An Efficient Procedure for the Synthesis of 5*H*-6-Substituted-pyrazolo[1,5-*d*]-1,2,4-triazine-4,7-diones

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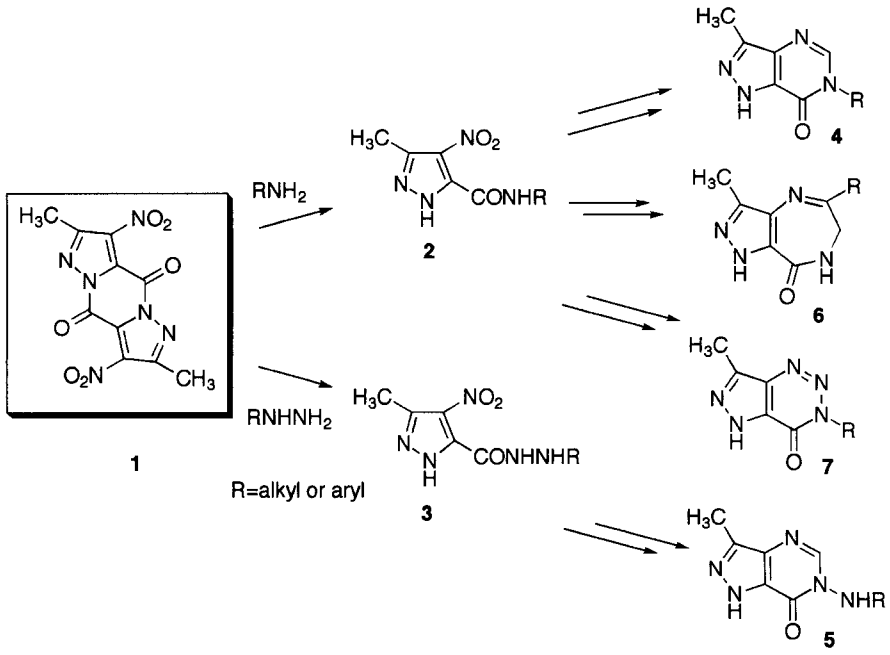
Abstract: A new series of 5,6-dihydropyrazolo[1,5-*d*]-1,2,4-triazine-4,7-diones substituted in the 6-position with various phenyl substituents has been synthesized and found to have activity, owing to their acylating properties, as inhibitors of the serine protease enzymes.

Key words: dioxopiperazine, 5-pyrazolecarboxhydrazides cyclization, trichloromethyl chloroformate, protease inhibitors

In several publications, we have reported the reactivity of the 2,7-dimethyl-3,8-dinitrodipyrazolo[1,5-*a*; 1',5'-*d*]-py-razine-4,9-dione (**1**)[1] towards nucleophilic reagents such as aliphatic and aryl amines/hydrazines to give the corresponding 3-methyl-4-nitropyrazole-5-carboxamides/hydrazides **2** and **3**, respectively, in high yields (Scheme 1). These latter compounds has been disclosed by our group as key chemical intermediates in the synthesis of 6-sub-stituted-3-methyl-1*H*-pyrazolo[4,3-*d*]pyrimidine-7(6*H*)-ones **4**,[2] 6-arylamino-substituted-3-methyl-1*H*-pyraz-olo[4,3-*d*]pyrimidine-7(6*H*)-ones **5**[3], 5-aryl-substituted-3-methyl-6,7-dihydropyrazolo[4,3-*e*]-[1,4]diazepin-8(7*H*)-ones **6**[4] and 4-substituted-7-methyl-5H-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones **7**[5].

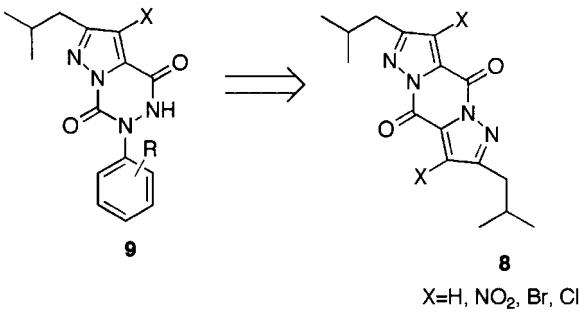
These results prompted us to the design and synthesis of some related 6-aryl-substituted-*5H*-pyrazolo[1,5-*d*]-1,2,4-triazine-4,7-diones of general formula **9** utilizing dipyrazolo[1,5-*a*; 1',5'-*d*]pyrazine-4,9-diones of general formula **8** as starting material (Scheme 2). Only Rabba et al.[6] have reported an efficient method for the synthesis of 5,6-dihydropyrazolo[1,5-*d*]-1,2,4-triazine-4,7-diones (with an hydrogen or bromine in the 3 position), which were achieved submitting to cyclization the *N*-carbethoxy hydrazides of the corresponding pyrazole-5-carboxylic acids under alkaline conditions.

