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An efficient chemo- and regioselective three-component synthesis of pyridazinones and phthalazinones using activated KSF

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Abstract

The first three-component and regioselective synthesis of pyridazinones and phthalazinones from arenes, anhydrides and $ArNHNH_2$ in the presence of efficient recyclable heterogeneous catalyst, montmorillonite-KSF, in high yield and short reaction time is reported.

Keywords: Regioselective; Pyridazinones; Phthalazinones; Montmorillonite-KSF

Pyridazinones are useful compounds with a broad array of biologically activities. They have been utilized as antimicrobial, potent analgesic, anti-inflammatory, antifeedant, herbicidal, antihypertensive and possess antiplatelet activities, anticancer effects and other anticipated biological and pharmacological properties [1].

Previously, numerous synthetic methods for the preparation of pyridazinones or phthalazinones such as condensation of Wittig reagents with arylhydrazones or condensation of α-ketoesters with hydrazinocarbonyl acetic acid esters [2] or catalytic reactions of alkynes with arylhydrazines (hydrohydrazination) [3] is reported. In the other route the synthesis of 4,5-dihydro-3(2*H*)-pyridazinones proceeds *via* reaction of γ-ketoacids and their derivatives with alkylhydrazines or phenylhydrazines to give the pyridazinones [4–9].

Recent development in the pyridazinone chemistry and our continued interest in the development of efficient and environmentally friendly procedure for the synthesis of pharmaceutical compounds [10–14] prompted us to explore the synthesis of pyridazinones (**1–9**) and phthalazinones (**10–13**) in the first three component procedure from arenes, anhydrides and $ArNHNH_2$ in the presence of montmorillonite KSF (Scheme 1).

This class of reactions is of particular interest in combinatorial chemistry because it allows the production of vast arrays of molecules in an efficient mode.

The mechanism of the reaction goes through acylation between arenes and anhydride to prepare keto-carboxylic acids. Chemo- and regioselective intermolecular hydrazone formation followed by intramolecular cyclization over an efficient acidic active catalyst [15] led to the formation of pyridazinones (**1–9**) and phthalazinones (**10–13**) (Scheme 2).

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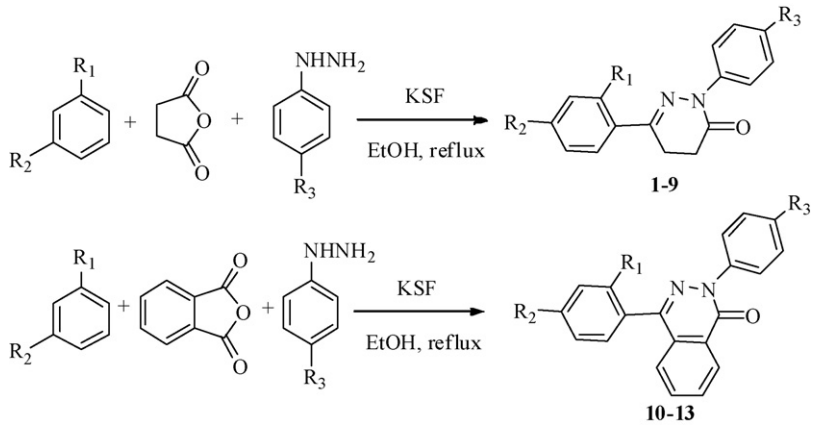
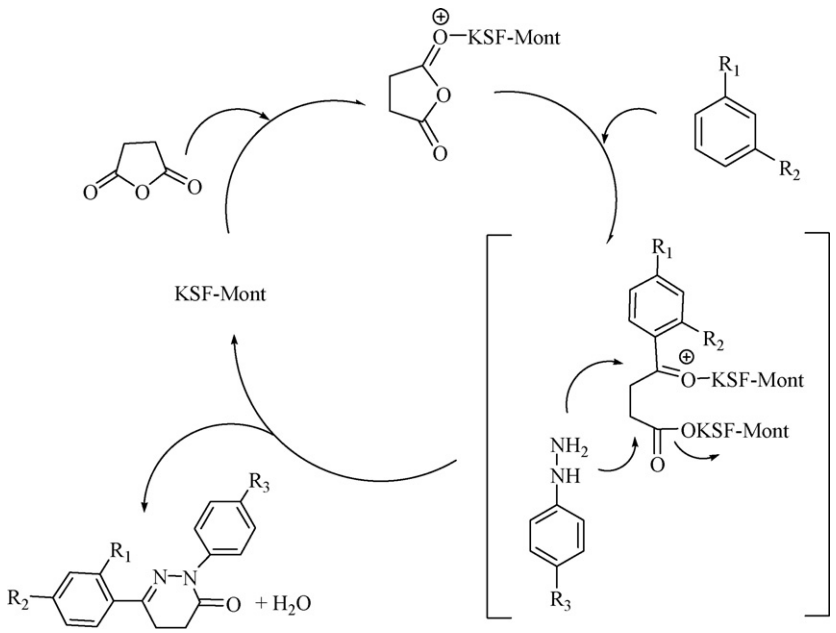


