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One-pot, three-component route to 2*H*-indazolo[2,1-*b*]phthalazine-triones

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Abstract

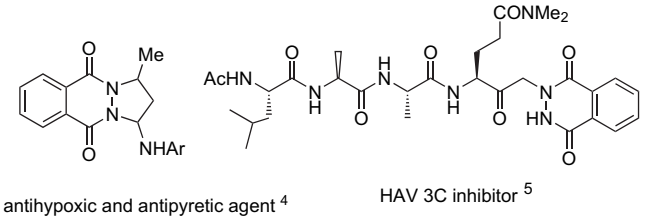
2*H*-Indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives were synthesized in a simple and efficient method from the three-component condensation reaction of phthalhydrazide, dimedone, and aromatic aldehydes under solvent-free conditions in excellent yields and short reaction times.

Keywords: Dimedone; Phthalhydrazide; Indazolophtalazine; One-pot reaction

1. Introduction

The rapid assembly of molecular diversity utilizing multicomponent reaction (MCRs) has received a great deal of attention, most notably for the construction of heterocyclic 'drug-like' libraries.[1–3] These methodologies have great utility, particularly, when they lead to the formation of privileged medicinal heterocyclic compounds.

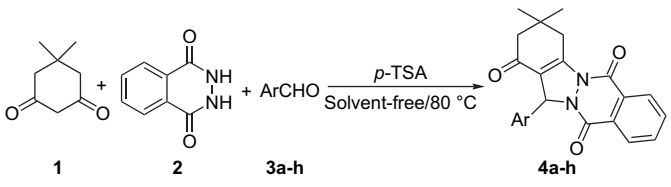
In the past few decades, the synthesis of new heterocyclic compounds has been a subject of great interest due to their wide applicability. Heterocyclic compounds occur very widely in nature and are essential to life. Among a large variety of heterocyclic compounds, heterocycles containing phthalazine moiety are of interest because they show some pharmacological and biological activities (Fig. 1).[4–6] Phthalazine derivatives were reported to possess anticonvulsant,[7] cardiotonic,[8] and vasorelaxant[9] activities. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives.[7,10–16] Despite the available methods, the development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment is therefore an interesting challenge.



antihypoxic and antipyretic agent [4] HAV 3C inhibitor [5]

Figure 1.

Multicomponent reactions of dimedone (5,5-dimethylcyclohexane-1,3-dione), an aldehyde, and *N*-nucleophilic heterocycles have recently attracted the interest of the synthetic community because the formation of different condensation products can be expected depending on the specific conditions and structure of the building blocks[17–21] Phthalhydrazide (2,3-dihydro-1,4-phthalazinedione) containing two NH-nucleophilic groups is a very interesting heterobicyclic compound. In the present work, we took advantage of NH groups in a three-component condensation reaction of dimedone **1**, phthalhydrazide **2**, and aromatic aldehydes **3a–h** in the preparation of 3,4-dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo[2,1-*b*]-phthalazine-1,6,11(13*H*)-trione derivatives **4a–h** (Scheme 1).



1 **2** **3a-h** **4a-h**

Scheme 1.

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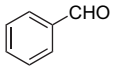
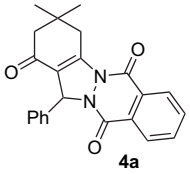
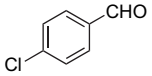
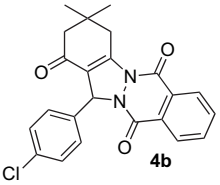
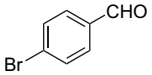
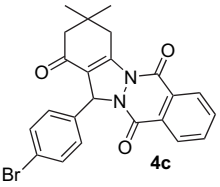
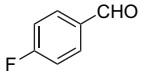
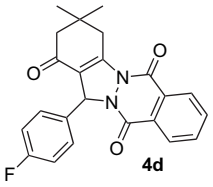
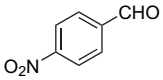
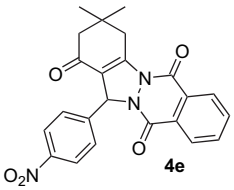
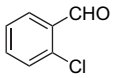
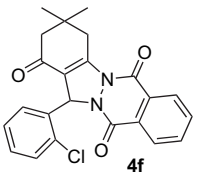
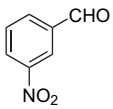
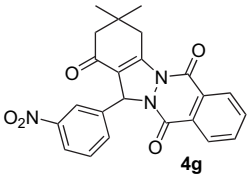
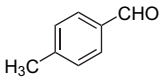
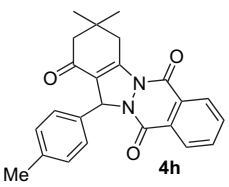
2. Results and discussion

