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Synthetic Utilization of Polynitroaromatic Compounds. 6. Remarkable Regioselectivity in Nucleophilic Displacement of Aromatic Nitro Groups with Amines

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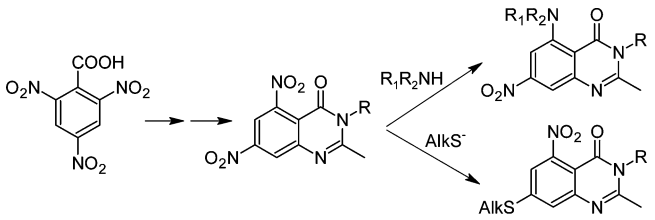
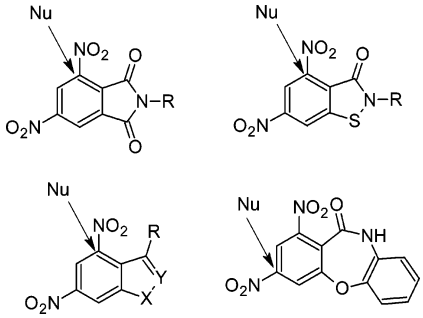


5,7-Dinitroquinazoline-4-ones undergo nucleophilic displacement of a nitro group with N-, S-, and O-nucleophiles. In contrast to previously studied dinitro-substituted benzoannulated five- and seven-membered heterocycles (where a high degree of selectivity was observed), these quinazolines mostly yield mixtures of regioisomeric substitution products. At the same time, primary and secondary amines react selectively to afford 5-aminoquinazolones (*peri*-substitution). A similar effect is observed for some other polynitroaromatic compounds with adjacent nitro and carbonyl groups. This phenomenon is attributed to a stabilization of the intermediate *peri*-σ-complex by intramolecular hydrogen bond N^+—H...O═C.

Introduction

It is known that dinitro-substituted benzoannulated five-membered heterocyclic systems — phthalimides,[1] benzo[*b*]-furans, indoles,[2a,b] benzo[*b*]thiophenes,[3] benz[*d*]isoxazoles,[4] indazoles,[5] benz[*d*]isothiazoles[6] — undergo selective nucleophilic displacement of a nitro group adjacent to a ring fusion point (*peri*-nitro group) with O-, N-, and S-nucleophiles. On the other hand, we recently demonstrated[7] that with 1,3-dinitrodibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-one just the opposite occurs; the nonadjacent nitro group (*para*-nitro group) is displaced with O- and S-nucleophiles (Scheme 1).

SCHEME 1. Selectivity of Aromatic Nitro Group Displacement in Some Benzoannulated Systems



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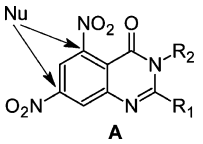
Naturally, with such a difference in reactivity between five- and seven-membered heterocycles, it was interesting to investigate a case of dinitro-substituted benzoannulated six-membered heterocycle.

Just in connection with the ongoing research on utilization of polynitroaromatic compounds,[7−10] we studied conversion of 2,4,6-trinitrobenzoic acid[7,8] to 2-amino-4,6-dinitrobenzoic acid and further to 5,7-dinitroquinazolones **A**[11]:



A

Dinitroquinazolines **A** proved to be the objects of choice for investigating substitution of a nitro group with various nucleophiles. Of particular interest were amines, since some amino-substituted quinazolines are promising anticancer agents that inhibit epidermal growth factor (EGF) receptor tyrosine kinase.[12−15]

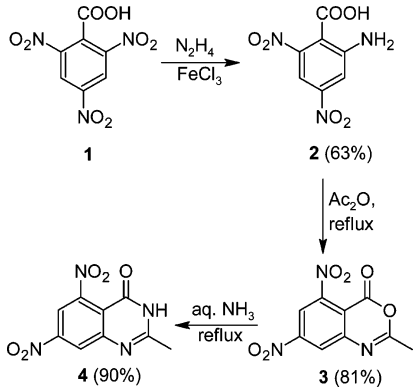
Results and Discussion

Initially, 2,4,6-trinitrobenzoic acid **1** (prepared through oxidation of TNT with dilute HNO_3[8]) is converted to 2-amino-4,6-dinitrobenzoic acid **2**[11,16] with hydrazine in the presence of catalytic amounts of $FeCl_3$.[17] Previously the acid **2** was prepared from **1** by the action of $TiCl_3$, but the reaction was accompanied by formation of 4-amino-2,6-dinitrobenzoic acid as a side product, and separation of the isomers was troublesome.[16] Refluxing acid **2** in acetic anhydride affords 2-methyl-5,7-dinitrobenzoxazine-4-one **3**, which undergoes facile recyclization to a corresponding quinazolone **4** upon heating in aqueous NH_3 (Scheme 2).

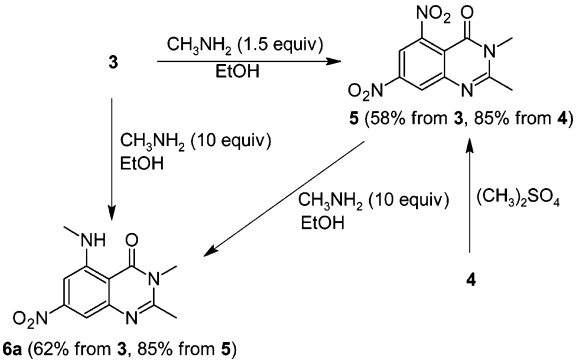
N-Methylquinazolone **5** is prepared by methylation of the compound **4** with dimethyl sulfate. It could also be obtained from benzoxazinone **3** by heating it in an ethanolic solution of methylamine (50% excess) (Scheme 3). With a large excess of methylamine the reaction does not stop at the formation of recyclization product **5** but proceeds further to afford a nucleophilic substitution product, 5-methylamino-7-nitroquinazolone **6a**.

