Transl.)].
21. A. V. Butin, G. D. Krapivin, V. E. Zavodnik, and V. G. Kul´nevich, *Khim. Geterotsikl. Soedin.*, 1993, 616 [*Chem. Heterocycl. Compd.*, 1993, **29**, 524 (Engl. Transl.)].
22. A. V. Gutnov, V. T. Abaev, A. V. Butin, V. E. Zavodnik, and V. G. Kul´nevich, *Khim. Geterotsikl. Soedin.*, 1996, 162 [*Chem. Heterocycl. Compd.*, 1996, **32**, 141 (Engl. Transl.)].
23. V. T. Abaev, A. V. Gutnov, and A. V. Butin, *Khim. Geterotsikl. Soedin.*, 1998, 603 [*Chem. Heterocycl. Compd.*, 1998, **34**, 529 (Engl. Transl.)].
24. A. V. Gutnov, A. V. Butin, V. T. Abaev, G. D. Krapivin, and V. E. Zavodnik, *Molecules*, 1999, **4**, 204.
25. A. V. Butin, V. T. Abaev, V. E. Zavodnik, and V. G. Kul´nevich, *Khim. Geterotsikl. Soedin.*, 1993, 627 [*Chem. Heterocycl. Compd.*, 1993, **29**, 534 (Engl. Transl.)].
26. S. M. Luk´yanov, L. N. Etmetchenko, and G. N. Dorofeenko, *Zh. Org. Khim.*, 1978, **14**, 399 [*J. Org. Chem.,* 1978, **14** (Engl. Transl.)].
27. A. V. Butin, A. V. Gutnov, V. T. Abaev, and G. D. Krapivin, *Khim. Geterotsikl. Soedin.*, 1998, 883 [*Chem. Heterocycl. Compd.*, 1998, **34**, 762 (Engl. Transl.)].
28. G. Jones and W. H. McKinley, *Tetrahedron Lett.*, 1977, **28**, 2457.
29. G. Jones and W. H. McKinley, *J. Chem. Soc., Perkin Trans. 1,* 1979, 599.
30. A. V. Butin, V. T. Abaev, and T. A. Stroganova, *Khim. Geterotsikl. Soedin.*, 1995, **31**, 1578 [*Chem. Heterocycl. Compd.*, 1995, **31**, 1371 (Engl. Transl.)].
31. A. V. Butin, T. A. Stroganova, V. T. Abaev, and V. E. Zavodnik, *Khim. Geterotsikl. Soedin.*, 1997, 1614 [*Chem. Heterocycl. Compd.*, 1996, **33**, 1393 (Engl. Transl.)].
32. A. V. Butin, V. T. Abaev, T. A. Stroganova, A. V. Gutnov, and I. V. Lodina, *Book of Abstracts. 17th International Congress of Heterocyclic Chemistry (Institute of Organic Chemistry Vienna University of Technology, August 1—6, 1999*), Vienna, 1999, 156.
33. A. V. Butin, T. A. Stroganova, I. V. Lodina, and G. D. Krapivin, *Tetrahedron Lett.*, 2001, **42**, 2031.
34. V. T. Abaev, A. A. Osipova, and A. V. Butin, *Abstracts of Papers. 8th Blue Danube Symp. on Heterocyclic Chemistry (Bled, Slovenia, 2000)*, Bled, Slovenia, 2000, 53.
35. V. T. Abaev, A. A. Osipova, and A. V. Butin, *Khim. Geterotsikl. Soedin.*, 2001, in press [*J. Chem. Heterocycl. Compd.*, 2001, in press (Engl. Transl.)].
36. M. B. Bartle, S. T. Gore, R. K. Mackie, S. Mhatre, and J. M. Tedder, *J. Chem. Soc., Perkin Trans. 1*, 1978, 401.
37. R. H. Eastman and F. L. Detert, *J. Am. Chem. Soc.*, 1948, **70**, 962.
38. M. Kocevar, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.*, 1978, **15**, 1175.
39. D. W. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2728.
40. A. V. Gutnov, V. T. Abaev, and A. V. Butin, *Proc. 12th Symp. on Chemistry of Heterocyclic Compounds and 6th Blue Danube Symp. on Heterocyclic Chemistry (Brno, Czech Republic, 1996)*, Brno, 1996, 24.
41. V. T. Abaev, A. V. Gutnov, A. V. Butin, and V. E. Zavodnik, *Tetrahedron*, 2000, **56**, 8933.

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