GRIFFITH UNIVERSITY

Dibenzo[b,f]pyrazolo[1,5-d][1,4]oxazepines: facile construction of a rare heterocyclic system via tandem aromatic nucleophilic substitution - Smiles rearrangement – denitrocyclization

Author

V. Sapegin, Alexander, A. Kalinin, Stanislav, V. Smirnov, Alexey, V. Dorogov, Mikhail, Krasavin, Mikhail

Published

2012

Journal Title

Synthesis: Journal of Synthetic Organic Chemistry

DOI

10.1055/s-0031-1289789

Rights statement

© 2012 Georg Thieme Verlag. This is the author-manuscript version of the paper. Reproduced in accordance with the copyright policy of the publisher. The definitive version is available at www.thieme-connect.com

Downloaded from

http://hdl.handle.net/10072/50041

Griffith Research Online

https://research-repository.griffith.edu.au

Dibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepines: a facile construction of a rare heterocyclic system via tandem aromatic nucleophilic substitution - Smiles rearrangement – denitrocyclization

Alexander V. Sapegin,[a] Stanislav A. Kalinin,[a] Alexey V. Smirnov,[a] Mikhail V. Dorogov[a] and Mikhail Krasavin[*b]

[a] The Ushinsky Yaroslavl State Pedagogical University, 108 Respublikanskaya St., Yaroslavl, 150000, Russian Federation

[b] Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, Queensland 4111, Australia

Phone: +61(0)73735 6041. Fax: +61(0)73735 6001

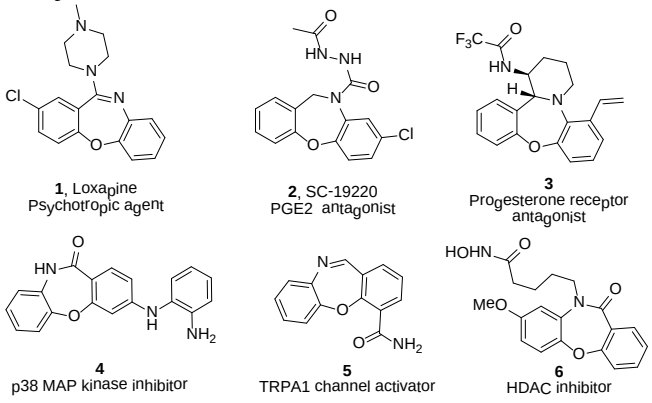
E-mail: m.krasavin@griffith.edu.au

Abstract: Condensation of 2-(1*H*-pyrazol-5-yl)phenols with *o*-chloronitrobenzenes under basic conditions in DMF results in a tandem, atom-economical aromatic nucleophilic substitution – Smiles rearrangement – denitrocyclization process to provide pyrazolo-fused dibenzo[*b*,*f*][1,4]oxazepines as a single regioisomer.

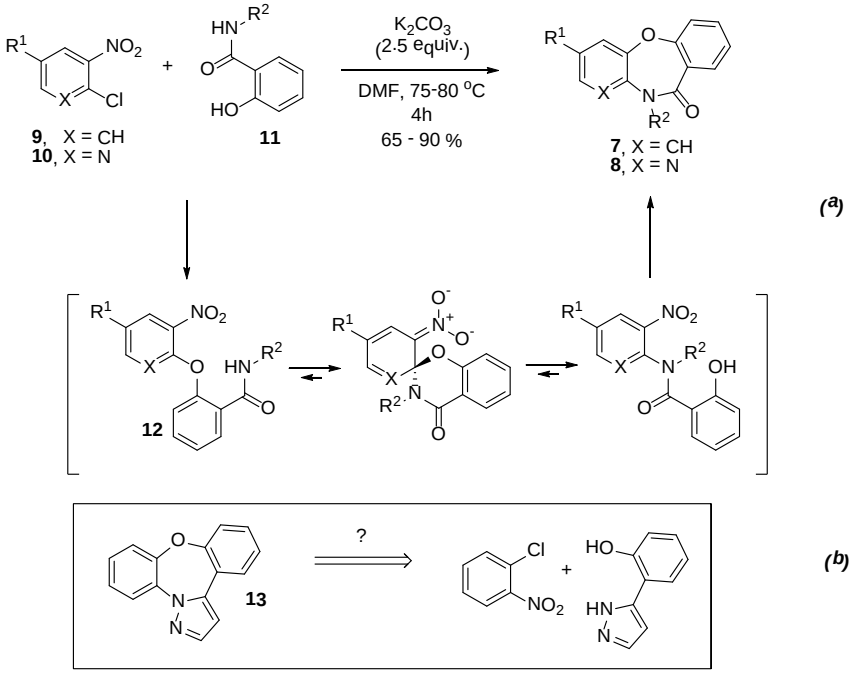
Key words: tetracyclic scaffolds, privileged structures, atom-economical syntheses, dibenzo[*b*,*f*][1,4]oxazepines, Smiles rearrangement, nucleophilic aromatic substitution, denitrocyclization, regiospecific reaction.