The displacement of a nitro group in *N*-methylquinazolone **5** with primary and secondary amines in EtOH or BuOH was

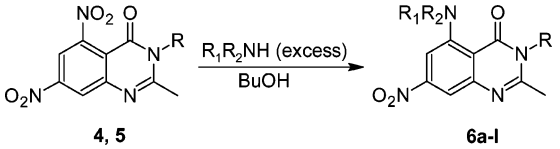
SCHEME 2. Preparation of 5,7-Dinitroquinazolone 4 from 2,4,6-Trinitrobenzoic Acid 1



SCHEME 3. Reactions of the Compounds 3 and 5 with Methylamine



SCHEME 4. Reactions of Dinitroquinazolones 4, 5 with Amines



shown to be a general approach to the corresponding amino derivatives (see Scheme 4 and Table 1). Hydrazine also reacts readily to furnish **6c**. At the same time, less nucleophilic aromatic amines require drastic conditions and use of DMF (instead of alcohols) as a solvent, as demonstrated by the reaction with *p*-anisidine affording **6k**. Interestingly, in this process 5-(dimethylamino)quinazolone **6g** is formed as a side product. The latter evidently results from the nucleophilic attack of the quinazolone **5** by dimethylamine, which, in turn, could arise from DMF upon prolonged heating with *p*-anisidine.[18]

Methylamine reacts with NH-quinazolone **4** much more slowly than with the N-methyl derivative **5** (cf. reaction time for **6a** and **6l**, Table 1). Methylamine probably acts as a base, abstracting an acidic NH-proton from the molecule **4** to form the corresponding anion, thus hampering the nucleophilic substitution.

Substitution selectivity was determined by ^{1}H NOE measurements. In a 2D ^{1}H NMR NOESY spectrum of the compound **6a** a cross-peak between the signals of methyl protons of the NHMe group (δ 2.94) and aromatic proton H(6) (δ 7.00) is observed, whereas a cross-peak between the signal at δ 2.94

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TABLE 1. Displacement of the Nitro Group with Amines in Quinazolones 4 and 5

product	R_1	R_2	R	*t*, h	*T*, °C	yield, %
6a[a]	CH_3	H	CH_3	2	80	85
6b	$PhCH_2$	H	CH_3	2	120	76
6c	NH_2	H	CH_3	2	80	68
6d	*cyclo*-C_3H_5	H	CH_3	2	120	72
6e	$Ph(CH_2)_2$	H	CH_3	2	120	74
6f	3,4-$(MeO)_2C_6H_3(CH_2)_2$	H	CH_3	2	120	83
6g[a]	CH_3	CH_3	CH_3	2	80	40
6h	$-(CH_2)_4-$		CH_3	2	120	49
6i	$-(CH_2)_5-$		CH_3	2	120	52
6j	$-(CH_2)_2O(CH_2)_2-$		CH_3	2	120	65
6k[b]	4-$MeOC_6H_4$	H	CH_3	10	100	35
6l[a]	CH_3	H	H	5	80	58

[a] EtOH used as a solvent. [b]DMF used as a solvent.

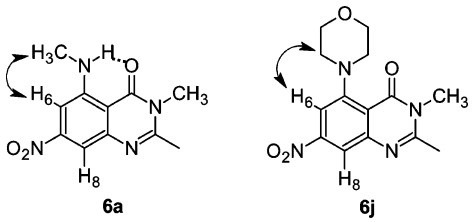
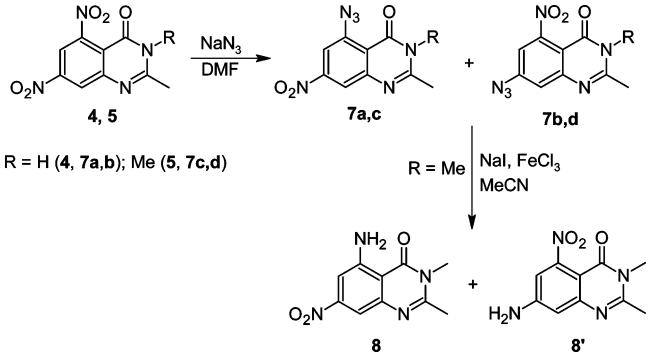


FIGURE 1. Key cross-peaks in 2D ^{1}H NMR NOESY spectra of **6a** and **6j**.

SCHEME 5. Reactions of Dinitroquinazolones 4, 5 with NaN_3



and a signal of aromatic proton H(8) (δ 7.21) is absent (Figure 1). This provides strong evidence of a $NHCH_3$ substituent entering position 5 (if it attacked position 7, then the corresponding cross-peaks would be observed for both H(6) and H(8) signals). It should be mentioned that the cross-peak between a signal of NH-proton (δ 8.83) and aromatic proton H(6) is not observed. Formation of an intramolecular hydrogen bond between the NH-proton and O atom of the carbonyl group could be a reasonable explanation for this fact (Figure 1).

In the same way, with the help of 2D NOE spectroscopy a morpholine substituent was shown to occupy position 5 in the **6j** molecule, as the methylamino group in **6a** does (Figure 1). Thus, both primary and secondary amines selectively attack the *peri*-position of 5,7-dinitroquinazolones in substitution reactions, with no isomeric products being observed.

