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A novel three-component method for the synthesis of triazolo[1,2-*a*]indazole-triones

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Abstract—An efficient synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives based on the three-component condensation of urazole, dimedone and aromatic aldehydes under solvent-free conditions is described.

With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules,[1] reactions that provide maximum diversity are especially desirable. Here, expeditious domino[2] and multicomponent[3] reactions (MCRs) have emerged as powerful strategies. MCRs are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step.

Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals and biologically active pharmaceuticals vital for enhancing the quality of life.[4] Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing a urazole (1,2,4-triazolidine-3,5-diones) moiety are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications (Fig. 1).[5] Urazole derivatives also exhibit anticonvulsant[6] or fungicidal activity[7] as well as catalytic activity in radical polymerization.[8] Novel methods for preparing heterocycles containing a urazole moiety have attracted much interest in recent years.[5a–c,9] Despite the available synthetic methods, there still exists

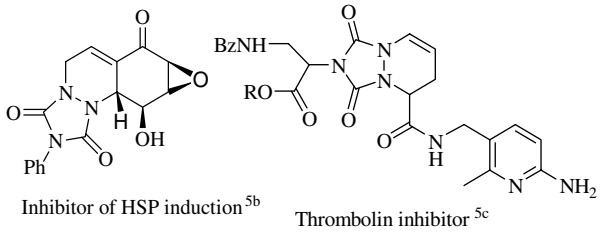

Figure 1.

a need for developing more efficient procedures, which allow the ready synthesis of urazole polycyclic systems.

Considering the above reports in conjunction with our previous work on the synthesis of nitrogen-containing heterocyclic compounds,[10] we report an efficient, one-pot, and three-component method for the preparation of 6,7-dihydro-6,6-dimethyl-2-phenyl-9-aryl-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione derivatives by condensation of 5,5-dimethylcyclohexane-1,3-dione (dimedone) **1**, urazole **2** and aromatic aldehydes **3** under solvent-free conditions (Scheme 1).

We found that a mixture of dimedone **1**, urazole **2** and aromatic aldehydes **3a–i**, in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) at 80 °C for 15–30 min under solvent-free conditions, afforded triazoloindazole-triones **4a–i** in good yields (Table 1).

The results were good in terms of yields and product purity in the presence of *p*-TSA, while without *p*-TSA and over long period of time (5–6 h) the yields of

Keywords: Dimedone; Urazole; Triazoloindazole; One-pot reaction.
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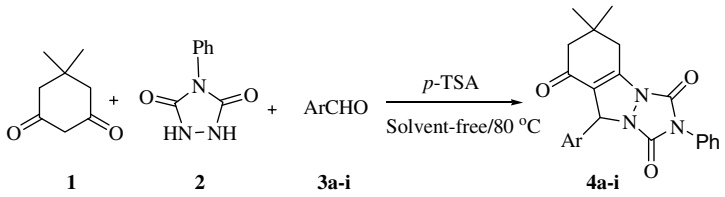
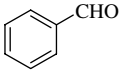
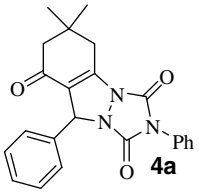
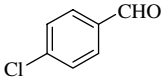
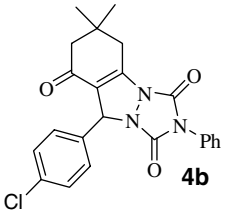
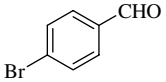
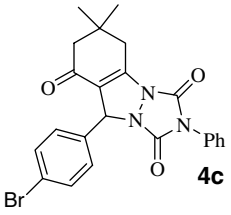
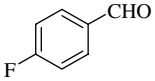
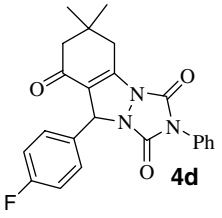
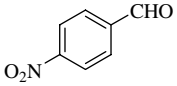
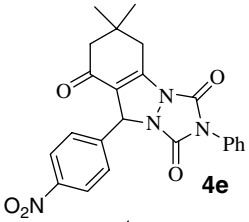
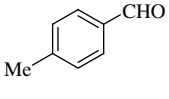
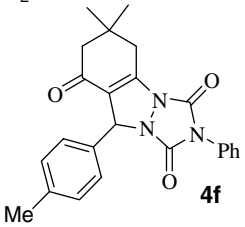