The range of biological activities displayed by the compounds containing dibenzo[*b*,*f*][1,4]oxazepine scaffold is strikingly vast. From the early applications of such compounds as psychotropic drugs (e. g., Loxapine, **1**[1]) and, even more prominently, as prostaglandin receptors antagonists (e. g., Searle's SC-19220, **2**[2]), the utility of dibenzo[*b*,*f*][1,4]oxazepines has recently extended to the design of potent progesterone receptor antagonists (**3**),[3] p38 MAP kinase inhibitors (**4**),[4] TRPA1 ion channel modulators (**5**)[5] and histone deacetylase inhibitors (**6**)[6] (Figure 1). This provides ample evidence for the privileged character of this scaffold (as defined by Evans[7]) and makes the development of novel synthetic methodologies toward this and related heterocyclic systems particularly worthwhile.

Figure 1. Examples of pharmacologically active dibenzo[*b*,*f*][1,4]-oxazepines.



Scheme 1. Strategies for construction of the dibenzo[*b*,*f*][1,4]oxazepine scaffold: *(a)* described earlier[9] and *(b)* investigated in present work.



Of special value are tandem synthetic strategies that are atom-economical,[8] generally more efficient and less time-consuming than linear multistep ones. Earlier, we reported a practically simple and streamlined entry into dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones **7** and their 9-aza analogs (**8**) via condensation of *o*-chloronitro derivatives of benzene and pyridine (**9** and **10**, respectively) with secondary salicylamides **11** under basic conditions.[9] The reaction proceeded, as anticipated, via a denitrocyclization[10] step but was accompanied by unexpected (though not unprecedented[11]) Smiles rearrangement of the initial diaryl ether adduct **12**. Encouraged by this finding, we became curious if NH-acidic azoles such as pyrazole could be effective participants in a similar tandem process in lieu of the secondary amide functionality. This would lead to the formation of a rare pyrazole-including framework **13** (Scheme 1). Such tetracyclic scaffolds are of much interest considering that fusion of five-membered cycles onto a dibenzo[*b*,*f*][1,4]oxazepine core has been shown to attenuate the pharmacological properties of the resulting compounds.[12] Moreover, dibenzo[*b*,*f*]pyrazolo[1,5-d][1,4]oxazepines **13** have recently found application in the design of organic light emitting devices (OLEDs).[13] Herein, we would like to report on a successful realization of a new synthetic strategy toward **13**.

The starting 2-(1*H*-pyrazol-5-yl)phenols **14a-e** were prepared via a Claisen condensation of *o*-hydroxyacetophenones **15** with aliphatic esters **16** followed by treatment of the isolated sodium phenolates **17a-e** with hydrazine hydrate (Scheme 2). Both steps involved only filtration as the means of solid product isolation and provided good to excellent yields of the desired material (Table 1).

Scheme 2. Preparation of 2-(1*H*-pyrazol-5-yl)phenols **14a-c**.

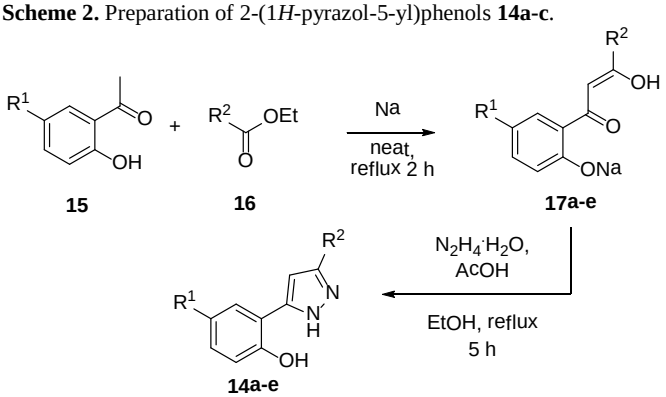


Table 1. 2-(1*H*-Pyrazol-5-yl)phenols **14a-e** and their precursors **17a-e** synthesized in this work.

Compound	R^1	R^2	Yield of **17** (%)	Yield of **14** (%)
14(17)a	H	H	75	84
14(17)b	H	Me	60	76
14(17)c	H	Et	58	65
14(17)d	Cl	Me	67	74
14(17)e	Me	Me	72	63

To our delight, compounds **14a-e** underwent a facile condensation with a set of *o*-chloronitrobenzenes **18**, on heating with 3 equiv. of anhydrous potassium carbonate in DMF. Moreover, ^{1}H NMR analyses of the crude reaction mixtures confirmed the disappearance of the characteristic broad singlets corresponding to both the pyrazole moiety (N-H δ 13.55…12.70 ppm) and the phenol functionality (O-H δ 11.40…10.03 ppm), clearly indicating that the former participated in the reaction. Additionally, the ^{1}H NMR signals corresponding to the aromatic portions of **14** and **18** exhibited pronounced (~0.3 ppm) downfield and upfield shifts, respectively. This, according to our previous denitrocyclization experience,[9] strongly attested to the formation of hitherto not described tetracyclic compounds **19a-o** (Scheme 3).

Scheme 3. Preparation of dibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepines **19a-o**.