Noteworthy, other nucleophiles fail to demonstrate such a high *peri*-selectivity. Thus, the nitro groups in quinazolones **4** and **5** undergo displacement with an azide anion to yield isomeric mixtures (ca. 6:1) in both cases (Scheme 5). To determine the relative ratio of azides **7c** and **7d**, a 2D NOE experiment was used, for which purpose the above azides were

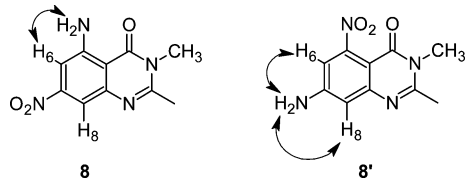
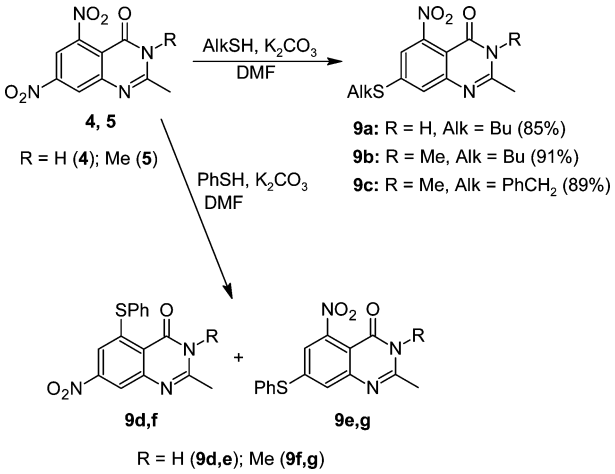


FIGURE 2. Key cross-peaks in 2D ^{1}H NMR NOESY spectra of **8** and **8′**.

SCHEME 6. Reactions of Dinitroquinazolones 4, 5 with S-Nucleophiles



converted in high yield to a mixture of amines **8** and **8′** via chemoselective reduction with NaI/$FeCl_3$ in MeCN.[19]

The 5-amino derivative **8** proved to be predominant, 7-amino isomer **8′** being a minor one (Figure 2). Hence, in the mixture of azides resulting from the nucleophilic substitution in 5,7-dinitroquinazolone **5**, 5-azido derivative **7c** (*peri*-isomer) also predominates over 7-azido derivative **7d** (*para*-isomer).

^{1}H NMR spectra of the mixtures (**7a** + **7b**) and (**7c** + **7d**) are quite similar − in both cases the signals of H(6) and H(8) protons of a minor isomer show a substantial upfield shift compared to the signals of a major one, and the corresponding chemical shifts are close (δ 7.83 and 7.98 ppm for the major isomer, δ 7.40 and 7.65 ppm for the minor one in the (**7a** + **7b**) mixture; δ 7.86 and 8.01 ppm for the major isomer, δ 7.42 and 7.69 ppm for the minor one in the (**7c** + **7d**) mixture). Thus, it is evident that a *peri*-substitution product (5-azido derivative **7a**) predominates in the (**7a** + **7b**) mixture as well.

While the azide anion preferentially attacks the *peri*-position, reactions of the compounds **4** and **5** with S- and O-nucleophiles often result in predominately *para*-substitution products. With S-nucleophiles substitution occurs in DMF at room temperature (Scheme 6). According to NOE measurements (Figure 3), with alkanethiols a nitro group in position 7 is displaced selectively (*para*-substitution), whereas thiophenol yields isomeric mixtures (3:1 for quinazolone **4** and 5:2 for **5**, with *peri*-isomers being major ones in both cases).

The reaction of compounds **4** and **5** with phenols requires more drastic conditions (80 °C compared to 20 °C with S-nucleophiles) and yields mixtures of isomers in all cases (Scheme 7), while aliphatic alcohols failed to afford substitution products.

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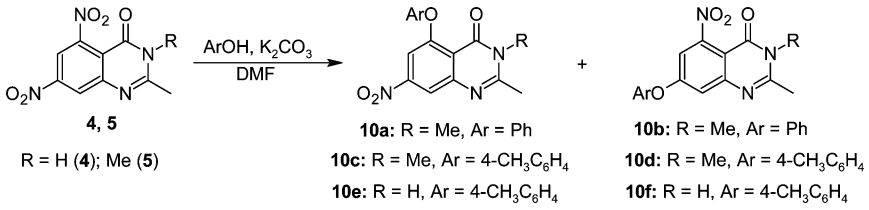
SCHEME 7. Reactions of Dinitroquinazolones 4, 5 with Phenols



According to a NOESY spectrum of an isomeric mixture resulting from a reaction between the quinazolone **5** and phenol (Figure 4), isomer **10b** with the phenoxy group in position 7 (*para*-isomer) is the major product, while isomer **10a** is a minor one (ratio 5:1). *Para*-substitution also predominates in reactions of the compounds **5** and **4** with *p*-cresol and phenol (ratios **10c/10d** and **10e/10f** are 1:6 and 1:4, respectively, according to NMR data).

As mentioned above, dinitro-substituted benzoannulated heterocyclic systems (both five- and seven-membered) undergo selective nucleophilic displacement of the nitro group (*peri*-group for five-membered heterocycles but *para*-group for the seven-membered one) with the various nucleophiles studied.[1−7] Thus, the incomplete selectivity of the nucleophilic substitution observed in the case of quinazolones and very strong dependence of the product ratio upon relatively minor changes of the structure of nucleophiles (i.e., $AlkS^-/ArS^-$ and ArS^-/ArO^-)[3b,20] are quite unusual. However, this is not at all unexpected; it is only natural to suppose that quinazolines, as six-membered benzoannulated heterocycles, should display a selectivity pattern somewhere between those of five- and seven-membered heterocycles.

It was assumed[7] that steric hindrance at the *peri*-position was more significant in the seven-membered benzoannulated heterocycle than in five-membered heterocycles (due to the different geometry of the molecule). At least, semiempirical calculations (method AM1, CS MOPAC application) demonstrated that the distance between the *peri*-carbon atom and O atom of the carbonyl group (which could be viewed as a measure of the steric hindrance, Scheme 8)[21] was noticeably shorter in 1,3-dinitrodibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-one **11** than in 3,5-dinitrophthalimide **B**[1b] (2.95 Å versus 3.20 Å, respectively),[7] while in 5,7-dinitroquinazoline-4(3*H*)-one **4** it is 2.98 Å.