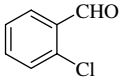
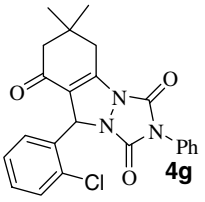
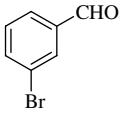
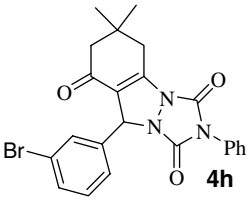
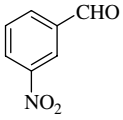
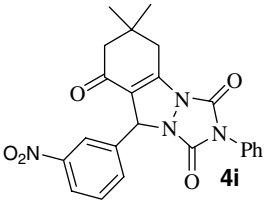
Scheme 1.

Table 1. Synthesis of triazoloindazoles **4a–i**

Entry	Aldehyde **3**	Product **4**	Time (min)	Yield (%)
1		 **4a**	15	78
2		 **4b**	15	88
3		 **4c**	15	80
4		 **4d**	30	90
5		 **4e**	20	81
6		 **4f**	25	79

(*continued on next page*)

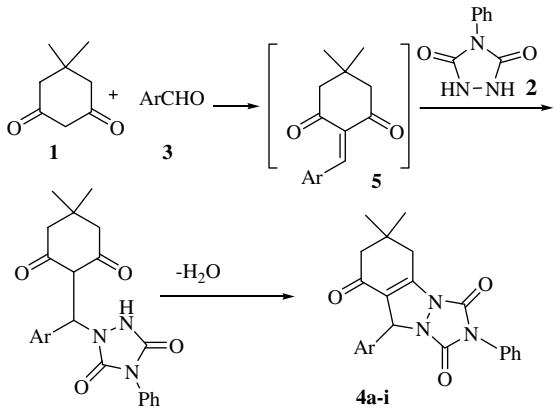
Table 1 (*continued*)

Entry	Aldehyde **3**	Product **4**	Time (min)	Yield (%)
7		 **4g**	15	79
8		 **4h**	20	81
9		 **4i**	15	83

products were low (<40%). Aliphatic aldehydes reacted poorly under the same conditions.

Compounds **4a**–**i** are stable solids whose structures were established by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectra of products **4a**–**i** displayed molecular ion peaks at appropriate values, which were consistent with the proposed 1:1:1 adduct of dimedone **1**, urazole **2** and aldehyde **3**.

The formation of products **4a**–**i** can be rationalized by initial formation of heterodiene **5** by standard Knoevenagel condensation of dimedone **1** and aldehyde **3**. Subsequent Michael-type addition of urazole **2** to heterodiene **5** followed by cyclization afforded the corresponding products **4a**–**i** and water (Scheme 2).



Scheme 2.

In conclusion, we have described an efficient, one-pot, three-component synthesis of triazoloindazole-trione derivatives via cyclocondensation reaction of dimedone, urazole and aromatic aldehydes under solvent-free conditions. To the best of our knowledge, this new procedure provides the first example of an efficient method for the synthesis of 6,7-dihydro-6,6-dimethyl-2-phenyl-9-aryl-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione.

1. Experimental

1.1. Typical procedure for the preparation of 6,7-dihydro-6,6-dimethyl-2,9-diphenyl-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4a)

A mixture of dimedone (1 mmol), urazole (1 mmol), benzaldehyde (1.2 mmol) and *p*-TSA (0.3 mmol) was heated at 80 °C for 15 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 pure **4a**. White powder (78%); mp 188–190 °C. IR (KBr) (ν_{max}/cm^{-1}): 2957, 1778, 1730, 1655. MS (EI, 70 eV) *m*/*z* (%): 387 (M^+, 25), 310 (90), 267 (95), 91 (75), 41 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.22 (6H, s, $2CH_3$), 2.35 (2H, s, CH_2), 2.93 (2H, AB system, $^{2}J_{HH} = 18.0$ Hz, CH_2), 6.23 (1H, s, CH), 7.35–7.49 (10H, m, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.3, 28.7, 34.8, 35.5, 51.3, 64.1, 120.1, 125.6, 127.1, 128.8, 128.9, 129.3, 130.7, 136.8, 149.0, 150.7, 151.0, 192.0. Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.22; H, 5.39; N, 10.93.