Dimedone **1**, phthalhydrazide **2**, and aromatic aldehydes **3a–h** in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) undergo a fast 1:1:1 addition reaction at 80 °C under solvent-free conditions for several minutes to produce 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones **4a–h** (Table 1). The results were excellent in terms of yields and product purity in the presence of *p*-TSA, while without it for long period of time (4–5 h) the yields of products were low (<30%).

Table 1
Synthesis of indazolo[2,1-*b*]phthalazine-triones **4**

Entry	Aldehyde	Product	Time (min)	Yield (%)
1		 **4a**	10	86
2		 **4b**	10	93
3		 **4c**	10	90
4		 **4d**	10	80
5		 **4e**	10	91
6		 **4f**	15	88
7		 **4g**	15	86
8		 **4h**	20	83

The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4a–h** are stable solids whose structures are fully supported by IR, ^{1}H, and ^{13}C NMR spectroscopies, mass spectrometry, and elemental analysis. The structure of **4c** was confirmed by a single-crystal X-ray analysis[22] (Fig. 2).

Under the same conditions, this reaction almost could not be observed when the aliphatic aldehyde was used as a starting material.

A possible mechanism for the formation of **4a–h** is proposed in Scheme 2. It is reasonable to assume that **4a–h** results from initial formation of a heterodiene **5** by standard Knoevenagel condensation of the dimedone **1** and aldehyde

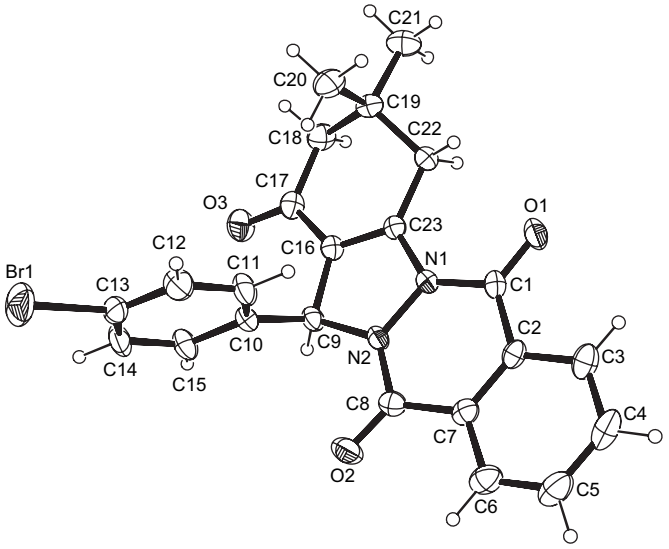
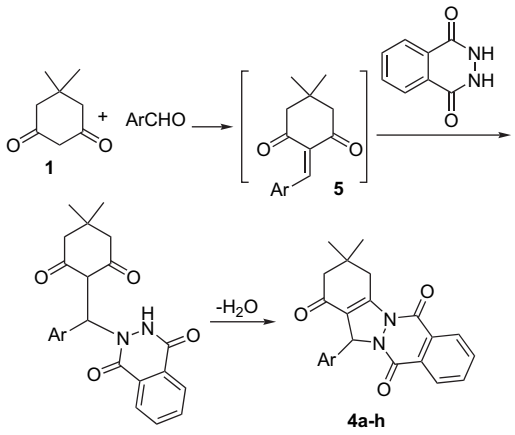


Figure 2. X-ray crystal structure of **4c**.



Scheme 2.

3. Then, the subsequent Michael-type addition of the phthalhydrazide **2** to the heterodyne **5** followed by cyclization affords the corresponding products **4** (Scheme 2).

In summary, we have described an efficient and one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones via a cyclocondensation reaction of dimedone, phthalhydrazide, and aromatic aldehydes under solvent-free conditions. To the best of our knowledge, this new procedure provides the first example of the efficient synthetic method for 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione by a three-component reaction.