Thus, quinazolones **4** and **5**, as six-membered benzoannulated heterocycles, evidently lie just between benzoannulated five- and seven-membered heterocycles both in terms of steric hindrance for the substitution and in selectivity of this process.

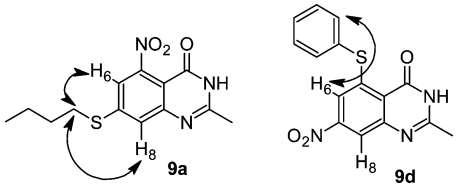


FIGURE 3. Key cross-peaks in 2D ^{1}H NMR NOESY spectra of **9a** and **9d**.

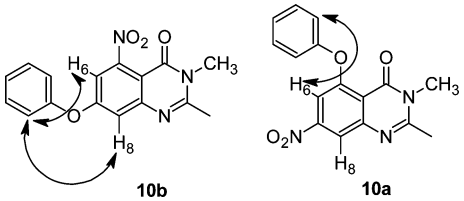
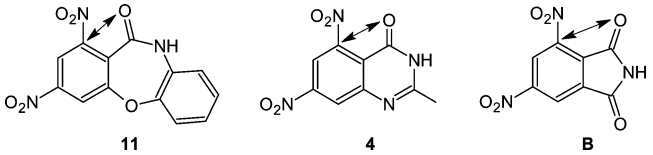
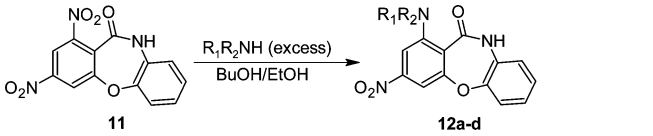


FIGURE 4. Key cross-peaks in 2D ^{1}H NMR NOESY spectra of **10a** and **10b**.

SCHEME 8. Relative Steric Hindrance in Some Benzoannulated Structures



SCHEME 9. Reaction of Dinitrodibenzoxazepinone 11 with Amines



12a: R_1 = H, R_2 = Me (77%)
12b: R_1 = H, R_2 = *cyclo*-C_3H_5 (88%)
12c: R_1, R_2 = - $(CH_2)_2O(CH_2)_2$ - (74%)
12d: R_1, R_2 = - $(CH_2)_5$ - (67%)

However, the high degree of *peri*-selectivity in the reaction of these quinazolones with amines still looked quite surprising. This prompted us to investigate the analogous reaction of 1,3-dinitrodibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-one **11**. To our surprise, amines (in contrast to O- and S-nucleophiles[7]) reacted with **11** with selective formation of *peri*-amino derivatives **12** (Scheme 9).

Selectivity of the substitution was confirmed by a 2D ^{1}H NMR NOESY spectrum of the compound **12a** (Figure 5). Notably, a cross-peak between a signal of NH-proton and aromatic proton H(2) is absent in the spectrum. The same phenomenon observed in the case of **6a** was accounted for by an intramolecular hydrogen bond between the NH-proton and O atom of the carbonyl group (Figure 1); thus, the analogous hydrogen bond might be present in **12a** as well.

Similarly, 2,4,6-trinitrobenzoic acid morpholide **13**[8] undergoes *ortho*-attack with methylamine to yield 2-methylamino derivative **14** (Scheme 10), though O-, S-nucleophiles and the azide anion selectively displace the *para*-nitro group of **13**.[8]

Thus, amines selectively attack ortho- (peri-) positions even of those very few known substrates (compound **11**[7] and tertiary

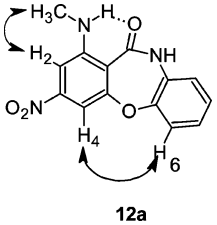
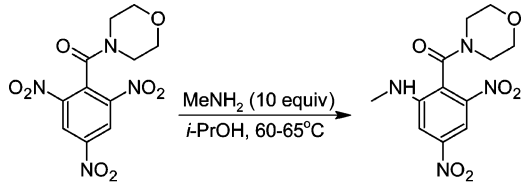


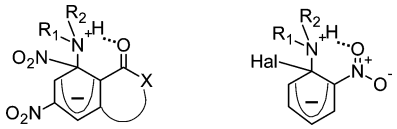
FIGURE 5. Key cross-peaks in 2D ^{1}H NMR NOESY spectrum of **12a**.

SCHEME 10. Reaction of 2,4,6-Trinitrobenzoyl Morpholide 13 with Methylamine



13 **14** (52%)

SCHEME 11. Stabilization of Anionic *σ*-Complexes by Intramolecular Hydrogene Bond



C **D**

amides of 2,4,6-trinitrobenzoic acid[8]), *which are selectively attacked in para-positions with other nucleophiles.* Such an "abnormal" substitution pattern is probably due to formation of a hydrogen bond between the amine proton and O atom of the carbonyl group, which stabilizes the intermediate *peri*-*σ*-complex **C** (Scheme 11). This assumption is in good agreement with the already mentioned 2D NOESY data providing evidence for the existence of a similar hydrogen bond in the substitution products **6a** and **12a** (see Figures 1 and 5). Such stabilization is impossible in the corresponding *para*-*σ*-complex and evidently is significant enough to "overpower" the steric factors favoring *para*-attack of the nucleophile (Scheme 8).

Noteworthy, this peculiar behavior of amines in nucleophilic substitution reactions (that is, their preferential attack in the position *ortho*- to the activating group) was reported earlier[22] for the displacement of halogen atoms in 2- and 4-halonitrobenzenes where formation of the intermediate **D** was postulated (in contrast to the complex **C**, in this case the nitro group rather than carbonyl is an acceptor of the hydrogen bond).

Experimental Section

Caution: Both we and other researchers[7,8,23] encountered no difficulties in working with multigram (0.1−0.5 kg) quantities of 2,4,6-trinitrobenzoic acid and its derivatives. Nevertheless, polynitroaromatic compounds are potential explosives, so proper protective measures (shields, glasses) should be used during experiments with these materials. Scale-up of the reported reactions requires appropriate chemical hazards testing.