In the course of an in vitro screening program of evaluation of new molecular entities, as Human Leukocyte elastase (HLE) inhibitors,[7] we have tested all these derivatives of general formula **9** as a novel class of serine protease inhibitors and more generally as a novel family of anti-proteases, endowed with a great therapeutical potential. The acyl–pyrazole bond of these pyrazolotriazinediones is thought to be involved in the mechanism of inhibition of the serine proteases. Therefore, on the basis of these findings, this new series of triazinones might be useful in the therapy of different inflammatory and immune diseases, including respiratory and muscoloskeletal pathologies. In particular, these compounds might repre-



Scheme 1

sent an important tool in the treatment of emphysema, cystic fibrosis, chronic bronchitis as well as osteoarthritis and osteoporosis.[8]

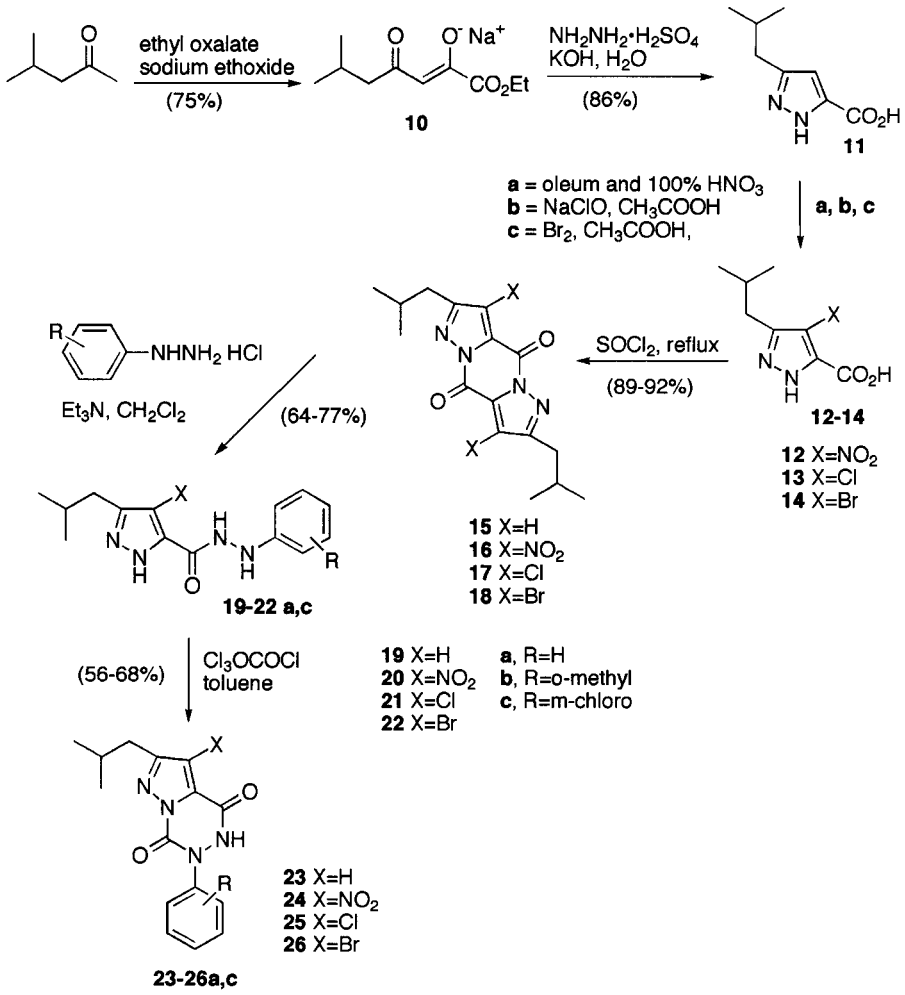


Scheme 2

In our synthetic strategy, triazinones of general formula **9** are obtained by a multistep process starting from the 3-isobutyl-5-pyrazolecarboxylic acid **11**, easily obtained by a well-known method which consists of the condensation between the hydrazine sulfate and the sodium enolate of the a,g dioxo carboxylic esters **10**[9] (prepared by Claisen condensation between isobutyl methyl ketone and diethyl oxalate in the presence of sodium ethoxide). This pyrazole derivative **11** has been subsequently nitrated with a mixture of fuming nitric acid and fuming sulfuric acid at 100°C or subjected to direct halogenation (with NaClO or Br_2 in HOAC) to give rise to their 4-substituted-5-pyrazolecarboxylic acid **12**, **13** and **14**, respectively. The treatment of **11** and these 4-substituted intermediates **12–14** with refluxing thionyl chloride for 18 h, to give the dioxopiperazines **15–18**, followed by the treatment with different phenylhydrazines allowed to obtain as expected, very high yields of the hydrazides **19a–c, 20a–c, 21a–c** and **22a–c** (Table 1).

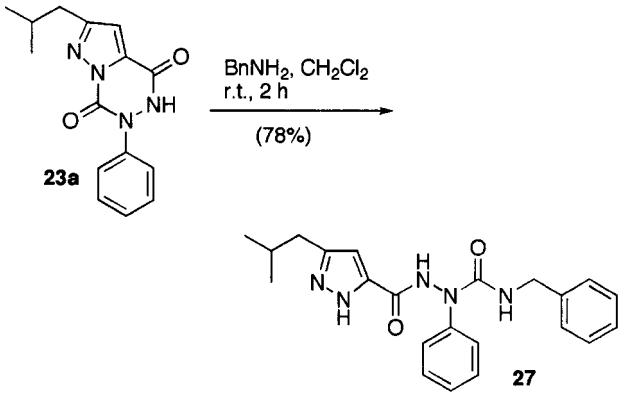
