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Novel route to spiropiperidines using *N*-methyl-4-piperidone, malononitrile and electrophiles

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ABSTRACT

A new pathway to spiropiperidine rings via sequential one pot reaction of *N*-methyl-4-piperidone, malononitrile, and electrophiles or Michael acceptor in the presence of triethyl amine in ethanol under reflux condition is reported.

The synthesis of piperidine rings has achieved much attention as they display a fascinating array of biological applications such as spasmolytic activity and potent cytotoxicity toward human Molt 4/C8 and CEM T-lymphocytes as well as murine P388 and L1210 leukemic cells.[1] Spiropiperidine nucleus is frequently recognized in several natural alkaloids since it possesses high agonistic activity and selectivity as Ro64-6198 and also shows anxiolytic properties.[2]

The oxindole framework bearing a spirocyclic quaternary stereocenter at the C3 position is a significant privileged heterocyclic scaffold since it appears in a plethora of natural alkaloids, such as horsifiline, spirotryprostatine A and B, elacomine etc and also acts as potent nonpeptide inhibitor of the p53-MDM2 interaction.[3,4] Inspite of the enormous importance of spiro-oxindoles and spiropiperidine derivatives due to their biological activities, only a few reports are existing on the assembly of spiro derivatives that incorporate both bioactive moieties in a single framework.[5]

Recently, Alizadeh et al. have synthesized spiro-oxindoles via four component reaction of amines, isatin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, and alkyl acetoacetate.[6] We have recently reported the synthesis of spiro-oxindoles via 1,3-dipolar cycloaddition and vinylogous nucleophilic addition[7] and also developed a new pathway to spiro-oxindoles through a one-pot reaction of isatin, sarcosine, and 3-phenyl-5-isoxazolone.[8] On the basis of our progressive endeavors in exploring new methodologies toward spiro-oxindoles, we herein wish to report a sequential one pot reaction involving isatin, *N*-methyl-4-piperidone and malononitrile in the presence of triethyl amine in ethanol under reflux to furnish spiroderivatives containing both spiro-oxindoles and spiropiperidines. Here, the unsaturated 2-(1-methyl-piperidin-4-ylidene)-malononitrile formed in situ from *N*-methyl-4-piperidone and malononitrile dimerizes to yield the dimer spiro-piperidinoisoquinoline[9] which plays a major role in the synthesis of spiro-oxindoles. To the best of our knowledge, this is the first report on the dimer (spiro-piperidinoisoquinoline) of 2-(1-methyl-piperidin-4-ylidene)-malononitrile involved to synthesize functionalized spiro-oxindoles.

Initially, in our pilot experiment, a mixture of *N*-methyl-4-piperidone 1 (1.0 mmol) and malononitrile **2** (1.0 mmol) in ethanol was stirred at room temperature in the presence of triethyl amine for 5 min to afford the dimer spiro-piperidinoisoquinoline **3** which was also confirmed by spectroscopic studies (Scheme 1).[9,10]

The dimer spiro-piperidinoisoquinoline **3** was treated with isatin **4a** in the presence of triethyl amine in various solvents like ethanol, toluene, and acetonitrile under reflux condition which led to the formation of functionalized spiro-oxindole containing spiropiperidine ring **5a** as a single diastereomer (Scheme 2, Table 1).

Moreover, the sequential one pot reaction of *N*-methyl-4-piperidone 1 (1.0 mmol), malononitrile **2** (1.0 mmol), and isatin **4a** (1.0 mmol) in ethanol under reflux in the presence of triethyl amine also resulted in the formation of spiro-oxindole containing spiropiperidine ring **5a** as a single diastereomer which was proved by ^{1}H NMR spectroscopy.

The best result was obtained by refluxing an equimolar mixture of *N*-methyl-4-piperidone **1**, malononitrile **2** (1.0 mmol) in ethanol

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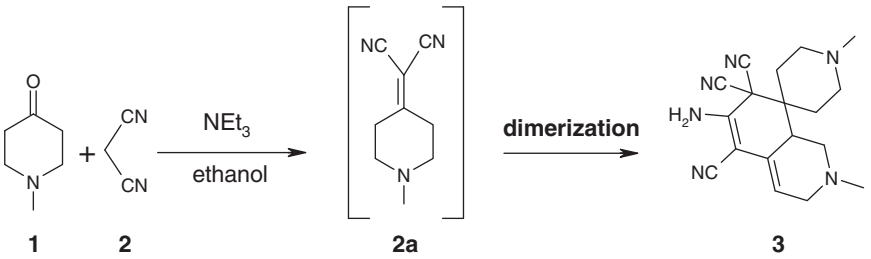
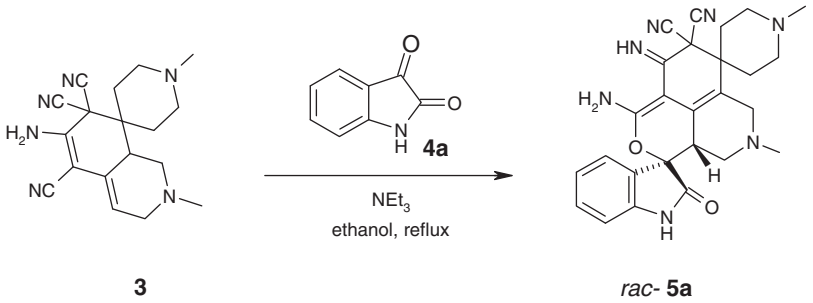


Scheme 1. Synthesis of dimer spiro-piperidinoisoquinoline **3**.