2-Amino-4,6-dinitrobenzoic Acid (2). To a suspension of the acid **1** (20.0 g, 77.8 mmol) and $FeCl_3 \cdot 6H_2O$ (5.0 g, 18.5 mmol) in 400 mL of EtOH a mixture of 70% $N_2H_4 \cdot H_2O$ (30 mL), AcOH (40 mL), and water (10 mL) is added portionwise for 30 min upon stirring at 42−47 °C. The mixture is stirred at the same temperature for an additional 2 h and cooled. A precipitate is filtered off, washed with EtOH (3 × 5 mL), and suspended in water (50 mL), and the suspension is acidified to pH 3. The resulting yellow precipitate is filtered off and dried. Yield: 9.2 g (52%). An additional amount of the product (2.0 g) is collected after acidifying and concentrating the filtrate. Overall yield: 11.2 g (63%), mp 264−265 °C (decomp) (lit.[11] mp 268−270 °C (decomp). ^{1}H NMR (DMSO-d_6, δ): 7.67 (s, 1H), 7.89 (s, 1H). EI-MS (70 eV) (*m*/*z*, *I*, *%*): 227 [M^+, 27], 209 [72], 183 [79], 64 [100]. ^{13}C NMR (DMSO-d_6, δ): 104.2, 111.4, 114.1, 148.6, 150.1, 151.0, 165.2. Anal. Calcd for $C_7H_5N_3O_6$: C, 37.02; H, 2.22; N, 18.50. Found: C, 36.70; H, 2.38; N, 18.69.

2-Methyl-5,7-dinitro-4*H*-benzo[*d*][1,3]oxazine-4-one (3).[24] A suspension of 4,6-dinitroanthranilic acid **2** (10.0 g, 44.0 mmol) is refluxed in Ac_2O (70 mL) for 1 h. Some insoluble material is filtered off, and the filtrate is evaporated to $^1/_{10}$ of the initial volume. The precipitate is filtered off and washed with dry ether. Yield: 9.0 g (81%), mp 148−150 °C. Signals of **3** in ^{1}H NMR spectrum (DMSO-d_6, δ): 2.47 (s, 3H), 8.43 (d, J = 2.0 Hz, 1H), 8.88 (d, J = 2.0 Hz, 1H). EI-MS (70 eV) (*m*/*z*, *I*, *%*): 251 [M^+, 44], 236 [100], 207 [55], 43 [45]. Anal. Calcd for $C_9H_5N_3O_6$: C, 43.04; H, 2.01; N, 16.73. Found: C, 43.36; H, 2.29; N, 16.41.

Signals of 2-acetylamino-4,6-dinitrobenzoic acid in ^{1}H NMR spectrum (DMSO-d_6, δ): 2.11 (s, 3H), 8.51 (d, J = 2.0 Hz, 1H), 8.82 (d, J = 2.0 Hz, 1H), 10.36 (br.s, 1H).

2-Methyl-5,7-dinitroquinazoline-4(3*H*)-one (4). To a 6% aq. NH_3 (80 mL) benzoxazinone **3** (4.0 g, 15.9 mmol) is added portionwise under vigorous stirring. The mixture is refluxed with stirring for 10 min, then the solvent evaporated to dryness, water (20 mL) is added, and the insoluble residue is filtered off, washed with water, and dried. Yield: 3.6 g (90%), mp 296−299 °C (MeOH) (decomp). ^{1}H NMR (DMSO-d_6, δ): 2.42 (s, 3H), 8.46 (s, 1H), 8.67 (s, 1H), 13.03 (s, 1H). ^{13}C NMR (DMSO-d_6, δ): 21.6, 113.9, 115.2, 123.7, 148.5, 150.5, 150.7, 157.7, 158.9. EI-MS (70 eV) (*m*/*z*, *I*, *%*): 250 [M^+, 100], 204 [16], 158 [21], 90 [13]. Anal. Calcd for $C_9H_6N_4O_5$: C, 43.21; H, 2.42; N, 22.40. Found: C, 42.93; H, 2.28; N, 22.67.

2,3-Dimethyl-5,7-dinitroquinazoline-4(3*H*)-one (5). (Procedure A − alkylation of the compound **4**). To a solution of quinazolinone **4** (2.0 g, 8.0 mmol) and NaOH (0.48 g, 12.0 mmol) in water (15 mL) $(CH_3)_2SO_4$ (1.51 g, 12.0 mmol) is added with stirring. The mixture is stirred for 1 h at room temperature. The resulting precipitate is filtered off, washed with 10% aq. NH_3 (3 × 10 mL) and then with water, and dried. Yield: 1.8 g (85%), mp 206−208 °C (EtOH). ^{1}H NMR (DMSO-d_6, δ): 2.65 (s, 3H), 3.53 (s, 3H), 8.47 (s, 1H), 8.70 (s, 1H). ^{13}C NMR (DMSO-d_6, δ): 23.4, 31.2, 114.0, 114.2, 124.1, 148.5, 148.7, 150.4, 157.2, 160.1. EI-MS (70 eV) (*m*/*z*, *I*, *%*): 264 [M^+, 100], 236 [19], 206 [21], 103 [26]. Anal. Calcd for $C_{10}H_8N_4O_5$: C, 45.46; H, 3.05; N, 21.21. Found: C, 45.09; H, 2.80; N, 21.53.

Procedure B (recyclization of the compound **3**). To a solution of 40% aq. methylamine (0.5 mL, 6.5 mmol) in EtOH (10 mL) is added benzoxazinone **3** (1.0 g, 4.0 mmol) under vigorous stirring. The mixture is refluxed with stirring for 10 min, and the solvent is evaporated to dryness. The residue is washed with water and dried. Yield: 0.61 g (58%), mp 206−208 °C (EtOH).