3. Experimental

*3.1. Typical procedure for the preparation of 3,4-dihydro-3,3-dimethyl-13-phenyl-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4a**)*

A mixture of dimedone (0.14 g, 1 mmol), phthalhydrazide (0.16 g, 1 mmol), benzaldehyde (0.13 g, 1.2 mmol), and *p*-TSA (0.3 mmol) was heated at 80 °C for 10 min (TLC). After cooling, the reaction mixture was washed with water (15 mL) and the residue recrystallized from ethyl acetate/*n*-hexane (1:3) to afford the pure product **4a** (0.32 g, 86%) as a yellow powder. Mp 204–206 °C; IR (KBr) (ν_{max}, cm^{-1}): 2958, 1661, 1575; δ_H (300 MHz, $CDCl_3$) 1.23 (6H, s, 2*Me*), 2.35 (2H, s, CH_2CO), 3.26 and 3.44 (2H, AB system, *J* 18.6 Hz, CH_aH_bCO), 6.47 (1H, s, *CH*N), 7.33–8.37 (9H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.5, 28.7, 34.7, 38.1, 50.9, 64.9, 118.6, 127.1, 127.7, 127.9, 128.7, 128.9, 129.1, 133.6, 134.5, 136.4, 150.9, 154.3, 156.1, 192.2; MS, *m/z* (%): 372 (M^+, 15), 295 (100), 104 (84), 76 (67). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52%. Found: C, 74.25; H, 5.36; N, 7.45%.

*3.2. 3,4-Dihydro-3,3-dimethyl-13-(4-chlorophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4b**)*

White powder (93%); mp 262–264 °C; IR (KBr) (ν_{max}, cm^{-1}): 2957, 1656, 1623; δ_H (300 MHz, $CDCl_3$) 1.22 (3H, s, *Me*), 1.23 (3H, s, *Me*), 2.35 (2H, s, CH_2CO), 3.25 and 3.43 (2H, AB system, *J* 19.1 Hz, CH_aH_bCO), 6.43 (1H, s, *CH*N), 7.31–8.39 (8H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.5, 28.7, 34.7, 38.0, 50.9, 64.3, 118.1, 127.7, 128.1, 128.5, 128.8, 128.9, 129.0, 133.7, 134.5, 134.6, 134.9, 151.1, 154.3, 156.0, 192.2; MS, *m/z* (%): 406 (M^+, 5), 295 (100), 104 (43), 76 (46). Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89%. Found: C, 67.81; H, 4.66; N, 6.81%.

*3.3. 3,4-Dihydro-3,3-dimethyl-13-(4-bromophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4c**)*

White powder (90%); mp 265–267 °C; IR (KBr) (ν_{max}, cm^{-1}): 2957, 1656, 1623; δ_H (300 MHz, $CDCl_3$) 1.21 (3H, s, *Me*), 1.22 (3H, s, *Me*), 2.35 (2H, s, CH_2CO), 3.24 and 3.41 (2H, AB system, *J* 19.2 Hz, CH_aH_bCO), 6.41 (1H, s, *CH*N), 7.29–8.38 (8H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.5, 28.7, 34.7, 38.0, 50.9, 64.4, 118.0, 122.8, 127.8, 128.1, 128.8, 128.9, 129.0, 131.9, 133.7, 134.7, 135.5, 151.1, 154.4, 156.0, 192.1; MS, *m/z* (%): 451 (M^+, 7), 295 (100), 104 (28), 76 (34). Anal. Calcd for $C_{23}H_{19}BrN_2O_3$: C, 61.21; H, 4.24; N, 6.21%. Found: C, 61.14; H, 4.17; N, 6.30%.

*3.4. 3,4-Dihydro-3,3-dimethyl-13-(4-fluorophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4d**)*

Yellow powder (80%); mp 217–219 °C; IR (KBr) (ν_{max}, cm^{-1}): 2958, 1664, 1655, 1626; δ_H (300 MHz, $CDCl_3$) 1.21 (6H, s, 2 *Me*), 2.34 (2H, s, CH_2CO), 3.23 and 3.41 (2H, AB system, *J* 19.0 Hz, CH_aH_bCO), 6.43 (1H, s, *CH*N), 6.99–8.35 (8H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.5, 28.7, 34.7, 38.0, 50.9, 64.3, 115.5, 115.9, 118.2, 127.7, 128.0, 128.9, 129.1, 132.2, 133.7, 134.6, 151.1, 154.4, 156.0, 192.2; MS, *m/z* (%): 390 (M^+, 9), 295 (100), 104 (52). Anal. Calcd for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18%. Found: C, 70.69; H, 4.96; N, 7.10%.