The cyclization of hydrazides **19–22a,c** with a slight excess (1.1 equiv.) of trichloromethyl chloroformate gave the corresponding 6-arylsubstituted-5*H*-pyrazolo[1,5-*d*]-1,2,4-triazine-4,7-diones **23 a–c, 24 a–c, 25 a–c** and **26 a–c** in good yields (Scheme 3 and Table 2).

In order to demonstrate the chemical reactivity of the acyl–pyrazole bond in this family of new pyrazolotriazinones **23–26 a,c** towards nucleophiles, we performed the reaction of the 2-isopropyl-6-phenyl-5*H*-pyrazolo[1,5-*d*]-1,2,4-triazine-4,7-dione **23a** with benzyl amine. This re-



Scheme 3

action gives rise to the formation of the corresponding product of addition, the acyl semicarbazide **27**, in high yield (Scheme 4).



Scheme 4

The general procedure here described is not necessarily limited to the only pyrazolo-5-carboxylic acid but appears of larger applicability, allowing us to aim at a wide number of different and closely related bicyclic and tricyclic fused 1,2,4-triazinediones.

All reactions were carried out under an inert atmosphere of Ar, unless otherwise described. Standard syringe techniques were applied for transferring anhyd solvents. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merk plates) and visualized with aq $KMnO_4$. ^1H NMR spectra were obtained in DMSO-d_6 or $CDCl_3$ solutions with a Bruker AC 200 spectrometer. Chemical shifts (d) are given in ppm upfield from TMS. Mps were determined on a Buchi-Tottoli apparatus and are uncorrected. Chromatography was performed with Merck 60–200 mesh silica gel. All products reported showed ^1H NMR spectra in agreement with the assigned structures. Organic solutions were dried over anhyd $MgSO_4$. Anhyd CH_2Cl_2 was distilled from $CaCl_2$ prior to use. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara. Mass spectra were performed with Maldi-Toff Helwett Packard G 2025 A instrument.

3-Isobutylpyrazole-5-carboxylic Acid (11)
The sodium salt of ethyl 6-methyl-2,4-dioxoheptanoate (45 g, 0.217 mol) was added in small portions to a 2 M aq KOH (100 mL) cooled to 0˚C. After 30 min at this temperature, hydrazine sulfate (25 g, 0.5 mol) was slowly added to this solution. After 10 min, the deposited white precipitate was collected by filtration and dried (P_2O_5) to give the pyrazole **11** (21 g, 58% yield) as a white solid. mp = 184 ˚C.