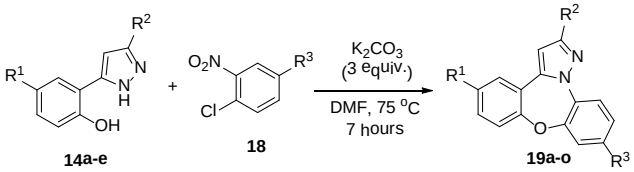


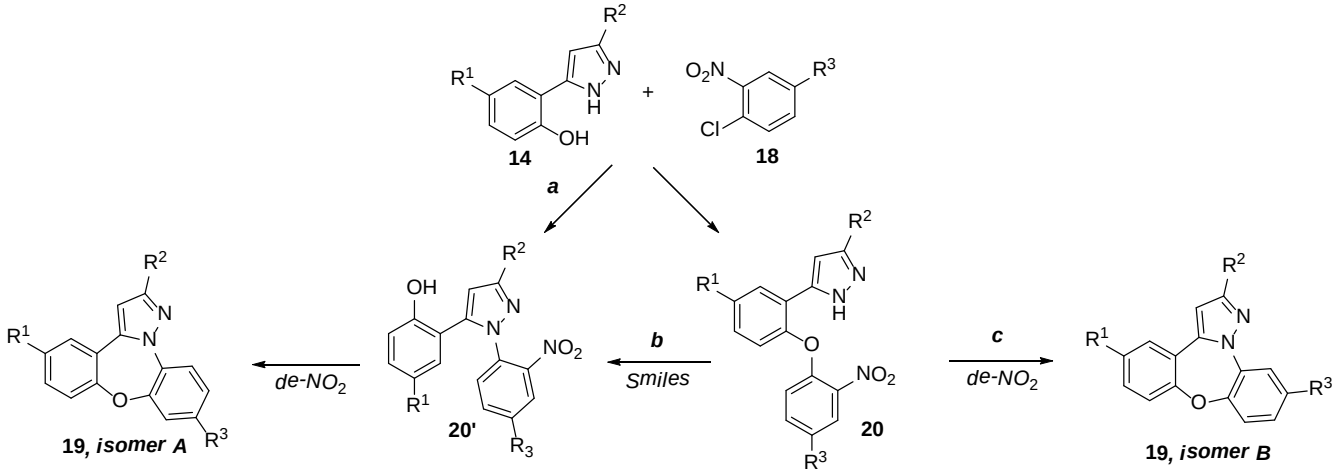
Table 2. Dibenzo[b,f]pyrazolo[1,5-d][1,4]oxazepines **19a-o** synthesized in this work.

Compound	R^1	R^2	R^3	Yield (%)
19a	H	H	COOMe	66
19b	H	H	CN	79
19c	H	H	NO_2	81
19d	H	Me	COOMe	77
19e	H	Me	CN	81
19f	H	Me	NO_2	68
19g	H	Et	COOMe	60
19h	H	Et	CN	73
19i	H	Et	NO_2	85
19j	Cl	Me	COOMe	74
19k	Cl	Me	CN	83
19l	Cl	Me	NO_2	85
19m	Me	Me	COOMe	76
19n	Me	Me	CN	69
19o	Me	Me	NO_2	80

The isolated yield of compounds **19a-o** were good to excellent (Table 2) and their analytical data (^{1}H and ^{13}C NMR as well elemental analyses) were consistent with the anticipated dibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepine structure. However, establishing the regiochemical identity of the products obtained presented a significant challenge, although it was evident from the NMR data that compounds **19a-o** belonged to the same isomeric series. Presumably, the regiochemistry of **19** would be determined (Scheme 4) by the ability of the pyrazole moiety to participate in the initial chlorine displacement event (path a) or in the

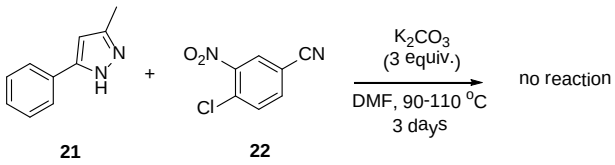
subsequent Smiles rearrangement (path b) of the initially formed diphenyl ether adduct **20**.[9] In both cases regioisomer A would be formed in contrast to regioisomer B that might result from two sequential nucleophilic displacements (of the chlorine atom and the nitro group), not accompanied by the Smiles rearrangement (path c), a possibility that also should be considered.

Scheme 4. Possible reaction pathways determining the regiochemistry of dibenzo[*b*,*f*]pyra-zolo[1,5-*d*][1,4]oxazepines **19a-o**.



Intermolecular displacement of the chlorine atom in **18** by the pyrazole moiety in **14** (path a) can be easily ruled out based on the results of a model experiment. Under the same reaction conditions, 3-methyl-5-phenyl-1*H*-pyrazole (**21**) failed to react with 4-chloro-3-nitrobenzonitrile (**22**), even on prolonged (3 days) heating at 110 °C (Scheme 5). Additionally, the absence in the reaction mixture of pyrazole *N*-arylation products regioisomeric to intermediate **20'** (which cannot be expected to participate in subsequent cyclization events due to steric reasons) also speak against the reaction's proceeding via path a.

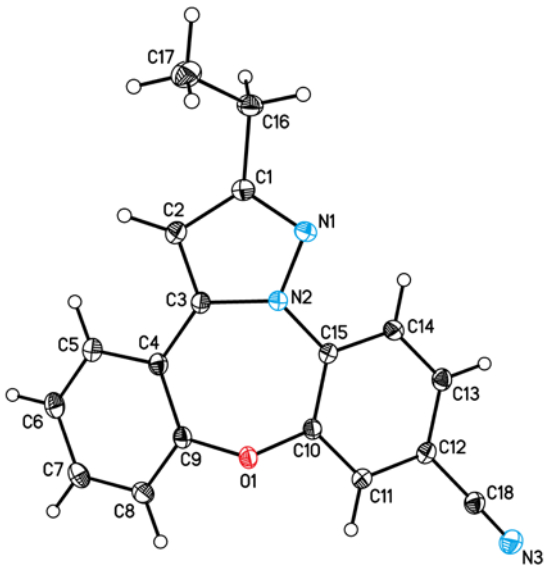
Scheme 5. Attempted reaction of a model pyrazole **21** with 3-chloro-4-nitrobenzonitrile (**22**).



