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A novel three-component reaction of anilines, formaldehyde and dimedone: simple synthesis of spirosubstituted piperidines

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ABSTRACT

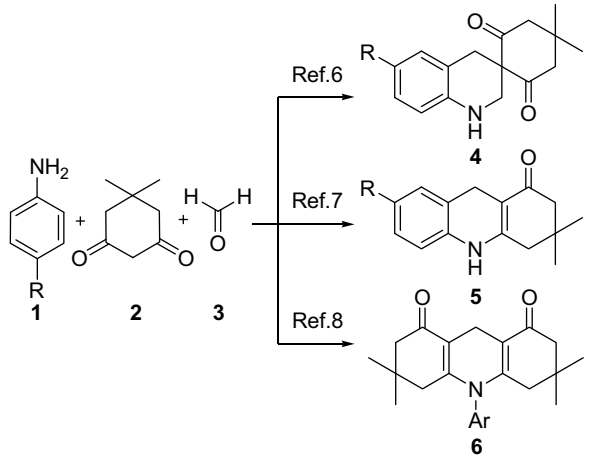
A three-component condensation of anilines with dimedone and formaldehyde leads to the formation of 3,5-dispirosubstituted piperidines. This simple reaction can serve as a convenient source of 3,5-disubstituted piperidines as well as polyfunctional 3-spirofused piperidines.

The piperidine ring system is one of the most common motifs found in numerous natural products, drugs and drug candidates. The important bioactivities of piperidines have stimulated the development of new synthetic approaches, and considerable synthetic effort has been devoted to the preparation of these compounds.[1]

Spirofused piperidines have attracted particular attention due to their miscellaneous interesting physiological activities.[2] In addition, spiropiperidinyl ring systems have been isolated from various plant alkaloids and animal toxins. For example, some neurotoxic 2-spirofused piperidines were isolated from the neotropical poisonous frog *Dendrobates histrionicus*[3] and their 3-spirofused analogues, the alkaloids sibirine, nitramine, isonitramine and nitrabirine, were isolated from plants of the genus *Nitraria*.[4] The *Nitraria* alkaloids incorporating a 2-azaspiro[5.5]undecane moiety have long attracted the interest of synthetic chemists, and many syntheses of such compounds have been published in the literature in recent years.[5]

In this Letter, we report a simple reaction leading to the formation of polysubstituted piperidine derivatives containing the 2-azaspiro[5.5]undecane unit. In our recent work, we described a three-component reaction of mono-N-substituted anilines, formaldehyde and cyclic β-diketones as a novel synthetic route to N-substituted 3-spirofused 1,2,3,4-tetrahydroquinolines.[6a] Following this procedure, we tested several *N*-unsubstituted anilines in the reaction in order to obtain the same spiro-tetrahydroquinolines but without any substituents on the N-atom. Surprisingly, the products were neither the desired tetrahydroquinolines **4** nor probable acridones **5**[7] or Hantzsch dihydropyridines **6**[8] (the expected products of the three-component condensation of anilines, formaldehyde and dimedone are shown in Scheme 1).

We have found that the condensation of anilines **1** with dimedone (5,5-dimethyl-1,3-cyclohexanedione, **2**) and formaldehyde **3** leads to the formation of 3,5-dispirosubstituted piperidines **7** (Scheme 2).



Scheme 1.

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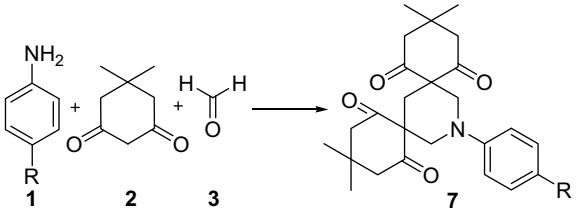


Scheme 2.

For example, treatment of *p*-anisidine (**1**, R = OMe) with 1 equiv of **2** in the presence of a large excess of formaldehyde gave spirane **7a** in 41% yield relative to the amine (82% relative to dimedone). The use of stoichiometric quantities of *p*-anisidine and dimedone improved the yield to 86%. *p*-Toluidine, *p*-phenethidine, *p*-phenoxyaniline and 4-aminobiphenyl behaved in the same manner. The reaction took place at room temperature for 12 h, during which time the spiroproducts crystallized from the reaction mixture in a nearly pure state and in very good yields.[9] The results are summarized in Table 1.