5-Methylamino-2,3-dimethyl-7-nitroquinazoline-4(3*H*)-one (6a) (from 3). A solution of benzoxazinone **3** (0.38 g, 1.52 mmol) and 40% aq. methylamine (1.2 mL, 15 mmol) in EtOH (10 mL) is refluxed with stirring for 4 h and cooled. The precipitate thus

(20) Dalinger, I. L.; Cherkasova, T. I.; Vorob'ev, S. S.; Aleksandrov, A. V.; Popova, G. P.; Shevelev, S. A. *Russ. Chem. Bull.* **2001**, *50*, 2401.

(21) The absence of a carbonyl group could favor *peri*-substitution by decreasing the steric hindrance (in particular, this factor could be essential for annulated six- and seven-membered heterocycles). Thus, the latest data show that reaction of 3-acetyl-2-methyl-5,7-dinitroquinoline with PhSH results in selective *peri*-substitution: Mezhnev, V. V.; Dutov, M. D.; Sapozhnikov, O. Yu.; Kachala, V. V.; Shevelev, S. A. *Mendeleev Commun.* **2007**, 234. For more detailed discussion, see Supporting Information.

(22) (a) De Boer, T. J.; Dirkx, I. P. In *The Chemistry of the Nitro and Nitroso Groups. Part 1*; Feuer, H., Ed.; Interscience: New York, 1969; Chapter 8. (b) Terrier, F. *Nucleophilic Aromatic Displacement: the Influence of the Nitro Group*; VCH Publishers: New York, 1991; pp 36−38.

(23) (a) *Organic Syntheses*; Wiley & Sons: New York, 1941; Collect. Vol. I, p 541. (b) *Organic Syntheses*; Wiley & Sons: New York, 1941; Collect. Vol. I, p 455.

(24) In the ^{1}H NMR spectrum of **3**, signals of 2-acetylamino-4,6-dinitrobenzoic acid are present, evidently due to hydrolysis of **3** in water-containing DMSO-d_6. This instability of 2-methylbenz[*d*][1,3]oxazine-4-ones (which leads, in particular, to the problems with NMR spectra interpretation) is well known: Rocco, S. A.; Barbarini, J. E.; Rittner, R. *Synthesis* **2004**, 429 and references cited therein.

formed is filtered off and washed with MeOH. Yield: 0.18 g (62%). Red crystals, mp 192−195 °C (EtOH). ^{1}H NMR (DMSO-d_6, δ): 2.55 (s, 3H), 2.94 (d, J = 5.0 Hz, 3H), 3.47 (s, 3H), 7.00 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 2.1 Hz, 1H), 8.83 (br.q, J = 5.0 Hz, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 23.1, 29.4, 30.4, 96.7, 105.0, 107.3, 149.6, 151.5, 151.7, 157.0, 162.8. EI-MS (70 eV) (*m*/*z*, *I*, %): 248 [M^+, 77], 202 [6], 56 [100]. Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.49; H, 4.71; N, 22.38.

Preparation of 5-Alkylamino-2,3-dimethyl-7-nitroquinazoline-4(3*H*)-ones 6a−j (General Procedure). A solution of 2,3-dimethyl-5,7-dinitroquinazolinone **5** (0.4 g, 1.52 mmol) and the corresponding amine (6.06 mmol) (in the case of methylamine and dimethylamine, a 10-fold excess of 40% aq. solution is used) in BuOH (5 mL) (in the case of methylamine and dimethylamine, EtOH is used) is refluxed for 1 h and cooled. The precipitate thus formed is filtered off in 3 h and washed with MeOH. The resulting red crystals could be recrystallized from EtOH (**6a, c**) or MeCN (**6b, d−j**).

5-((4-Methoxyphenyl)amino)-2,3-dimethyl-7-nitroquinazoline-4(3*H*)-one (6k). A solution of 2,3-dimethyl-5,7-dinitroquinazolinone **5** (0.26 g, 1.0 mmol) and *p*-methoxyaniline (0.37 g, 3.0 mmol) in DMF (5 mL) is stirred at 100 °C for 10 h. The mixture is poured into water (100 mL) and acidified to pH 3, and the precipitate is filtered off and purified by flash-chromatography (silica gel, eluent: heptane−EtOAc from 9:1 to 1:1). Yield: 0.12 g (35%). Red powder, mp 150−152 °C (MeCN). ^{1}H NMR (DMSO-d_6, δ): 2.60 (s, 3H), 3.52 (s, 3H), 3.80 (s, 3H), 7.05 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 2.1 Hz, 1H), 10.51 (br.s, 1H). EI-MS (70 eV) (*m*/*z*, *I*, %): 340 [M^+, 100], 325 [70], 279 [31], 165 [30]. Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 60.26; H, 4.81; N, 16.22.

5-Methylamino-2-methyl-7-nitroquinazoline-4(3*H*)-one (6l). A solution of 2-methyl-5,7-dinitroquinazolinone **4** (0.38 g, 1.52 mmol) and 40% aq. methylamine (1.2 mL, 15 mmol) in EtOH (5 mL) is refluxed for 5 h and cooled. The resulting precipitate is filtered off and washed with MeOH. Yellowish-brown crystals. Yield: 0.21 g (58%), decomp > 290 °C (EtOH). ^{1}H NMR (DMSO-d_6, δ): 2.31 (s, 3H), 2.92 (d, J = 5.0 Hz, 3H), 7.01 (d, J = 2.1 Hz, 1H), 7.23 (d, J = 2.1 Hz, 1H), 8.79 (br.s, 1H); 12.37 (br.s, 1H). EI-MS (70 eV) (*m*/*z*, *I*, %): 234 [M^+, 100], 188 [34], 159 [32], 147 [73]. Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.59; H, 4.39; N, 23.76.