^1H NMR ($CDCl_3$): d = 0.84 (d, 6H, *J* = 6.4 Hz), 1.86 (m, 1H), 2.47 (m, 2H), 6.48 (s, 1H), 11.5 (br s, 1H), 13 (br s, 1H).

IR (KBr, cm^{-1}): n = 3200, 1710, 1356, 1210, 1015.

3-Isobutyl-4-nitropyrazole-5-carboxylic Acid (12)
To a mixture of fuming H_2SO_4 (29 mL, 27–33% SO_3) and 100% HNO_3 (19 mL) cooled to 0˚C, was added portionwise **11** (20 g; 19 mmol) with stirring. The solution was then heated at 100˚C for 6 h., cooled to ambient temperature and poured into ice. The resulting precipitate was collected, recrystallized from water and dried to give the product **12** as white needles (19.6 g, 84% yield), mp = 177–180˚C.

^1H NMR (DMSO-d_6): d = 0.89 (d, 6H, *J* = 6.2 Hz), 1.86 (m, 1H), 2.77 (m, 2H, *J* = 8 Hz), 13.8 (br s, 1H), 14 (s, 1H).

IR (KBr, cm^{-1}): n = 3180, 2820, 2785, 1700, 1410, 1320, 635.

4-Chloro-3-isobutylpyrazole-5-carboxylic Acid (13)
To a solution of 3-isobutylpyrazole-5-carboxylic acid **11** (3 g; 17.9 mmol) in glacial HOAc (50 mL) cooled at 0˚C was added portionwise aq 14% sodium hypochlorite (d = 1.25) (38 mL; 71.5 mmol of NaClO).The solution should be acid (pH = 5), and the mixture can be adjusted to acid pH with concentrated glacial HOAc. After being stirred at r.t. for 4 h, the solvent was evaporated and the residue crystallized from Et_2O/petroleum ether, to give the product **13** (3.2 g, 90% yield) as white solid, m.p.=205˚C.

^1H NMR (DMSO-d_6) d = 0.85 (d, 6H, *J* = 6 Hz), 1.92 (m, 1H), 2.42 (m, 2H, *J* = 7 Hz), 2.49 (s, 1H), 11 (br s, 1H).

IR (KBr, cm^{-1}): n = 3200, 2810, 2760, 1430, 1340, 650.

4-Bromo-3-isobutylpyrazole-5-carboxylic Acid (14)
To a solution of 3-isobutylpyrazole-5-carboxylic acid **11** (3 g; 17.9 mmol) in glacial HOAc (50 ml) cooled at 0˚C was added dropwise Br_2 (3.7 g; 23.21 mmol). After being stirred at r.t. for 4 h, the solvent was evaporated and the residue crystallized from Et_2O/petroleum ether, to give the product **14** (4.14 g; 94% yield) as pale yellow solid, mp = 199˚C.

^1H NMR (DMSO-d_6): d = 0.83 (d, 6H, *J* = 6 Hz), 1.98 (m, 1H), 2.46 (m, 2H, *J* = 8 Hz), 2.51 (s, 1H), 8.13 (br s, 1H).

IR (KBr, cm^{-1}): n = 3170, 2800, 2760, 1410, 1320, 640.

2,7-Diisobutyl-3,8-disubstituted-dipyrazolo[1,5-*a*;1',5'-*d*]-pyrazine-4,9-dione (15–18); General Procedure
A mixture of 3-isobutyl-4-substituted-pyrazole-5-carboxylic acid (15 mmol) and thionyl chloride (10.9 ml, 150 mmol, 10 equiv.) was heated under reflux for 18 h. The mixture was then cooled and excess thionyl chloride removed by evaporation under vacuo. The residue was used without purification for the next reaction.

2,7-Diisobutyldipyrazolo[1,5-*a*;1',5'-*d*]pyrazine-4,9-dione (15)
Using a procedure similar to that described above, **15** (85% yield) was obtained as a pale yellow solid, mp = 130˚C.