A possible mechanism for the spiropiperidine ring formation is outlined in Scheme 3.

The spirocyclization seems to proceed as a domino sequence of Knoevenagel, Michael and double Mannich reactions. The well-known reaction of dimedone with formaldehyde leads to the formation of the standard dimedone–formaldehyde adduct **8**. In turn, this undergoes two consecutive Mannich reactions with a suitable aniline **1** to produce the spiro-piperidine **7**.

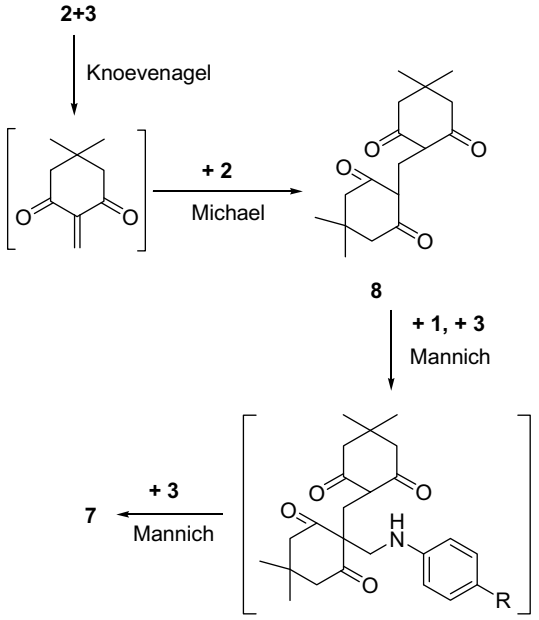
Unfortunately, the chemistry worked well only for a limited number of electron-rich *para*-substituted anilines. Aniline itself (**1**, R = H) as well as *para*-unsubstituted anilines containing an *ortho*- or *meta*-substituent gave resinous products (entry 7).[10] Anilines bearing electron-withdrawing groups (e.g., NO_2, $COOCH_3$, entries 8 and 9) did not give any spiro-products, and the dimedone–formaldehyde adduct **8** was the only isolated product.[11] Nevertheless, *p*-bromoaniline (**1**, R = Br) led to the desired spirane in an excellent yield (entry 6) although a prolonged reaction time (up to two weeks) was required. The low reactivity of anilines containing electron-withdrawing groups can be attributed to their relatively weak nucleophilicity and therefore decreased activity in the Mannich steps of the reaction.

It is noteworthy that *p*-phenylenediamine (**1**, R = NH_2) reacted very quickly (the reaction time was less than 5 min) with **2** and **3** in refluxing ethanol to form the interesting product **9** containing two spiropiperidine ring systems (entry 10). It should also be noted that 2-naphthalenamine (entry 11) did not give the corresponding spiropiperidine but instead a mixture of two products, namely

Table 1
The reaction of anilines **1** with dimedone **2** and formaldehyde **3**

Entry	R	Product[a]	Yield[b] (%)
1	OMe	**7a**	86
2	Me	**7b**	84
3	OEt	**7c**	83
4	OPh	**7d**	97
5	Ph	**7e**	90
6	Br	**7f**	84
7	H	—	—
8	NO_2	**8**	62
9	COOMe	**8**	57
10	NH_2	**9**	37
11	3,4-(–CH=CH–CH=CH–)	**10+11**	52+27

[a] All new compounds gave satisfactory 500 MHz ^{1}H and 100 MHz ^{13}C NMR and IR spectral data.
[b] Yield refers to pure isolated products.

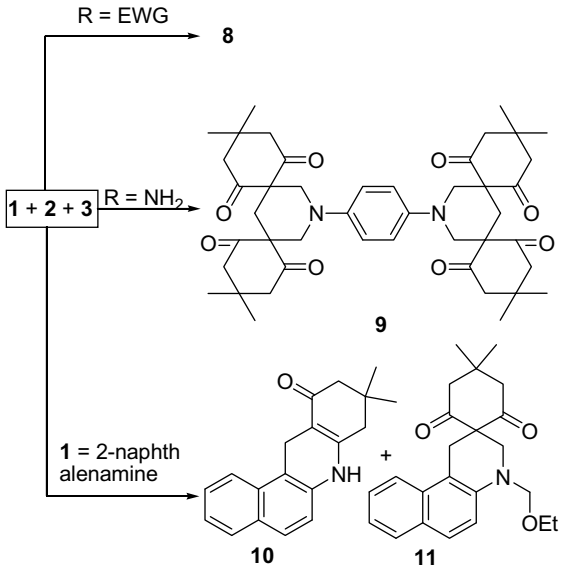


Scheme 3.