Scheme 1.

For these reasons, we used KSF because of its environmental compatibility, reusability, operational simplicity, no toxicity, noncorrosiveness, low cost and ease of isolation [16–21]. High catalytic activity and excellent chemo- and regioselectivity remained essentially the same even after third reuse of the catalyst. After more than three cycles the yield of product slightly decreased (~7–11% yield). The results are summarized in Table 1.

This three-component reaction is applicable to the some of the arenes corresponding pyridazinones and phthalazinones in varying yields (Table 1) [22,23]. The reaction using the arenes bearing NO_2 or CN exhibit no positive reaction because of the high electron deficiency at the phenyl ring of these arenes limits the Friedel–Crafts acylation. Overall, the electron-donating group gave the best results. To the best of our knowledge, this is the first report on the three-component synthesis of pyridazinones and phthalazinones. This multicomponent reaction has several advantages such as virtue of their convergence, productivity, ease of execution and work-up, the small amount of waste, short reaction time and chemo- and regioselectivity.

In conclusion we have demonstrated a convenient chemo- and regioselective three-component synthesis of pyridazinones and phthalazinones from arenes, anhydrides and $ArNHNH_2$ in the presence of active-KSF catalyst in high yield and short reaction time.



Scheme 2.

Table 1
Synthesis of pyridazinones and phthalazinones by the multicomponent reaction.

Entry	R_1	R_2	R_3	Yield[a] (%)	Time (h)	mp (°C)
1	H	H	H	75	9	92–94
2	H	H	CH_3	65	9	Oil
3	H	H	OCH_3	63	9	Oil
4	H	CH_3	H	65	8	Oil
5	CH_3	CH_3	H	62	8.5	Oil
6	H	Cl	H	60	10	Oil
7	H	OCH_3	H	55	8	Oil
8	H	OCH_3	CH_3	60	8	Oil
9	H	OCH_3	OCH_3	67	8	Oil
10	H	H	H	75	9	161–163
11	H	CH_3	H	85	8	124–126
12	CH_3	CH_3	H	82	8.5	156–158
13	H	Cl	H	78	10	164–165

Identified by spectroscopic analysis (IR, ^{1}H NMR, ^{13}C NMR and elemental analysis) for selected compounds **1**,**4**–**6** and **9**–**13**.
[a] Isolated yield.

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[22] Chemicals were purchased from Merck and Fluka and used as purchased. KSF montomorillonites were purchased from Aldrich. The clays were dried overnight at 398 K prior to use. Melting points were measured on an Electro-thermal 9100 apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker DRX 500, 250 and those of ^{13}C NMR spectra on a Bruker DRX 125 Avance spectrometer in $CDCl_3$ as solvent and with TMS as internal standard. FT-IR spectra were recorded on a Shimadzu FT-IR-8400S spectrometer. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer.
[23] Typical procedure: a mixture of anhydride and arenes (10 mmol) each and 0.1 g KSF-H in 96% EtOH (20 mL) was refluxed for the required reaction time. The progress of the reaction was monitored by TLC (EtOAc:petroleum ether 1:4). After completion of the reaction, $PhNHNH_2$