Unfortunately, correlational NMR spectroscopy (NOESY, HSQC, HMBC) provided insufficient information for an unequivocal regiochemistry assignment of products **19a-o** and thus for distinguishing between the reaction paths b and c. To our relief, we were able to obtain a single-crystal X-ray structure of a representative compound, **19h** (Figure 2).[14] It clearly showed the compound's belonging to the isomeric series A and thus confirmed that the compounds **19** formed as a result of tandem aromatic nucleophilic substitution – Smiles rearrangement – denitrocyclization.

In summary, we have developed a streamlined synthetic methodology toward hitherto not described dibenzo[*b*,*f*][1,4]oxazepines from readily available precursors. The compounds were obtained in high yields as a single regioisomer as a result of three chemical events occurring in tandem. This represents a remarkable example of atom economy and efficiency in constructing polycyclic heterocycles. Similar strategies involving other potentially nucleophilic azoles are being investigated in our laboratories and will be reported in due course.

Figure 2. Single-crystal X-ray structure of compound **19h**.



All reactions were run in oven-dried glassware in atmosphere of nitrogen. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Analytical thin-layer chromatography was carried out on Silufol UV-254 silica gel plates

using an appropriate mixtures of ethyl acetate and hexane. Compounds were visualized with short-wavelength UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker MSL-300 spectrometers in DMSO-d_6 using TMS as an internal standard. Elemental analyses were obtained at Research Institute for Chemical Crop Protection (Moscow, Russia) using Carlo Erba Strumentazione 1106 analyzer. The IR spectra were recorded using Specord M-80 spectrophotometer on compound samples prepared as KBr tablets. All and reagents were obtained from commercial sources and used without purification. DMF was dried according to the standard procedure[15] and potassium carbonate was dried at 200 °C for 5 hours prior to use.

4-Chloro-2-(3-methyl-1*H*-pyrazol-5-yl)phenol (14d); Typical Procedure for the Synthesis of Compounds 14a-e.

Sodium metal (6.44 g, 0.280 mol) was carefully added to a solution of 5'-chloro-2'-hydroxyacetophenone (11.9 g, 0.070 mol) in ethyl propanoate (100 mL) over 1 hour. The resulting mixture was heated at reflux for 2 h, cooled down to rt and poured over crushed ice – water mixture (total volume – 1 L). The resulting precipitate was filtered off, washed with cold isopropyl alcohol (50 mL), air dried and further dried in vacuum at 60 °C overnight to provide 10.9 g (67%) of 1-(5-chloro-2-hydroxyphenyl)-3-hydroxybut-2-en-1-one, sodium salt (**17d**) as light-yellow solid: ^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 16.87…17.11 (br s, 1H, OH), 7.44 (s, 1H, Ar), 7.11 (d, *J* = 8.2 Hz, 1H, Ar), 6.61 (d, *J* = 8.5 Hz, 1H, Ar), 5.35…5.50 (br s, 1H, –CH=).
Hydrazine hydrate (65% solution in water, 5 mL) and glacial acetic acid (0.021 mol) were added to a solution of this compound (3.65 g, 0.016 mol) in ethanol (30 mL). The resulting mixture was heated at reflux for 5 h, cooled down to rt and the volatiles were removed *in vacuo*. The resulting precipitate was suspended in water (100 mL), filtered off, washed with more water, air dried and further dried in vacuum at 60 °C overnight to provide 2.4 g (74%) of the title compound.

Off-white solid; mp 95-97 °C.

IR (KBr): 3442, 3153, 1610 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 12.70…13.06 (br s, 1H, pyrazole NH), 10.03…11.40 (br s, 1H, ArOH), 7.64 (s, 1H, Ar), 7.10 (d, *J* = 8.5 Hz, 1H, Ar), 6.87 (d, *J* = 8.5 Hz, 1H, Ar), 6.63 (s, 1H, Pyrazole CH), 2.31 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 154.1, 158.0, 128.0, 125.9, 122.9, 119.1, 118.1, 100.7, 10.7.

Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.41; H, 4.35; N, 13.49.

2-(1*H*-Pyrazol-5-yl)phenol (14a).

Yield 1.78 g (84%).

White solid; mp 128-131 °C.

IR (KBr): 3435, 3140, 1620 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 13.00…13.49 (br s, 1H, pyrazole NH), 10.73…11.08 (br s, 1H, ArOH), 7.86 (s, 1H, Pyrazole CH), 7.72 (d, *J* =7.9 Hz, 1H, Ar), 7.17 (t, *J* = 7.5 Hz, 1H, Ar), 6.79…6.95 (m, 3H, Ar + Pyrazole).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.3, 139.1, 128.6, 128.6, 126.7, 119.2, 119.1, 117.2, 116.4, 101.0.

Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.31; H, 5.04; N, 17.58.

2-(3-Methyl-1*H*-pyrazol-5-yl)phenol (14b).

Yield 1.4 g (76%).

White solid; mp 128-131 °C.