^1H NMR (DMSO-d_6): d = 0.92 (d, 12H, *J* = 6.4 Hz), 2.03 (m, 2H), 2.58 (m, 4H, *J* = 8 Hz), 7.40 (s, 2H).

IR (KBr, cm^{-1}): n = 3000, 1780, 1470, 1420, 1290, 1090, 860, 780, 720.

FAB (Maldi-Toff): *m/z* = 301.6 $[M+1]^+$.

2,7-Diisobutyl-3,8-dinitrodipyrazolo[1,5-*a*;1',5'-*d*]pyrazine-4,9-dione (16)
Using a procedure similar to that described above, **16** (88% yield) was obtained as a yellow solid, mp = 196˚C.

^1H NMR ($CDCl_3$): d = 0.88 (d, 6H, *J* = 6.4 Hz), 0.99 (d, 6H, *J* = 6.4 Hz), 1.93 (m, 1H), 2.11 (m, 1H), 2.72 (m, 2H, *J* = 8 Hz), 2.93 (d, 2H, *J* = 8 Hz).

IR (KBr, cm^{-1}): n = 3000, 1780, 1560, 1480, 1430, 1370, 1280, 1100, 865, 790, 730.

FAB (Maldi-Toff): *m/z* = 393.5 $[M+1]^+$.

3,8-Dichloro-2,7-diisobutyldipyrazolo[1,5-*a*;1',5'-*d*]pyrazine-4,9-dione (17)
Using a procedure similar to that described above, **17** (80% yield) was obtained as a yellow solid; 80% yield; mp = 257˚C.

^1H NMR ($CDCl_3$): d = 0.99 (d, 12H, *J* = 6.4 Hz), 2.23 (m, 2H), 2.73 (m, 4H, *J* = 8 Hz).

IR (KBr, cm^{-1}): n = 3000, 1770, 1550, 1480, 1400, 1300, 1100, 840, 750.

FAB (Maldi-Toff): *m/z* = 372.3 $[M+1]^+$.

3,8-Dibromo-2,7-diisobutyldipyrazolo[1,5-*a*;1',5'-*d*]pyrazine-4,9-dione (18)

Using a procedure similar to that described above, **18** (88% yield) was obtained as a yellow solid. mp = 208°C.

^{1}H NMR ($CDCl_3$) d = 0.98 (d, 12H, *J* = 6.4 Hz), 2.11 (m, 2H), 2.69 (m, 4H, *J* = 7.4 Hz).

IR (KBr, cm^{-1}): n = 3000, 1780, 1550, 1450, 1430, 1280, 1050, 840, 770, 730.

FAB (Maldi-Toff): *m/z* = 461.2 $[M+1]^+$.

3-Isobutyl-4-substituted-pyrazole-5-carboxyhydrazides (19–22 a,c); General Procedure

To a stirred solution of Et_3N (1.5 ml, 11 mmol, 2.2 equiv.) in 100 mL of CH_2Cl_2, cooled at 0°C, was added the appropriate phenylhy-

Table 1 *N2*-Phenylsubstituted 3-Isobutyl-4-substituted-pyrazole-5-carboxhydrazides **19–22 a,c** Prepared