benzo[*a*]acridin-11-one **10** and spirobenzo[*f*]quinoline **11** (Scheme 4).[12]

The piperidine derivatives **7a**–**f** and **9** obtained incorporate a polysubstituted 2-azaspiro[5.5]undecane unit and also contain highly reactive cyclic β-dicarbonyl systems that could be utilised for further chemical modification of the substances. In addition, these compounds are examples of 3,5-disubstituted piperidines, compounds which have a range of important pharmaceutical properties.[13] Thus, the reported reaction could serve as a convenient source of 3,5-disubstituted piperidines as well as polyfunctional 3-spirofused piperidines. Further studies on this reaction are in progress in our laboratory.

In conclusion, a novel three-component reaction of anilines, dimedone and formaldehyde is shown to provide a simple synthetic route to unusual 3,5-dispirosubstituted piperidines. The reaction is mild, operationally simple and offers high yields. The



Scheme 4.

starting materials are readily available and the products are easy to isolate.

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9. *General procedure for the reaction of anilines, formaldehyde and dimedone. Preparation of 3,3,11,11-tetramethyl-15-aryl-15-azadispiro[5.1.5.3]hexadecane-1,5,9,13- tetrones* (**7a**–**f**): A solution of 1 (2.5 mmol) and paraformaldehyde (0.45 g, 15 mmol) in ethanol (20 mL) was prepared by gentle warming (2–3 min). Dimedone 2 (0.7 g, 5 mmol) was added to this solution in one portion. The mixture was heated under reflux for 3–5 min to dissolve all the reactants and then allowed to stand overnight at room temperature. The resulting colourless precipitate was filtered off, washed with ethanol (2 × 5 mL) and dried to give the desired spirane. Selected analytical data: *3,3,11,11-Tetramethyl-15-(4-methylphenyl)-15-azadispiro[5.1.5.3]hexadecane-1,5,9,13-tetrone* (**7b**): Mp 199 °C. IR (KBr): 2958, 2921, 2869, 1732, 1721, 1702, 1689, 1613, 1514, 1249, 1237, 1224, 1069, 808, 523 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.97 (s, 6H), 0.98 (s, 6H), 2.25 (s, 3H), 2.46 (s, 2H), 2.63 (d, J = 13.5 Hz, 4H), 2.81 (d, J = 13.5 Hz, 4H), 3.37 (s, 4H), 6.99 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.78, 28.57, 28.88, 30.98, 32.46, 51.43, 55.83, 66.00, 119.50, 129.84, 131.60, 149.78, 206.13. Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.78; H, 7.88; N, 3.33. *15-[1,1′-Biphenyl]-4-yl-3,3,11,11-tetramethyl-15-azadispiro[5.1.5.3]hexadecane-1,5,9,13-tetrone* (**7e**): Mp 186 °C. IR (KBr): 2958, 2930, 2870, 1729, 1698, 1609, 1519, 1486, 1215, 1065, 769, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.97 (s, 6H), 0.98 (s, 6H), 2.50 (s, 2H), 2.66 (d, J = 13.5 Hz, 4H), 2.81 (d, J = 13.5 Hz, 4H), 3.48 (s, 4H), 7.15 (d, J = 8.5 Hz, 2H), 7.25–7.29 (m, 1H), 7.36–7.39 (m, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.51–7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.45, 28.40, 28.70, 30.84, 32.33, 51.27, 54.70, 58.25, 65.71, 118.83, 126.68, 127.81, 128.77, 134.17, 140.76, 150.81, 206.07. Anal. Calcd for $C_{31}H_{35}NO_4$: C, 76.67; H, 7.26; N, 2.88. Found: C, 76.70; H, 7.25; N, 2.90. *15-(4-Bromophenyl)-3,3,11,11-Tetramethyl-15-azadispiro[5.1.5.3]hexadecane-1,5,9,13-tetrone* (**7f**): Mp 