5-Azido-2-methyl-7-nitroquinazoline-4(3*H*)-one (7a), 7-Azido-2-methyl-5-nitroquinazoline-4(3*H*)-one (7b). A suspension of 2-methyl-5,7-dinitroquinazolinone **4** (0.38 g, 1.52 mmol) and NaN_3 (0.10 g, 1.54 mmol) in DMF (7 mL) is stirred at 60 °C for 2 h. The mixture is poured into water (100 mL) and acidified to pH 3. The precipitate is filtered off and washed with water. Yield of the mixture of isomers is 0.26 g. Additional amount of the product (0.05 g) is obtained by extraction of the filtrate with EtOAc and evaporation of the solvent. Total yield is 0.31 g (83%). The major isomer is 5-azido-2-methyl-7-nitroquinazoline-4(3*H*)-one **7a**, decomp > 170 °C (50% aq. MeCN). ^{1}H NMR (DMSO-d_6, δ): 2.37 (s, 3H), 7.83 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 12.58 (br.s., 1H). EI-MS (70 eV) (*m*/*z*, *I*, %): 221 [20], 220 [M^+ − 26, 100], 218 [15]. Anal. Calcd for $C_9H_6N_6O_3$: C, 43.91; H, 2.46; N, 34.14. Found: C, 44.24; H, 2.23; N, 33.90. Signals of minor isomer **7b** observed in the spectrum: 7.40 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H). Ratio **7a/7b** 6:1.

5-Azido-2,3-dimethyl-7-nitroquinazoline-4(3*H*)-one (7c), 7-Azido-2,3-dimethyl-5-nitroquinazoline-4(3*H*)-one (7d). Prepared from **5** as described above for **7a** and **7b**. Yield of the mixture of isomers: 85%. EI-MS (70 eV) (*m*/*z*, *I*, %): 260 [M^+, 4], 234 [M^+ − 26, 44], 232 [48], 186 [72], 56 [100]. Major isomer is 5-azido-2,3-dimethyl-7-nitroquinazoline-4(3*H*)-one **7c**. ^{1}H NMR (DMSO-d_6, δ): 2.60 (s, 3H), 3.50 (s, 3H), 7.86 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H). Signals of minor isomer **7d** observed in the spectrum: 2.59 (s, 3H), 3.48 (s, 3H), 7.42 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H). Ratio **7c/7d** 6:1.

5-Amino-2,3-dimethyl-7-nitroquinazoline-4(3*H*)-one (8), 7-Amino-2,3-dimethyl-5-nitroquinazoline-4(3*H*)-one (8′). To a solution of the mixture of isomers **7c** and **7d** (0.34 g, 1.31 mmol) in MeCN (10 mL) NaI (1.77 g, 11.78 mmol) and $FeCl_3$ (0.32 g, 1.96 mmol) are added. The mixture is stirred for 30 min and filtered. The filtrate is evaporated to dryness, and the residue is washed with 10% aq. $Na_2S_2O_3$ and then with water. Yield of the mixture of isomers: 0.28 g (92%). Red crystals. Major isomer is 5-amino-2,3-dimethyl-7-nitroquinazoline-4(3*H*)-one **8**. ^{1}H NMR (DMSO-d_6, δ): 2.55 (s, 3H), 3.47 (s, 3H), 7.17 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.65 (br.s., 2H). Signals of the minor isomer **8′** in ^{1}H NMR spectrum (DMSO-d_6, δ): 2.56 (s, 3H), 3.40 (s, 3H), 6.55 (br.s, 2H), 6.66 (s, 1H), 6.82 (s, 1H). Ratio **8/8′** 6:1. EI-MS (70 eV) (*m*/*z*, *I*, %): 234 [M^+, 67], 204 [22], 188 [47], 56 [100].

Preparation of 7-Alkylsulfanyl-5-nitroquinazoline-4(3*H*)-ones 9a−c (General Procedure). A suspension of 5,7-dinitroquinazolinone **4** or **5** (1.50 mmol), a corresponding alkanethiol (1.52 mmol), and K_2CO_3 (0.31 g, 2.27 mmol) in DMF (7 mL) is stirred for 40 min at rt. The mixture is poured into water (100 mL) and acidified to pH 3. The precipitate is filtered off and washed with water.

7-Butylsulfanyl-2-methyl-5-nitroquinazoline-4(3*H*)-one (9a). Yield: 85%, mp 218−220 °C (MeOH). ^{1}H NMR (DMSO-d_6, δ): 0.91 (t, 3H, J = 7.5 Hz); 1.43 (m, 2H), 1.62 (m, 2H), 2.36 (s, 3H), 3.18 (t, J = 7.5 Hz, 2H), 7.54 (s, 1H), 7.71 (s, 1H), 12.53 (br.s, 1H). ^{13}C NMR (DMSO-d_6, δ): 13.5, 21.4, 21.5, 30.0, 30.4, 107.6, 117.5, 123.8, 146.8, 148.4, 150.2, 157.2, 158.0. EI-MS (70 eV) (*m*/*z*, *I*, %): 294 [12], 293 [M^+, 82], 237 [100]. Anal. Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32; S, 10.93. Found: C, 53.51; H, 5.27; N, 14.12; S, 10.65.