1.2. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-chlorophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4b)

White powder (88%); mp 166–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 2963, 1788, 1729, 1665. MS (EI, 70 eV) *m*/*z* (%): 421 (M$^+$, 35), 310 (90), 301 (100), 91 (75), 41 (55). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.20 (6H, s, $2CH_3$), 2.33 (2H, s, CH_2), 2.90 (2H, AB system, $^2J_{HH} = 18.7$ Hz, CH_2), 6.18 (1H, s, CH), 7.38–7.49 (9H, m, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.2, 28.7, 34.7, 35.5, 51.2, 63.5, 119.7, 125.6, 128.6, 128.8, 129.0, 129.4, 130.7, 134.6, 135.6, 149.1, 151.0, 151.3, 192.0. Anal. Calcd for $C_{23}H_{20}ClN_3O_3$: C, 65.48; H, 4.78; N, 9.96. Found: C, 65.55; H, 4.83; N, 9.84.

1.3. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-bromophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4c)

White powder (80%); mp 184–186 °C. IR (KBr) (ν_{max}/cm^{-1}): 2961, 1789, 1728, 1665. MS (EI, 70 eV) *m*/*z* (%): 465 (M$^+$, 30), 345 (65), 310 (100), 91 (45), 41 (43). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.20 (6H, s, $2CH_3$), 2.33 (2H, s, CH_2), 2.90 (2H, AB system, $^2J_{HH} = 19.6$ Hz, CH_2), 6.17 (1H, s, CH), 7.32–7.54 (9H, m, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.3, 28.7, 34.8, 35.5, 51.2, 63.6, 119.7, 122.9, 125.6, 128.8, 129.4, 130.6, 132.1, 135.9, 149.1, 150.9, 151.2, 191.9. Anal. Calcd for $C_{23}H_{20}BrN_3O_3$: C, 59.24; H, 4.32; N, 9.01. Found: C, 59.17; H, 4.26; N, 8.93.

1.4. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-fluorophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4d)

White powder (90%); mp 102–104 °C. IR (KBr) (ν_{max}/cm^{-1}): 2960, 1786, 1720, 1660. MS (EI, 70 eV) *m*/*z* (%): 405 (M$^+$, 20), 368 (55), 310 (57), 91 (85), 41 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.21 (3H, s, CH_3), 1.22 (3H, s, CH_3), 2.35 (2H, AB system, $^2J_{HH} = 17.5$ Hz, CH_2), 2.92 (2H, AB system, $^2J_{HH} = 19.5$ Hz, CH_2), 6.18 (1H, s, CH), 7.42–7.58 (9H, m, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.4, 28.6, 34.8, 35.5, 51.2, 63.4, 119.7, 122.9, 125.6, 126.0, 128.9, 129.4, 130.0, 130.4, 131.9, 139.1, 149.1, 151.1, 151.3, 191.9. Anal. Calcd for $C_{23}H_{20}FN_3O_3$: C, 68.14; H, 4.97; N, 10.36. Found: C, 68.21; H, 5.06; N, 10.27.

1.5. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-nitrophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4e)

White powder (81%); mp 175–177 °C. IR (KBr) (ν_{max}/cm^{-1}): 2958, 1788, 1730, 1660. MS (EI, 70 eV) *m*/*z* (%): 432 (M$^+$, 39), 310 (100), 91 (40), 41 (33). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.19 (3H, s, CH_3), 1.21 (3H, s, CH_3), 2.34 (2H, s, CH_2), 2.92 (2H, AB system, $^2J_{HH} = 18.7$ Hz, CH_2), 6.30 (1H, s, CH), 7.46–8.27 (9H, m, H-Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.2, 28.7, 34.8, 35.6, 51.2, 63.3, 119.2, 124.1, 125.6, 128.2, 129.0, 129.4, 130.5, 143.9, 148.0, 149.2, 151.6, 191.9. Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.82; H, 4.58; N, 12.88.