202 °C. IR (KBr): 2959, 2949, 2922, 1732, 1721, 1703, 1689, 1590, 1492, 1250, 1223, 1078, 826, 516 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (s, 6H), 0.97 (s, 6H), 2.46 (s, 2H), 2.61 (d, J = 13.5 Hz, 4H), 2.79 (d, J = 13.5 Hz, 4H), 3.38 (s, 4H), 6.95 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.20,28.50, 30.66, 32.01, 51.05, 54.43, 65.36, 113.67, 120.21, 131.80, 150.38, 205.76. Anal. Calcd for $C_{25}H_{30}BrNO_4$: C, 61.48; H, 6.19; Br, 16.36; N, 2.87. Found: C, 61.51; H, 6.20; Br, 16.35; N, 2.90. 3,3,11,11-tetramethyl-15-[4-(3,3,11,11-tetramethyl-1,5,9,13-tetraoxo-15-azadispiro[5.1.5.3]hexadec-15-yl)phenyl]-15-azadispiro-[5.1.5.3]hexadecane-1,5,9,13-tetrone (**9**): Mp (acetone) 230 °C (decomp.). IR (KBr): 2968, 2951, 2928, 2869, 2819, 1731, 1509, 1245, 1218, 1159 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.89 (s, 12H), 0.93 (s, 12H), 2.47 (s, 4H), 2.70 (d, J = 13.5 Hz, 8H), 2.82 (d, J = 13.5 Hz, 8H), 3.29 (s, 8H), 6.98 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.61, 28.00, 30.50, 31.47, 50.43, 54.26, 65.07, 119.01, 145.35, 206.50. Anal. Calcd for $C_{44}H_{56}N_2O_8$: C, 71.33; H, 7.62; N, 3.78. Found: C, 71.34; H, 7.60; N, 3.80.
10. 2-Methylaniline, 2-methoxyaniline, 3-methylaniline and 3-methoxyaniline were tested. We suppose that in these cases dimedone works as an acid catalyst resulting in some kind of aniline–formaldehyde polymerization involving the *para*-position and the N-atom of aniline.
11. Reaction of 4-nitroaniline (0.34 g, 2.5 mmol) with paraformaldehyde and dimedone following the general procedure gave 0.45 g (62%) of 2-[(4,4-dimethyl-2,6-dioxocyclohexyl)methyl]-5,5-dimethyl-1,3-cyclohexanedione (**8**). Mp (EtOH) 190 °C.
12. (a) Reaction of 2-naphthalenamine (0.72 g, 5 mmol) with paraformaldehyde (0.9 g, 30 mmol) and dimedone (1.4 g, 10 mmol) following the general procedure gave 0.73 g (52%) of **10** (the substance precipitated from the hot reaction mixture which was filtered off, washed with 10 mL of $CHCl_3$ and dried) and 0.48 g (27%) of **11** (the substance precipitated from the combined mother liquors on standing overnight). Analytical data: *9,9-Dimethyl-8,9,10,12-tetrahydrobenzo[a]acridin-11(7H)-one* (**10**): Mp (DMF) 256 °C. IR (KBr): 3300, 2980, 2945, 2840, 1640, 1625, 1600, 1585, 1520, 1500, 1480, 1400, 1252, 1155, 1040, 810 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6/Py-d_5, 2:1): δ 1.06 (s, 6H), 2.30 (s, 2H), 2.43 (s, 2H), 4.02 (s, 2H), 7.26 (d, J = 8.6 Hz, 1H), 7.37 (ddd, J = 8.0, 7.1, 0.8 Hz, 1H), 7.52 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8 Hz, 1H), 9.22 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.47, 27.52, 31.45, 40.24, 50.08, 102.30, 113.12, 116.56, 121.70, 123.05, 126.16, 126.96, 127.65, 129.66, 131.83, 133.93, 150.93, 193.18. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.27; H, 6.68; N, 5.01. *4-Ethoxymethyl-1,4-dihydro-4′,4′-dimethyl-2′H,3H,6′H-spiro[benzo(f)quinoline-2,1′-cyclohexane]-2′,6′-dione* (**11**): Mp (EtOH) 137 °C (lit.[6b] 137 °C).; (b) The mechanistic explanations for the formation of similar products were given earlier. See Refs. 6,7.
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