*3.5. 3,4-Dihydro-3,3-dimethyl-13-(4-nitrophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4e**)*

Yellow powder (91%); mp 223–225 °C; IR (KBr) (ν_{max}, cm^{-1}): 2924, 1695, 1659, 1615; δ_H (300 MHz, $CDCl_3$) 1.21 (3H, s, *Me*), 1.23 (3H, s, *Me*), 2.33 and 2.38 (2H, AB system, *J* 16.5 Hz, CH_aH_bCO), 3.26 and 3.43 (2H, AB system, *J* 19.2 Hz, CH_aH_bCO), 6.52 (1H, s, *CH*N), 7.61–8.41 (8H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.4, 28.7, 34.7, 38.0, 50.8, 64.2, 117.3, 124.1, 127.8, 128.1, 128.3, 128.6, 128.9, 133.9, 134.9, 143.4, 147.9, 151.7, 154.6, 155.9, 192.1; MS, *m/z* (%): 417 (M^+, 5), 295 (100), 104 (48), 76 (75). Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07%. Found: C, 66.24; H, 4.65; N, 9.98%.

*3.6. 3,4-Dihydro-3,3-dimethyl-13-(2-chlorophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4f**)*

Yellow powder (88%); mp 264–266 °C; IR (KBr) (ν_{max}, cm^{-1}): 2956, 1663, 1625; δ_H (300 MHz, $CDCl_3$) 1.22 (3H, s, *Me*), 1.23 (3H, s, *Me*), 2.33 (2H, s, CH_2CO), 3.24 and 3.42 (2H, AB system, *J* 19.1 Hz, CH_aH_bCO), 6.69 (1H, s, *CH*N), 7.25–8.40 (8H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.4, 28.8, 34.6, 38.0, 50.9, 64.0, 116.7, 127.2, 127.6, 128.0, 128.7, 129.0, 129.9, 130.5, 132.6, 133.0, 133.6, 134.5, 151.9, 154.2, 156.2, 192.1; MS, *m/z* (%): 406 (M^+, 8), 295 (100), 104 (43), 76 (46). Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89%. Found: C, 67.83; H, 4.79; N, 6.80%.

*3.7. 3,4-Dihydro-3,3-dimethyl-13-(3-nitrophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4g**)*

Yellow powder (86%); mp 270–272 °C; IR (KBr) (ν_{max}, cm^{-1}): 2926, 1660, 1625; δ_H (300 MHz, DMSO-d_6) 1.12 (6H, s, 2*Me*), 2.27 (2H, s, CH_2CO), 3.23 (2H, br s, CH_2CO), 6.46 (1H, s, *CH*N), 7.60–8.37 (8H, m, Ph); δ_H (300 MHz, DMSO-d_6) 28.3, 28.9, 34.6, 38.2, 51.5, 64.2, 116.9, 127.3, 127.3, 128.4, 128.7, 129.2, 129.8, 131.5, 132.7, 133.1, 133.6, 134.5, 135.5, 151.8, 154.4, 156.4, 192.2; MS, *m/z*

(%): 417 (M^+, 10), 295 (100), 104 (48), 76 (75). Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07%. Found: C, 66.11; H, 4.52; N, 10.15%.

*3.8. 3,4-Dihydro-3,3-dimethyl-13-(4-methylphenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**4h**)*

Yellow powder (83%); mp 227–229 °C; IR (KBr) (ν_{max}, cm^{-1}): 2956, 1663, 1621; δ_H (300 MHz, $CDCl_3$) 1.23 (6H, s, 2*Me*), 2.30 (3H, s, CH_3), 2.35 (2H, s, CH_2CO), 3.24 and 3.43 (2H, AB system, *J* 18.5 Hz, CH_aH_bCO), 6.43 (1H, s, *CH*N), 7.12–8.38 (8H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.3, 28.5, 28.8, 34.7, 38.1, 50.9, 64.9, 118.7, 127.1, 127.7, 127.9, 128.9, 129.2, 129.5, 133.4, 133.5, 134.5, 138.5, 150.8, 154.2, 156.1, 192.2; MS, *m/z* (%): 386 (M^+, 10), 295 (100), 104 (45), 76 (46). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25%. Found: C, 74.53; H, 5.69; N, 7.36%.