1.6. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-methylphenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4f)

White powder (79%); mp 160–162 °C. IR (KBr) (ν_{max}/cm^{-1}): 2947, 1783, 1725, 1666. MS (EI, 70 eV) *m*/*z* (%): 401 (M$^+$, 50), 364 (35), 310 (100), 91 (85), 41 (48). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.21 (6H, s, $2CH_3$), 2.35 (5H, s, CH_3 and CH_2), 2.92 (2H, s, CH_2), 6.18 (1H, s, CH), 7.19–7.48 (9H, m, H-Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 21.3, 28.3, 28.8, 34.8, 35.5, 51.3, 64.0, 120.1, 125.6, 127.0, 128.7, 129.3, 129.6, 130.8, 133.9, 138.8, 148.9, 150.5, 150.9, 192.0. Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.74; H, 5.82; N, 10.51.

1.7. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(2-chlorophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4g)

White powder (79%); mp 173–175 °C. IR (KBr) (ν_{max}/cm^{-1}): 2966, 1777, 1728, 1658. MS (EI, 70 eV) *m*/*z* (%): 421 (M$^+$, 15), 386 (20), 310 (60), 267 (100), 91 (75), 41 (65). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.22 (6H, s, $2CH_3$), 2.32 (2H, AB system, $^2J_{HH} = 16.7$ Hz, CH_2), 2.93 (2H, AB system, $^2J_{HH} = 18.3$ Hz, CH_2), 6.35 (1H, s, CH), 7.32–7.47 (9H, m, H-Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.3, 28.9, 34.6, 35.4, 51.2, 63.6, 118.5, 125.8, 127.6, 128.7, 129.3, 130.5, 130.7, 130.8, 131.3, 131.9, 132.8, 148.4, 150.0, 150.7, 191.8. Anal. Calcd for $C_{23}H_{20}ClN_3O_3$: C, 65.48; H, 4.78; N, 9.96. Found: C, 65.40; H, 4.73; N, 9.87.

1.8. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(3-bromophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4h)

White powder (81%); mp 174–176 °C. IR (KBr) (ν_{max}/cm^{-1}): 2946, 1774, 1729, 1665. MS (EI, 70 eV) *m*/*z* (%): 465 (M$^+$, 35), 310 (100), 91 (49), 41 (54). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.19 (3H, s, CH_3), 1.21 (3H, s, CH_3), 2.34 (2H, AB system, $^2J_{HH} = 16.4$ Hz, CH_2), 2.92 (2H, AB system, $^2J_{HH} = 19.7$ Hz, CH_2), 6.17 (1H, s, CH), 7.24–7.58 (9H, m, H-Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.3, 28.6, 34.8, 35.5, 51.2, 63.4, 119.6, 122.9, 125.6, 126.1, 128.9, 129.4, 130.0, 130.4, 130.6, 131.9, 139.2, 149.1, 151.1, 151.3, 191.9. Anal. Calcd for $C_{23}H_{20}BrN_3O_3$: C, 59.24; H, 4.32; N, 9.01. Found: C, 59.31; H, 4.24; N, 8.91.

1.9. 6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(3-nitrophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4i)

White powder (83%); mp 126–128 °C. IR (KBr) (ν_{max}/cm^{-1}): 2953, 1781, 1721, 1662. MS (EI, 70 eV) *m*/*z* (%): 432 (M$^+$, 43), 310 (100), 91 (54), 41 (65). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.21 (6H, s,

$2CH_3$), 2.35 (2H, s, CH_2), 2.95 (2H, AB system, $^2J_{HH} = 18.3$ Hz, CH_2), 6.32 (1H, s, CH), 7.44–8.31 (9H, m, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.4, 28.6, 34.9, 35.5, 51.2, 63.3, 119.2, 121.8, 123.8, 125.7, 129.0, 129.4, 129.9, 130.4, 133.8, 139.2, 148.6, 149.2, 151.6, 192.1. Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.80; H, 4.59; N, 12.87.

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References and notes

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