Compound	R	X	Yield[a] (%)	mp (°C)	^{1}H NMR (DMSO-d_6) δ	IR (KBr) cm^{-1}
19a	H	H	78	197	0.89 (d, 6H, *J* = 6 Hz), 1.9 (m, 1H), 2.51 (d, 2H, *J* = 7.2 Hz), 6.45 (s, 1H), 6.59 (d, 1H, *J* = 7.8 Hz), 6.71 (t, 2H, *J* = 7.8 Hz), 7.13 (t, 2H, *J* = 7.8 Hz), 7.82 (s, 1H), 9.94 (s, 1H), 13.01 (s, 1H)	3340, 2820, 1720, 1630, 1520, 1400, 880, 770
20a	H	NO_2	83	189	0.92 (d, 6H, *J* = 6.2 Hz), 2.10 (m, 1H), 2.51 (d, 2H, *J* = 7.4 Hz), 6.77 (t, 1H, *J* = 7 Hz), 6.83 (d, 2H, *J* = 8.2 Hz), 7.18 (t, 2H, *J* = 7.8 Hz), 8.09 (s, 1H), 10.33 (s, 1H), 13.9 (br s, 1H)	3310, 2800, 1710, 1640, 1550, 1410, 880, 740
21a	H	Cl	80	200–202	0.89 (d, 6H, *J* = 6 Hz), 2.03 (m, 1H), 2.51 (d, 2H, *J* = 7 Hz), 6.73 (t, 1H, *J* = 6.8 Hz), 6.77 (d, 2H, *J* = 8 Hz), 7.14 (t, 2H, *J* = 8 Hz), 7.84 (s, 1H), 10.02 (s, 1H), 13.43 (br s, 1H)	3350, 2900, 1700, 1600, 1520, 1380, 850, 780
22a	H	Br	85	180–182	0.89 (d, 6H, *J* = 6 Hz), 2.05 (m, 1H), 2.51 (d, 2H, *J* = 7 Hz), 6.70 (t, 1H, *J* = 6.8 Hz), 6.76 (d, 2H, *J* = 7.6 Hz), 7.14 (t, 2H, *J* = 7.6 Hz), 7.84 (s, 1H), 10.01 (s, 1H), 13.48 (br s, 1H)	3350, 2910, 1720, 1600, 1520, 1380, 880, 780
19b	*o*-CH_3	H	75	75	0.93 (d, 6H, *J* = 6.4 Hz), 1.94 (m, 1H), 2.29 (s, 3H), 2.54 (d, 2H, *J* = 8 Hz), 6.14 (br s, 1H), 6.58 (s, 1H), 6.96 (m, 4H), 8.9 (br s, 1H), 14.02 (br s, 1H)	3480, 3000, 1700, 1380, 1260, 850, 770
20b	*o*-CH_3	NO_2	90	95	0.92 (d, 6H, *J* = 6.4 Hz), 2.02 (m, 1H), 2.28 (s, 3H), 2.84 (d, 2H, *J* = 8 Hz), 6.98 (m, 4H), 7.26 (s, 1H), 10.25 (br s, 1H), 14.02 (br s, 1H)	3420, 2820, 1720, 1620, 1550, 1430, 1220, 890, 730
21b	*o*-CH_3	Cl	82	135	0.89 (d, 6H, *J* = 6.4 Hz), 2.00 (m, 1H), 2.22 (s, 3H), 2.78 (d, 2H, *J* = 8.2 Hz), 7.02 (m, 4H), 7.30 (s, 1H), 10.23 (br s, 1H), 14.14 (br s, 1H)	3320, 2960, 1680, 1610, 1560, 1390, 820, 720
22b	*o*-CH_3	Br	87	151–153	0.92 (d, 6H, *J* = 6.2 Hz), 2.12 (m, 1H), 2.24 (s, 3H), 2.73 (d, 2H, *J* = 8 Hz), 6.88 (m, 4H), 7.29 (s, 1H), 10.33 (s, 1H), 14.08 (br s, 1H)	3370, 2980, 1690, 1620, 1580, 1390, 830, 740
19c	*m*-Cl	H	70	140	0.88 (d, 6H, *J* = 6.4 Hz), 1.82 (m, 1H), 2.47 (d, 2H, *J* = 8 Hz), 6.59 (s, 1H), 6.73 (d, 1H, *J* = 7.8 Hz), 6.86 (d, 1H, *J* = 7.4 Hz), 7.06 (t, 2H, *J* = 7.8 Hz), 7.24 (br s, 1H), 9.4 (br s, 1H), 13.9 (br s, 1H)	3350, 2900, 1700, 1600, 1520, 1380, 850, 780
20c	*m*-Cl	NO_2	70	216–219	0.95 (d, 6H, *J* = 6.4 Hz), 2.02 (m, 1H), 2.81 (d, 2H, *J* = 8 Hz), 6.71 (d, 1H, *J* = 8 Hz), 6.83 (d, 1H, *J* = 7.8 Hz), 7.18 (t, 2H, *J* = 7.8 Hz), 8.35 (s, 1H), 10.41 (br s, 1H), 14.02 (br s, 1H)	3380, 3000, 1700, 1620, 1600, 1450, 1380, 1290, 920, 790
21c	*m*-Cl	Cl	82	138	0.86 (d, 6H, *J* = 6.2 Hz), 2.08 (m, 1H), 2.88 (d, 2H, *J* = 7.6 Hz), 6.72 (d, 1H, *J* = 8 Hz), 6.94 (d, 1H, *J* = 7.8 Hz), 7.14 (t, 2H, *J* = 7.8 Hz), 8.46 (s, 1H), 10.40 (br s, 1H), 13.8 (br s, 1H)	3360, 2860, 1710, 1600, 1480, 1330, 870, 780
22d	*m*-Cl	Br	86	156	0.90 (d, 6H, *J* = 6.4 Hz), 2.11 (m, 1H), 2.90 (d, 2H, *J* = 7.6 Hz), 6.64 (d, 1H, *J* = 8 Hz), 6.86 (d, 1H, *J* = 7.8 Hz), 7.12 (t, 2H, *J* = 7.8 Hz), 8.36 (s, 1H), 10.24 (br s, 1H), 13.98 (br s, 1H)	3360, 2920, 1710, 1610, 1530, 1430, 880, 760