Acknowledgements

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References and notes

1. Gerencser, J.; Dormon, G.; Darvas, F. *QSAR Comb. Sci.* **2006**, 439.
2. Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.
3. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
4. AÍ-Assar, F.; Zelenin, K. N.; Lesiovskaya, E. E.; Bezhan, I. P.; Chakchir, B. A. *Pharm. Chem. J.* **2002**, *36*, 598.
5. Jain, R. P.; Vederas, J. C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3655.
6. Carling, R. W.; Moore, K. W.; Street, L. J.; Wild, D.; Isted, C.; Leeson, P. D.; Thomas, S.; O'Conner, D.; McKernan, R. M.; Quirk, K.; Cook, S. M.; Atack, J. R.; Wafford, K. A.; Thompson, S. A.; Dawson, G. R.; Ferris, P.; Castro, J. L. *J. Med. Chem.* **2004**, *47*, 1807.
7. Grasso, S.; DeSarro, G.; Micale, N.; Zappala, M.; Puia, G.; Baraldi, M.; Demicheli, C. *J. Med. Chem.* **2000**, *43*, 2851.
8. Nomoto, Y.; Obase, H.; Takai, H.; Teranishi, M.; Nakamura, J.; Kubo, K. *Chem. Pharm. Bull. (Tokyo)* **1990**, *38*, 2179.
9. Watanabe, N.; Kabasawa, Y.; Takase, Y.; Matsukura, M.; Miyazaki, K.; Ishihara, H.; Kodama, K.; Adachi, H. *J. Med. Chem.* **1998**, *41*, 3367.
10. Sheradsky, T.; Moshenberg, R. *J. Org. Chem.* **1986**, *51*, 3123.
11. Heine, H. W.; Baclawski, L. M.; Bonser, S. M.; Wachob, G. D. *J. Org. Chem.* **1976**, *41*, 3229.
12. Ramtohup, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 3169.
13. Liu, L. P.; Lu, J. M.; Shi, M. *Org. Lett.* **2007**, *9*, 1303.
14. Csampai, A.; Kormendy, K.; Ruff, F. *Tetrahedron* **1991**, *47*, 4457.
15. Amarasekara, A. S.; Chandrasekara, S. *Org. Lett.* **2002**, *4*, 773.
16. Hwang, J. Y.; Choi, H. S.; Gong, Y. D. *Tetrahedron Lett.* **2005**, *46*, 3107.
17. Quiroga, J.; Mejia, D.; Insuasty, B.; Abonia, R.; Nogueras, M.; Sanchez, A.; Cobo, J.; Low, J. N. *Tetrahedron* **2001**, *57*, 6947.
18. Quiroga, J.; Hormaza, A.; Insuasty, B.; Ortiz, A. J.; Sanchez, A.; Nogueras, M. *J. Heterocycl. Chem.* **1998**, *35*, 231.
19. Tu, S.; Fang, F.; Li, T.; Zhu, S.; Zhang, X. *J. Heterocycl. Chem.* **2005**, *42*, 707.
20. Quiroga, J.; Insuasty, B.; Hormaza, A.; Saitz, C.; Jullian, C. *J. Heterocycl. Chem.* **1998**, *35*, 575.
21. Shaabani, A.; Rahmati, A.; Naderi, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5553.
22. *X-ray data for **4c***: ($C_{23}H_{19}BrN_2O_3$), *M*=451.30 g/mol, monoclinic system, space group *P*21/*n*, *a*=6.2540(9), *b*=13.3953(12), *c*=24.335(3) Å, *β*=93.320(11)°, *V*=2035.3(4) $Å^3$, *Z*=4, D_c=1.473 g cm^{-3}, *μ*(Mo Kα)=2.047 mm^{-1}, crystal dimension of 0.5×0.1×0.1 mm. The structure was solved by using SHELXS. The structural refinement and data reduction were carried out with SHELXL of the X-Step32 suite of programs. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final *R*1=0.0756, *wR*2=0.1396 and *S*=1.145 with 263 parameters using 5473 independent reflection (*θ* range=1.68–29.26°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **4c** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 660455, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.