(10 mmol) was added to the mixture and then refluxed for 8–10 h. The progress of the reaction was monitored by TLC (EtOAc:petroleum ether 1:4). Subsequently, the catalyst was removed by filtration and the product (2–9) was purified by column chromatography (petroleum ether/EtOAc: 4/1) and the product **1** and **10**–**13** was recrystallized from EtOH to furnish the desired pyridazinones and phthalazinones. The pure products were collected in 60–85% yields; 2,6-diphenyl-4,5-dihydropyridazin-3(2H)-one (**1**): off white solid, ^{1}H NMR ($CDCl_3$): δ 2.84 (t, 2H, J = 8.5 Hz), 3.15 (t, 2H, J = 8.5 Hz), 7.30–7.33 (m, 1H), 7.45–7.48 (m, 5H), 7.64 (d, 2H, J = 7.5 Hz), 7.85–7.86 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 165.69, 151.93, 141.68, 135.91, 130.42, 129.07, 128.94, 127.00, 126.51, 125.31, 28.47, 23.33. IR (neat): ν 1680 (C═O), 1600, 1541, 1330, 1490. Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.62; H, 5.77; N, 11.10; 6-(4-methylphenyl)-4,5-dihydropyridazin-3(2H)-one (**4**): red oil, ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.78 (t, 2H, J = 8.5 Hz), 3.06 (t, 2H, J = 8.5 Hz), 7.27 (d, 2H, J = 8.1 Hz), 7.32 (t, 1H, J = 7.4 Hz), 7.47 (t, 2H, J = 7.6 Hz), 7.67 (d, 2H, J = 8.3 Hz), 7.75 (d, 2H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$): δ 165.87, 152.16, 140.71, 133.12, 129.82, 129.01, 128.97, 126.96, 126.53, 125.33, 28.48, 23.21, 21.86. IR (neat): (ν_{max}/cm^{-1}) 1680 (C═O), 1595, 1492, 1326. Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.26; H, 77.26; N, 10.58; 6-(2,4-dimethylphenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (**5**): red oil, ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.5 (s, 3H), 2.8 (t, 2H, J = 8.5 Hz), 3.0 (t, 2H, J = 8.5 Hz), 7.10 (s, 1H), 7.12 (s, 1H), 7.28–7.33 (m, 2H), 7.45 (t, 2H, J = 8.2 Hz), 7.61 (d, 2H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 165.75, 155.60, 141.49, 139.66, 136.22, 134.02, 132.51, 128.93, 127.12, 126.93, 125.30, 28.74, 26.95, 21.61, 21.60. IR (KBr): (ν_{max}/cm^{-1}) 1677, 1600, 1494, 1326. Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52. N, 10.06; found: C, 77.56; H, 6.23; N, 10.18; 6-(4-chlorophenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (**6**): red oil. ^{1}H NMR ($CDCl_3$): δ 2.8 (t, 2H, J = 8.5 Hz), 3.08 (t, 2H, J = 8.5 Hz), 7.33 (t, 1H, J = 7.3 Hz), 7.41 (d, 2H, J = 8.6 Hz), 7.48 (t, 2H, J = 8.2 Hz), 7.62 (d, 2H, J = 7.4 Hz), 7.77 (d, 2H, J = 8.62 Hz). ^{13}C NMR ($CDCl_3$): δ 165.53, 150.68, 141.59, 136.44, 129.29, 129.00, 127.91, 127.14, 125.39, 125.26, 28.31, 23.17. IR (KBr): (ν_{max}/cm^{-1}) 1683, 1595, 1490, 1326, 1012. Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.21; H, 4.58; N, 9.81; 2,6-bis(4-methoxyphenyl)-4,5-dihydropyridazin-3(2H)-one (**9**): red oil; ^{1}H NMR ($CDCl_3$): δ 2.73 (t, 2H, J = 8.5 Hz), 3.02 (t, 2H, J = 7.64 Hz), 3.81 (s, 3H), 3.83 (s, 3H), 6.90–6.94 (m, 4H), 7.47 (d, 2H, J = 8.9 Hz), 7.73 (d, 2H, J = 8.86 Hz). ^{13}C NMR ($CDCl_3$): δ 165.86, 161.53, 158.50, 151.61, 134.95, 128.42, 128.07, 126.83, 114.40, 114.24, 55.92, 55.81, 28.37, 23.23. IR (neat): (ν_{max}/cm^{-1}) 1683, 1595, 1490, 1326; Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.51; H, 5.69; N, 9.45; 2,4-diphenylphthalazin-1(2H)-one (**10**): light brown solid. ^{1}H NMR ($CDCl_3$): δ 7.41 (t, 1H, J = 7.3 Hz), 7.51–7.57 (m, 5H), 7.69 (d, 2H, J = 5.5 Hz), 7.78 (d, 2H, J = 7.6 Hz), 7.84–7.87 (m, 3H), 8.66 (d, 1H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$): δ 159.37, 148.05, 142.43, 135.47, 133.59, 132.18, 131.98, 130.06, 129.87, 129.40, 129.11, 128.20, 128.08, 127.18, 126.18. IR (KBr): (ν_{max}/cm^{-1}) 1656, 1580, 1487, 1325. Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.25; H, 4.51; N, 9.27; 2-phenyl-4-o-tolyl-2H phthalazin-1-one (**11**): brown solid.^{1}H NMR ($CDCl_3$): δ 2.5 (s, 3H), 7.37–7.42 (m, 3H), 7.52 (t, 2H, J = 8.0 Hz), 7.59 (d, 2H, J = 7.9 Hz), 7.79 (d, 2H, J = 7.7 Hz), 7.82–7.86 (m, 3H), 8.66 (d, 1H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 159.37, 148.07, 142.50, 139.67, 133.51, 132.62, 131.99, 129.88, 129.74, 129.65, 129.41, 129.11, 128.15, 128.00, 127.35, 126.26, 21.80. IR (KBr): (ν_{max}/cm^{-1}): 1662, 1595, 1490, 1330. Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.35; H, 5.87; N, 8.43; 4-(2,4-dimethylphenyl)-2-phenyl-2H phthalazin-1-one (**12**): light brown solid, ^{1}H NMR ($CDCl_3$,): δ 2.25 (s, 3H), 2.45 (s, 3H), 7.17 (d, 1H, J = 7.6 Hz), 7.21 (s, 1H), 7.30 (d, 1H, J = 7.5 Hz), 7.38–7.43 (m, 2H), 7.50 (t, 2H, J = 7.7 Hz), 7.76 (d, 3H, J = 7.8 Hz), 7.83 (t, 1H, J = 7.3 Hz), 8.63 (d, 1H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 159.48, 148.42, 142.41, 139.54, 137.30, 133.74, 133.54, 131.98, 131.78, 130.30, 129.14, 127.98, 127.28, 127.07, 126.35, 126.17, 21.70, 20.28. IR (KBr): (ν_{max}/cm^{-1}) 1662 (C═O), 1583, 1492, 1330. Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.80; H, 5.57; N, 8.39; 4-(2-chlorophenyl)-2-phenyl-2H phthalazin-1-one (**13**): light brown solid, ^{1}H NMR ($CDCl_3$): δ 7.40 (t, 1H, J = 7.4 Hz), 7.51–7.59 (m, 5H), 7.68 (d, 2H, J = 7.2 Hz), 7.78 (d, 2H, J = 7.6 Hz), 7.83–7.88 (m, 2H), 8.66 (d, 1H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 159.37, 148.04, 142.44, 135.48, 133.59, 132.08, 129.98, 129.66, 129.55, 129.40, 129.15, 129.07, 128.18, 128.08, 127.30, 126.27, 126.27. IR (KBr): (ν_{max}/cm^{-1}) 1662 (C═O), 1593, 1569, 1490, 1323, 1139. Anal. Calcd. for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.94; N, 8.42. Found: C, 72.52; H, 3.57; N, 8.27.