[a] Yield of isolated, purified products after crystallization

drazine hydrochloride (2.2 equiv.). The suspension was then stirred for 1 h and to this ice-cooled suspension was added the appropriate dioxo-piperazine (5 mmol) and the resulting solution was stirred overnight at r.t. At the end of the reaction, the system was washed with H_2O (25 mL), the organic phase separated, dried (Na_2SO_4), concentrated under reduced pressure to give a residue which was purified by crystallization.

6-Aryl-substituted-5*H*-pyrazolo[1,5-*d*]-1,2,4-triazine-4,7-diones (23-26a,c); General Procedure

To a suspension of **19–22a,c** (2 mmol) in anhyd toluene (5 mL) was added trichloromethylchloroformate (266 mL, 2.2 mmol, 1.1 equiv.) and the system heated to reflux for 1 h. After this time, the reaction was cooled, stirred for 1 h. at r.t. and concentrated in vacuo. The residue was purified by coloumn chromatography using EtOAc:petroleum ether as mobile phase (starting with 1:4 v/v and then with 1:1 v/v).

3-Isobutylpyrazole-5-(*N2*-benzylcarbamoyl, *N2*-phenyl) carboxyhydrazide (27)

To a solution of **23a** (285 mg, 1 mmol) in anhyd CH_2Cl_2 (5 mL) at r.t. was added benzyl amine (107 mg, 1 mmol). After being stirred at r.t. for 2 h, the mixture was concentrated in vacuo and the residue was chromatographed with EtOAc:petroleum ether (1:2, v/v) to

Table 2 2-Isobutyl-3-substituted-5*H*-6-phenylsubstituted-pyrazolo[1,5-*d*]-1,2,4-triazine-4,7-diones **23–26 a,c** Prepared