2-Methyl-7-nitro-5-(phenylsulfanyl)quinazoline-4(3*H*)-one (9d), 2-Methyl-5-nitro-7-(phenylsulfanyl)quinazoline-4(3*H*)-one (9e). A suspension of 2-methyl-5,7-dinitroquinazolinone **4** (0.70 g, 2.80 mmol), thiophenol (0.58 g, 4.20 mmol) and K_2CO_3 (0.58 g, 2.80 mmol) in DMF (10 mL) is stirred for 40 min at rt. The resulting precipitate is filtered off and washed with water to yield 2-methyl-7-nitro-5-(phenylsulfanyl)quinazolin-4(3*H*)-one **9d**. Yield: 0.44 g (50%). Yellow crystals, mp 260−263 °C (DMF). ^{1}H NMR (DMSO-d_6, δ): 2.38 (s, 3H), 7.11 (s, 1H), 7.64 (m, 5H), 7.84 (s, 1H), 12.56 (br.s, 1H). EI-MS (70 eV) (*m*/*z*, *I*, %): 313 [M^+, 100], 266 [18], 171 [23]. Anal. Calcd for $C_{15}H_{11}N_3O_3S$: C, 57.50; H, 3.54; N, 13.41; S, 10.23. Found: C, 57.92; H, 3.58; N, 13.30; S, 10.33. The filtrate is poured into water (100 mL) and acidified to pH 3, and the precipitate is filtered off and washed with water. Yield of the mixture of isomers **9d** and **9e**: 0.23 g (26%). Overall ratio **9d/9e** 3:1.

Reaction of 5,7-Dinitroquinazoline-4(3*H*)-ones 4 and 5 with Phenols (Preparation of 10a−f, General Procedure). A suspension of 5,7-dinitroquinazolinone **4** or **5** (1.52 mmol), a corresponding phenol (1.56 mmol), and K_2CO_3 (0.32 g, 2.34 mmol) in DMF (7 mL) is stirred at 80 °C for 4 h. The mixture is poured into water (100 mL) and acidified to pH 3, and the precipitate is filtered off and dissolved in benzene (20 mL). The filtrate is extracted with benzene (3 × 20 mL). The combined benzene solutions are filtered through silica gel, and the solvent evaporated to dryness.

2,3-Dimethyl-7-nitro-5-phenoxyquinazoline-4(3*H*)-one (10a), 2,3-Dimethyl-5-nitro-7-phenoxyquinazoline-4(3*H*)-one (10b). Yield of the mixture of isomers: 55%. Major isomer is 2,3-dimethyl-5-nitro-7-phenoxyquinazoline-4(3*H*)-one **10b**. ^{1}H NMR (DMSO-d_6, δ): 2.52 (s, 3H), 3.46 (s, 3H), 6.90 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 2H), 7.64 (d, J = 2.0 Hz, 1H). Signals of the minor isomer **10a**: 2.60 (s, 3H), 3.47 (s, 3H), 7.07 (d, J = 8.1 Hz, 2H), 7.22 (t, J = 8.1 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.43 (t, J = 8.1 Hz, 2H), 7.99 (d, J = 2.0 Hz, 1H). EI-MS (70 eV) (*m*/*z*, *I*, %): 311 [M^+, 35], 281 [53], 253 [24], 97 [65], 56 [100]. Ratio **10a/10b** 1:5.

Preparation of 1-Alkylamino-3-nitrodibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-ones 12a−d (General Procedure). A suspension of 1,3-

dinitrodibenz[*b,f*][1,4]oxazepine-11(10*H*)-one **11** (0.40 g, 1.33 mmol) and the corresponding amine (5.5 mmol) (in the case of methylamine, a 10-fold excess of 40% aq. solution is used) in BuOH (5 mL) (in the case of methylamine, EtOH is used) is refluxed for 4 h and cooled. The mixture is kept overnight, and the resulting crystals are filtered off and washed with MeOH (2 × 3 mL).

1-Methylamino-3-nitrodibenz[*b,f*][1,4]oxazepine-11(10*H*)-one (12a). Yield: 77%, mp 260−262 °C. ^{1}H NMR (DMSO-d_6, δ): 2.87 (d, J = 5.4 Hz, 3H), 7.14−7.23 (m, 4H), 7.30 (d, J = 2.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.50 (br.q, J = 5.4 Hz, 1H), 10.81 (br.s, 1H). EI-MS (70 eV) (*m*/*z*, *I*, *%*): 285 [M^+, 100], 268 [22], 238 [48], 211 [30]. Anal. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.66; H, 3.99; N, 14.95.

2-Methylamino-4,6-dinitrobenzoic Acid Morpholide (14). A solution of 2,4,6-trinitrobenzoyl morpholide **13**[8] (0.65 g, 2 mmol) and 40% aq. methylamine (1.6 mL, 20 mmol) in *i*-PrOH (5 mL) is stirred for 1 h at 60−65 °C. Upon cooling, the resulting precipitate is filtered off and washed with MeOH. Yield 0.25 g. The filtrate is filtered through silica gel, the solvent evaporated to dryness, and the residue crystallized from *i*-PrOH to afford an additional 0.07 g of the product. Yellowish-brown crystals. Total yield 52%, mp 216−218 °C. ^{1}H NMR (DMSO-d_6, δ): 2.87 (d, J = 4.7 Hz, 3H), 3.20 (m, 2H), 3.50−3.65 (m, 4H), 3.71 (m, 1H), 3.84 (m, 1H), 6.40 (br.q, J = 4.7 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H). EI-MS (70 eV) (*m*/*z*, *I*, *%*): 310 [M^+, 31], 224 [42], 86 [48], 56 [100]. Anal. Calcd for $C_{12}H_{14}N_4O_6$: C, 46.45; H, 4.55; N, 18.06. Found: C, 46.77; H, 4.62; N, 17.78.

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Supporting Information Available: Additional comments to Scheme 8, characterization data for compounds **6b**−**j**, **9b,c,f,g**, **10c**−**f**, **12b**−**d**; ^{1}H NMR spectra for all compounds described in this paper (**2**−**5**, **6a**−**l**, **7a**−**d**, **8**, **8′**, **9a**−**g**, **10a**−**f**, **12a**−**d**, **14**); ^{13}C NMR spectra for **2**, **4**, **5**, **6a**, **9a**; and 2D ^{1}H NMR NOESY spectra of the following compounds and mixtures: **6a**, **6j**, (**8** + **8′**), **9a**, **9d**, (**10a** + **10b**), **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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