IR (KBr): 3430, 3143, 1628 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 12.80…13.09 (br s, 1H, pyrazole NH), 10.97…11.21 (br s, 1H, ArOH), 7.63 (d, *J* =7.9 Hz, 1H, Ar), 7.15 (t, *J* = 7.9 Hz, 1H, Ar), 6.82…6.94 (m, 2H, Ar), 6.59 (s, 1H, Pyrazole CH), 2.30 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.3, 128.6, 128.6, 126.6, 119.2, 119.1, 117.2, 116.4, 101.3, 10.6.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.76; H, 5.79; N, 16.15.

2-(3-Ethyl-1*H*-pyrazol-5-yl)phenol (14c).

Yield 2.31 g (65 %).

White solid; mp 50-52 °C.

IR (KBr): 3431, 3140, 1620 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 13.04…13.55 (br s, 1H, pyrazole NH), 10.86…11.18 (br s, 1H, ArOH), 7.60 (d, *J* =7.5 Hz, 1H, Ar), 7.12 (t, *J* = 7.0 Hz, 1H, Ar), 6.84 (m, 2H, Ar), 6.53 (s, 1H, Pyrazole CH), 2.70 (m, 2H, $C\underline{H}_2CH_3$), 1.28 (t, *J* = 7.5 Hz, CH_2CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.3, 128.6, 128.5, 126.6, 119.2, 119.1, 117.3, 116.4, 99.9, 18.5, 13.4.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.01; H, 6.44; N, 14.95.

Off-white solid; mp 95-97 °C.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 12.70…13.06 (br s, 1H, pyrazole NH), 10.03…11.40 (br s, 1H, ArOH), 7.64 (s, 1H, Ar), 7.10 (d, *J* = 8.5 Hz, 1H, Ar), 6.87 (d, *J* = 8.5 Hz, 1H, Ar), 6.63 (s, 1H, Pyrazole CH), 2.31 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 154.1, 158.0, 128.0, 125.9, 122.9, 119.1, 118.1, 100.7, 10.7.

Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.41; H, 4.35; N, 13.49.

4-Methyl-2-(3-methyl-1*H*-pyrazol-5-yl)phenol (14e).

Yield 1.6 g (63 %).

White solid; mp 61-63 °C.

IR (KBr): 3426, 3139, 1618 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 12.85…13.12 (br s, 1H, pyrazole NH), 10.71…11.22 (br s, 1H, ArOH), 7.36 (s, 1H, Ar), 6.91 (d, *J* = 6.6 Hz, 1H, Ar), 6.73 (d, *J* = 7.5

Hz, 1H, Ar), 6.47 (s, 1H, Pyrazole CH), 2.32 (s, 3H, $ArCH_3$), 2.27 (s, 3H, Pyrazole CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 153.3, 129.1, 129.1, 127.2, 126.9, 126.8, 116.9, 116.2, 101.1, 20.2, 10.7.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.98; H, 6.42; N, 14.91.

Methyl 2-ethyldibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carboxylate (19g); Typical Procedure for the Synthesis of Compounds 19a-o.

A mixture of **14c** (1.88 g, 10 mmol), methyl 4-chloro-3-nitrobenzoate (2.16 g, 10 mmol) and K_2CO_3 (1.15 g, 30 mmol) in dry DMF (15 mL) was stirred at 75 °C for 7 h, then cooled down to rt and poured into water (100 mL). The resulting precipitate was filtered off and crystallized from isopropyl alcohol to provide 1.92 g (60 %) of the title compound.

White solid; mp 94-96 °C.

IR (KBr): 1744, 1623, 1219, 1201 cm^{-1}.

^1H NMR (DMSO-d_6, 300 K, ppm): δ 8.01 (s, 1H, Ar), 7.83…7.96 (m, 2H, Ar), 7.69 (d, *J* = 7.9 Hz, 1H, Ar), 7.57 (d, *J* = 8.2 Hz, 1H, Ar), 7.49 (t, *J* = 7.2 Hz, 1H, Ar), 7.33 (t, *J* = 7.2 Hz, 1H, Ar), 6.87 (s, 1H, pyrazole CH), 3.88 (s, 3H, $COOCH_3$), 2.71 (m, 2H, $C\underline{H}_2CH_3$), 1.29 (t, *J* = 7.9 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 165.0, 157.1, 155.5, 149.1, 141.0, 136.5, 131.4, 129.2, 128.9, 127.2, 126.4, 123.4, 122.9, 121.6, 121.4, 106.1, 52.5, 21.1, 13.4.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.03; H, 5.04; N, 8.79.

Methyl dibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carboxylate (19a).

Yield 0.78 g (66%).

White solid; mp 173-175 °C (EtOH).

IR (KBr): 1745, 1619, 1223, 1200 cm^{-1}.

^1H NMR (DMSO-d_6, 300 K, ppm): δ 8.02…8.05 (m, 2H, Ar + pyrazole), 7.83…7.94 (m, 2H, Ar), 7.68 (d, *J* = 7.3 Hz, 1H, Ar), 7.56 (d, *J* = 7.5 Hz, 1H, Ar), 7.51 (t, *J* = 7.0 Hz, 1H, Ar), 7.35 (t, J = 7.5 Hz, 1H, Ar), 6.10 (s, 1H, pyrazole CH), 3.87 (s, 3H, $COOCH_3$).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 165.0, 155.6, 151.4, 149.0, 141.1, 140.2, 136.5, 131.5, 129.2, 128.9, 127.2, 126.4, 123.4, 122.9, 121.4, 107.4, 52.5.

Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.67; H, 4.16; N, 9.63.

Dibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carbonitrile (19b).

Yield 1.3 g (79 %).

Light-yellow solid; mp 196-196 °C (EtOH/DMF).

IR (KBr): 2239, 1615 cm^{-1}.

^1H NMR (DMSO-d_6, 300 K, ppm): δ 8.34 (s, 1H, Ar), 8.21 (d, *J* = 8.5 Hz, 1H, Ar), 7.98…8.03 (m, 2H, Ar + pyrazole), 7.63 (d, *J* = 7.4 Hz, 1H, Ar), 7.42…7.60 (m, 2H, Ar), 7.34 (t, *J* = 7.5 Hz, 1H, Ar), 6.11 (s, 1H, pyrazole CH).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.0, 151.6, 149.3, 141.3, 140.2, 136.8, 131.5, 130.3, 129.2, 126.5, 126.2, 124.1, 117.5, 110.2, 107.6.

Anal. Calcd for $C_{16}H_9N_3O$: C, 74.12; H, 3.50; N, 16.21. Found: C, 73.90; H, 3.51; N, 16.29.

5-Nitrodibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepine (19c).

Yield 0.67 g (81 %).

Dark-yellow solid; mp 217-219 °C (EtOH/DMF).

IR (KBr): 1682, 1619, 1223, 1200 cm^{-1}.

^1H NMR (DMSO-d_6, 300 K, ppm): δ 8.46 (s, 1H, Ar), 8.24 (d, *J* = 8.5 Hz, 1H, Ar), 8.00…8.13 (m, 2H, Ar + pyrazole), 7.77 (d, *J* = 7.5 Hz, 1H, Ar), 7.66 (d, *J* = 7.9 Hz, 1H, Ar), 7.55 (t, *J* = 7.2 Hz, 1H, Ar), 7.39 (t, *J* = 6.9 Hz, 1H, Ar), 6.08 (s, 1H, pyrazole CH).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.4, 153.0, 148.5, 145.9, 141.3, 140.2, 138.0, 131.7, 129.3, 126.7, 123.7, 121.9, 121.6, 121.4, 118.1, 108.2.

Anal. Calcd for $C_{15}H_9N_3O_3$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.32; H, 3.27; N, 15.12.

Methyl 2-methyldibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carboxylate (19d).

Yield 1.64 g (77%).

White solid; mp 146-148 °C (*i*PrOH).

IR (KBr): 1741, 1622, 1220, 1205 cm^{-1}.

^1H NMR (DMSO-d_6, 300 K, ppm): δ 8.01 (s, 1H, Ar), 7.83…7.95 (m, 2H, Ar), 7.67 (d, *J* = 7.2 Hz, 1H, Ar), 7.55 (d, *J* = 7.9 Hz, 1H, Ar), 7.50 (t, *J* = 6.9 Hz, 1H, Ar), 7.34 (t, *J* = 7.5 Hz, 1H,

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 165.0, 155.5, 151.4, 149.0, 141.1, 136.5, 131.5, 129.2, 128.9, 127.2, 126.4, 123.4, 122.9, 121.4, 107.4, 52.5, 13.5.

Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.41; H, 4.60; N, 9.19.

2-Methyldibenzo[*b*,*f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carbonitrile (19e).

Yield 1.1 g (81 %).

Light-yellow solid; mp 208-209 °C (EtOH/DMF).

IR (KBr): 2241, 1606 cm^{-1}.

^1H NMR (DMSO-d_6, 300 K, ppm): δ 8.36 (s, 1H, Ar), 8.20 (d, *J* = 8.8 Hz, 1H, Ar), 7.99 (d, *J* = 9.0 Hz, 1H, Ar), 7.67 (d, *J* = 7.5 Hz, 1H, Ar), 7.43…7.60 (m, 2H, Ar), 7.34 (t, *J* = 7.5 Hz, 1H, Ar), 6.80 (s, 1H, pyrazole CH), 2.38 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.4, 151.8, 149.2, 141.3, 136.8, 131.5, 130.3, 129.2, 126.5, 126.2, 124.1, 117.5, 110.2, 107.7, 13.3.

Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.79; H, 4.07; N, 15.45.

2-Methyl-10-ntirodibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepine (19f).

Yield 0.88 g (68 %).

Dark-yellow solid; mp 237-239 °C (EtOH/DMF).

IR (KBr): 1680, 1617, 1352 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.42 (s, 1H, Ar), 8.21 (d, *J* = 8.9 Hz, 1H, Ar), 7.99 (d, *J* = 9.2 Hz, 1H, Ar), 7.71 (d, *J* = 7.9 Hz, 1H, Ar), 7.63 (d, *J* = 8.2 Hz, 1H, Ar), 7.53 (t, J = 7.5 Hz, 1H, Ar), 7.37 (t, *J* = 7.9 Hz, 1H, Ar), 6.89 (s, 1H, pyrazole), 2.37 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.1, 152.2, 148.6, 145.9, 141.3, 138.0, 131.7, 129.3, 126.7, 123.7, 121.8, 121.6, 121.2, 118.1, 108.1, 13.5.

Anal. Calcd for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.38; H, 3.77; N, 14.40.

2-Ethyldibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carbonitrile (19h).

Yield 1.07 g (73 %).