Compound	R	X	Yield [a] (%)	m.p (°C)	^{1}H NMR (DMSO-d_6) d δ	IR (KBr) cm^{-1}
23a	H	H	56	84–86	0.95 (d, 6H, *J* = 6 Hz), 1.9 (m, 1H), 2.62 (d, 2H, *J* = 7 Hz), 6.61 (s, 1H), 7.28 (d, 2H, *J* = 7.6 Hz), 7.45 (m, 2H), 7.90 (d, 2H, *J* = 7.6 Hz).	3250, 3150, 2990, 1790, 1650, 1500, 1370, 1080, 750
24a	H	NO_2	67	97	0.92 (d, 6H, *J* = 6 Hz), 2.06 (m, 1H), 2.46 (d, 2H, *J* = 7.2 Hz), 7.30 (m, 2H,), 7.48 (d, 2H, *J* = 7.4 Hz), 7.92 (d, 2H, *J* = 8.2 Hz)	3270, 2780, 1700, 1670, 1550, 1380, 1020, 860
25a	H	Cl	58	133	0.97 (d, 6H, *J* = 6 Hz), 2.10 (m, 1H), 2.65 (d, 2H, *J* = 7 Hz), 7.32 (m, 2H), 7.50 (d, 2H, *J* = 8.2 Hz), 7.94 (d, 2H, *J* = 7.8 Hz)	3210, 3000, 1820, 1660, 1590, 1380, 1280, 1180, 890
26a	H	Br	59	144–147	0.91 (d, 6H, *J* = 6.1 Hz), 1.96 (m, 1H), 2.62 (d, 2H, *J* = 7.2 Hz), 7.52 (m, 2H), 7.74 (d, 2H, *J* = 7.4 Hz), 7.92 (d, 2H, *J* = 7.8 Hz)	3380, 2900, 1670, 1520, 1430, 840, 770
23b	*o*-CH_3	H	53	125	0.99 (d, 6H, *J* = 6.4 Hz), 2.04 (m, 1H), 2.35 (s, 3H), 2.69 (d, 2H, *J* = 8 Hz), 6.64 (s, 1H), 7.35 (m, 5H)	3150, 3000, 1800, 1740, 1390, 1240, 1090, 970, 780
24b	*o*-CH_3	NO_2	61	159–161	1.02 (d, 6H, *J* = 6.4 Hz), 2.15 (m, 1H), 2.41 (s, 3H), 2.98 (d, 2H, J = 7.8 Hz), 7.37 (m, 5H)	3285, 1770, 1650, 1520, 1480, 1390, 1140, 1040, 950, 810
25b	*o*-CH_3	Cl	63	141	0.96 (d, 6H, *J* = 6.2 Hz), 2.06 (m, 1H), 2.13 (s, 3H), 2.68 (d, 2H, *J* = 8 Hz), 7.32 (m, 5H).	3180, 2860, 1690, 1620, 1540, 1360, 800, 730
26b	*o*-CH_3	Br	59	98	0.96 (d, 6H, *J* = 6 Hz), 2.08 (m, 1H), 2.20 (s, 3H), 2.58 (d, 2H, *J* = 8 Hz), 7.29 (m, 5H)	3370, 2980, 1690, 1620, 1580, 1390, 830, 740
23c	*m*-Cl	H	56	145	0.97 (d, 6H, *J* = 6.2 Hz), 1.94 (m, 1H), 2.59 (d, 2H, *J* = 8.2 Hz), 6.62 (s, 1H), 7.22 (d, 1H, *J* = 7.4 Hz), 7.46 (d, 1H, *J* = 7.4 Hz), 7.76 (m, 2H), 7.98 (s, 1H)	3150, 3000, 1660, 1500, 1280, 1160, 1000, 800, 760
24c	*m*-Cl	NO_2	59	155–158	0.94 (d, 6H, *J* = 6.2 Hz), 1.98 (m, 1H), 2.67 (d, 2H, *J* = 7.8 Hz), 7.23 (d, 1H, *J* = 8 Hz), 7.38 (d, 1H, *J* = 7.6 Hz), 7.68 (m, 2H), 8.12 (s, 1H)	3220, 3150, 1810, 1660, 1530, 1380, 1180, 1100, 890, 760
25c	*m*-Cl	Cl	63	112	0.88 (d, 6H, *J* = 6.2 Hz), 2.02 (m, 1H), 2.72 (d, 2H, *J* = 6.8 Hz), 7.24 (d, 1H, *J* = 8 Hz), 7.45 (d, 1H, *J* = 7.8 Hz), 7.64 (m, 2H), 8.02 (s, 1H)	3260, 1780, 1630, 1505, 1360, 890, 780
26c	*m*-Cl	Br	68	139	0.97 (d, 6H, *J* = 6.4 Hz), 1.94 (m, 1H), 2.59 (d, 2H, *J* = 7.8 Hz), 7.23 (d, 1H, *J* = 7.8 Hz), 7.38 (d, 1H, *J* = 7.8 Hz), 7.72 (m, 2H), 8.02 (s, 1H)	3220, 3150, 1800, 1660, 1620, 1380, 1180, 1160, 890, 760

[a] Yield of isolated, purified products after crystallization from EAOAc-petroleum ether

give **27** (305 mg, 78% yield) as a brown solid, mp (EtOAc/petroleum ether) = 158 ˚C.

^{1}H NMR ($CDCl_3$): d = 0.82 (d, 6H, *J* = 6.4 Hz), 1.81 (m, 1H), 2.37 (d, 2H, *J* = 7.2 Hz), 4.44 (d, 2H, *J* = 5.8 Hz), 5.30 (t, 1H, *J* = 4.8 Hz), 6.53 (s, 1H), 7.30 (m, 10H), 7.48 (d, 1H, *J* = 6.6 Hz), 11.1 (s, 1H).

IR (KBr, cm^{-1}): n = 3320, 3180, 3050, 1670, 1610, 890, 720, 630.

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