Light-yellow solid; mp 178-181 °C (EtOH/DMF).

IR (KBr): 2235, 1610 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.01 (s, 1H, Ar), 7.93 (d, *J* = 8.5 Hz, 1H, Ar), 7.76 (d, *J* = 8.5 Hz, 1H, Ar), 7.67 (d, *J* = 7.9 Hz, 1H, Ar), 7.43…7.51 (m, 2H, Ar), 7.33 (t, J = 7.0 Hz, 1H, Ar), 6.81 (s, 1H, pyrazole CH), 2.74 (m, 2H, $C\underline{H}_2CH_3$), 1.32 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.0, 151.7, 149.2, 141.1, 136.8, 131.5, 130.3, 129.2, 126.5, 126.2, 124.1, 117.51 110.2, 107.7, 20.9, 13.3.

Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.03; H, 4.57; N, 14.70.

2-Ethyl-10-nitrodibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepine (19i).

Yields 0.92 g (85 %).

Dark-yellow solid; mp 221-223 °C (EtOH/DMF).

IR (KBr): 1689, 1620, 1347 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.42 (s, 1H, Ar), 8.22 (d, *J* = 8.9 Hz, 1H, Ar), 7.99 (d, *J* = 9.2 Hz, 1H, Ar), 7.72 (d, *J* = 7.2 Hz, 1H, Ar), 7.63 (d, *J* = 7.5 Hz, 1H, Ar), 7.53 (t, *J* = 7.5 Hz, 1H, Ar), 7.37 (t, *J* = 7.2 Hz, 1H, Ar), 6.94 (s, 1H, pyrazole), 2.74 (m, 2H, $C\underline{H}_2CH_3$), 1.30 (t, *J* = 7.5 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 155.8, 155.1, 148.6, 145.8, 141.2, 138.1, 131.6, 129.2, 126.7, 123.7, 121.8, 121.5, 121.3, 118.1, 106.7, 21.1, 13.2.

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.24; H, 4.26; N, 13.67. Found: C, 66.28; H, 4.27; N, 13.74.

Methyl 5-chloro-2-methyldibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carboxylate (19j).

Yield 0.73 g (74%).

Grey solid; mp 192-195 °C (DMF).

IR (KBr): 1745, 1620, 1224, 1205 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.00 (s, 1H, Ar), 7.85…7.93 (m, 2H, Ar), 7.70 (s, 1H, Ar), 7.55 (d, *J* = 9.5 Hz, 1H, Ar), 7.48 (d, *J* = 9.4 Hz, 1H, Ar), 6.85 (s, 1H, pyrazole CH), 3.89 (s, 3H, $COOCH_3$), 2.37 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 165.0, 154.3, 151.5, 148.8, 139.8, 136.3, 130.8, 130.4, 129.4, 128.3, 127.2, 123.4, 123.2, 122.8, 108.1, 52.3, 13.3.

Anal. Calcd for $C_{18}H_{13}ClN_2O_3$: C, 63.44; H, 3.85; N, 8.22. Found: C, 63.27; H, 3.87; N, 8.26.

5-Chloro-2-methyldibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carbonitrile (19k).

Yield 1.52 g (83%).

Light-yellow solid; mp 215-217 °C (DMF).

IR (KBr): 2241, 1604 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.02 (s, 1H, Ar), 7.91 (d, *J* = 8.5 Hz, 1H, Ar), 7.77 (d, *J* = 8.5 Hz, 1H, Ar), 7.71 (s, 1H, Ar), 7.44…7.55 (m, 2H, Ar), 6.88 (s, 1H, pyrazole), 2.37 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 153.7, 151.9, 148.7, 139.8, 136.5, 131.2, 130.8, 130.6, 128.5, 126.5, 124.1, 123.3, 123.1, 117.6, 110.1, 104.7, 13.5.

Anal. Calcd for $C_{17}H_{10}ClN_3O$: C, 66.35; H, 3.28; N, 13.65. Found: C, 66.14; H, 3.31; N, 13.72.

5-Chloro-2-methyl-10-nitrodibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepine (19l).

Yield 1.06 g (85%).

Brown solid; mp 224-226 °C (DMF).

IR (KBr): 1681, 1615, 1341 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.39 (s, 1H, Ar), 8.21 (d, *J* = 8.5 Hz, 1H, Ar), 7.99 (d, *J* = 9.2 Hz, Ar), 7.73 (s, 1H, Ar), 7.62 (d, *J* = 8.5 Hz, Ar), 7.51 (d, *J* = 8.5 Hz, Ar), 6.92 (s, 1H, pyrazole), 2.38 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 153.8, 152.3, 148.4, 146.2, 140.0, 137.9, 131.0, 130.7, 128.3, 123.7, 123.3, 123.1, 121.7, 117.9, 108.7, 13.3.

Anal. Calcd for $C_{16}H_{10}ClN_3O_3$: C, 58.64; H, 3.08; N, 12.82. Found: C, 58.64; H, 3.10; N, 12.89.

Methyl 2,5-dimethyldibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]-oxazepine-10-carboxylate (19m).

Yield 1.44 g (76%).

White solid; mp 131-133 °C (*i*-PrOH).

IR (KBr): 1741, 1622, 1221, 1200 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 7.97 (s, 1H, Ar), 7.89 (d, *J* = 8.4 Hz, 1H, Ar), 7.65 (d, *J* = 7.0 Hz, 1H, Ar), 7.49 (s, 1H, Ar), 7.27…7.42 (m, 2H, Ar), 6.79 (s, 1H, pyrazole), 3.88 (s, 3H, $COOCH_3$), 2.35 (s, 3H, $ArCH_3$), 2.32 (s, 3H, pyrazole CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 165.0, 153.1, 151.7, 149.2, 141.3, 136.7, 135.9, 131.9, 130.5, 129.3, 127.5, 126.3, 124.1, 121.0, 120.9, 117.7, 52.3, 20.3, 13.5.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.12; H, 5.05; N, 8.71.

2,5-Dimethyldibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]oxazepine-10-carbonitrile (19n).

Yield 0.63 g (69%)

Light-yellow solid; mp 182-185 °C (EtOH/DMF).

IR (KBr): 2241, 1608 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.08 (s, 1H, Ar), 7.90 (d, *J* = 8.5 Hz, 1H, Ar), 7.79 (d, *J* = 7.9 Hz, 1H, Ar), 7.50 (s, 1H, Ar), 7.27…7.42 (m, 2H, Ar), 6.83 (s, 1H, pyrazole CH), 2.35 (s, 3H, $ArCH_3$), 2.32 (s, 3H, pyrazole CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 153.2, 151.7, 149.2, 141.3, 136.7, 135.9, 132.0, 130.4, 129.3, 126.3, 124.1, 121.0, 120.9, 117.7, 109.9, 107.6, 20.3, 13.5.

Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.11; H, 4.56; N, 14.68.

2,5-Dimethyl-10-nitrodibenzo[*b,f*]pyrazolo[1,5-*d*]-[1,4]oxazepine (19o).

Yield 1.38 g (80%).

Dark-grey solid; mp 207-209 °C (EtOH/DMF).

IR (KBr): 1685, 1619, 1354 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 K, ppm): δ 8.39 (s, 1H, Ar), 8.21 (d, *J* = 8.9 Hz, 1H, Ar), 7.99 (d, *J* = 8.9 Hz, 1H, Ar), 7.47…7.56 (m, 2H, Ar), 7.33 (d, *J* = 8.5 Hz, 1H, Ar), 6.87 (s, 1H, pyrazole CH), 2.36 (s, 3H, $ArCH_3$), 2.33 (s, 3H, pyrazole CH_3).

^{13}C NMR (DMSO-d_6, 300 K, ppm): δ 153.1, 152.1, 148.8, 145.8, 141.4, 138.1, 136.1, 132.1, 129.3, 123.7, 121.7, 121.2, 120.8, 118.0, 107.9, 20.3, 13.5.

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.25; H, 4.23; N, 13.71.

Acknowledgment

This research was supported by the Russian Federation Ministry of Science and Education (Contract 13.G25.31.0079 “Development of Cooperation of Higher Education Institutions and Organizations Implementing Complex High-Technology Production”, in accordance with Government Act 218, 09.04.2010). Mikhail Krasavin acknowledges 2012 Griffith University New Researcher Grant.

References and notes

(1) Davies, J. M. *Am. J. Phychiatry* **1976**, *133*, 208-214.
(2) Hallinan, E. A.; Stapelfeld, A.; Savage, M. A.; Reichman, M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 509-514.
(3) Dols, P. P. M. A.; Folmer, B. J. B.; Hamersma, H.; Kuil, C. W.; Lucas, H.; Ollero, L.; Rewinkel, J. B. M.; Hermkens, P. H. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1461-1467.
(4) Dorn, A.; Schattel, V.; Laufer, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3074-3077.
(5) Gijsen, H. J. M.; Berthelot, D.; Zaja, M.; Brone, B.; Geuens, I.; Mercken, M. *J. Med. Chem.* **2010**, *53*, 7011-7020.
(6) Binaschi, M.; Boldetti, A.; Gianni, M.; Maggi, C. A.; Gensini, M.; Bigioni, M.; Parlani, M.; Giolitti, A.; Fratelli, M.; Valli, C.; Terao, M.; Garattini, E. *ACS Med. Chem. Lett.* **2010**, *1*, 411-415.
(7) Evans, B. E. *J. Med. Chem.* **1988**, *31*, 2235-2246.
(8) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259-281.
(9) Sapegin, A. V.; Sakharov, V. N.; Kalandadze, L. S.; Smirnov, A. V.; Khristolyubova, T. A.; Plakhtinskii, V. V.; Ivashchenko, A. V. *Mendeleev Commun.* **2008**, *18*, 281-283.
(10) Radl, S. *Adv. Heterocycl. Chem.* **2002**, *83*, 189-257.
(11) Rotas, G.; Kimbaris, A.; Varvounis, G. *Tetrahedron* **2004**, *60*, 10825-10832.
(12) Walther, G.; Daniel, H.; Bechtel, W. D.; Brandt, K. *Arzneimittel-Forschung* **1990**, *40*, 440-446.
(13) Nazeeruddin, M. K.; Baranoff, E. D.; Graetzel, M. PCT Intl. Application WO2012019948, 61 pp.; *Chem. Abstr.* **2012**, *156*, 311226.
(14) Crystallographic data (excluding structure factors) for the structure 19h have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 871488. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
(15) In *Purification of Laboratory Chemicals.* Armarego, W. L. F. and Perrin, D. D., Eds. Butterworth-Heinemann, Woburn, MA. 4th Edition, **2002**, p. 192.