Scheme 2. Synthesis of spiro-oxindole derivatives containing spiropiperidine ring **5a**.

Table 1
Synthesis of spiro-oxindoles having spiropiperidine ring **5a** by Scheme 2

Entry	Solvent	Reflux temperature[a](°C)	Yield[b] (%)
1	Ethanol	79	82
2	Acetonitrile	82	79
3	Toluene	110	67

[a] Reflux temperature of the solvent.
[b] Isolated yield by recrystallization.

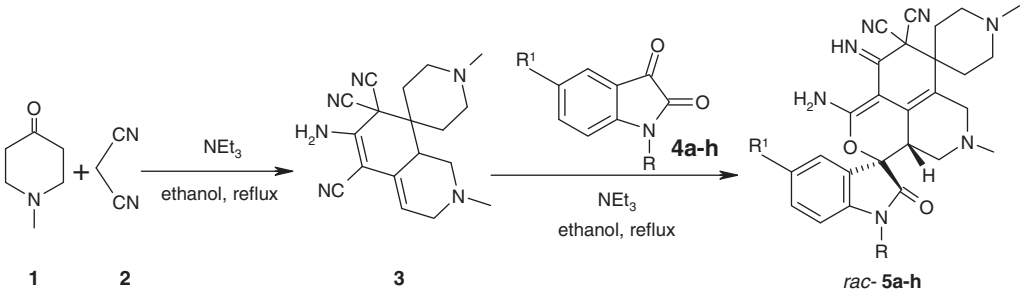
for 5 min followed by the addition of isatin **4a** (1.0 mmol) and the reflux was continued until the completion of the reaction to yield the spiro-oxindole **5a** with good yield (85%) (Scheme 3, Table 2).[11]

The optimized protocol of this cyclization reaction was then expanded to a variety of substituted isatin derivatives **4a–h** and other cyclic ketones such as ninhydrin **6**, acenaphthenequinone **8,** and indeno[1,2-*b*]quinoxalin-11-one **10** to provide spiro frameworks containing spiro piperidine ring **5a–h**, **7**, **9,** and **11,** respectively, as single diastereomer with good yields (71–85%) as evidenced by TLC and spectral analysis (Table 2 and Schemes 3 and 4).

The structures of the compounds **5a–h**, **7**, **9,** and **11** were confirmed by spectroscopic studies and elemental analysis. In IR spectrum of compound **5a**, the absorptions at frequencies 2249 and 1742 cm^{-1} correspond to cyano and amide functional groups. In the ^1H NMR spectrum, there are thirteen aliphatic protons. Two singlets were observed at δ 2.13 and 2.17 ppm which showed the presence of protons of two –NCH_3 groups. The characteristic singlets at δ 8.29, 9.07, and 10.02 ppm were assigned to –NH_2 protons, –N*H* proton of the imine group and –N*H* proton of the oxindole ring, respectively, which proved the incorporation of oxindole ring in the structure. The amide carbonyl carbon atom of oxindole ring resonated at δ 172.6 ppm in ^{13}C NMR spectrum. The presence of a molecular ion peak at *m*/*z* 470.20 in the mass spectrum which further supported the formation of the product **5a**.[12]

The IR spectrum of compound **7** showed peaks at 1739 and 1706 cm^{-1} for indandione carbonyl groups. The ^1H NMR spectrum of compound **7** exhibited four characteristic singlets at δ 2.09, 2.15, 8.20, and 8.60 ppm for two –NCH_3 protons, –NH_2 protons and –N*H* proton of imine group, respectively. The two keto carbonyl carbon atoms of indandione showed peaks at δ 194.2 and 195.0 ppm in ^{13}C NMR spectrum. These observed chemical shift values confirmed the proposed structure. A distinguishing peak was observed at *m*/*z* 483.32 in the mass spectrum. The relative stereochemistry of the products **5a–h**, **9,** and **11** was established through single–crystal X-ray analysis of compound **5a** (Fig. 1).[13]

On the basis of the above results, a tentative mechanistic interpretation to explain the formation of product **5a** is proposed (Scheme 5). Usually, *N*-methyl-4-piperidone **1** involves Knoevenagel condensation with malononitrile **2** to give 2-(1-methyl-piperidin-4-ylidene)-malononitrile **2a** which is unstable and dimerizes



Scheme 3. Synthesis of spiro-oxindole derivatives containing spiropiperidine ring **5a**–**h** by sequential one pot approach.

Table 2
Synthesis of spiro-oxindoles having spiropiperidine ring **5a–h** by sequential one pot approach (Scheme 3)

Entry	Isatin (**4a–h**)	R	R^1	Product (**5**)[a]	Time (min)	Yield[b] (%)
1	**4a**	H	H	**5a**	45	85
2	**4b**	H	Cl	**5b**	45	83
3	**4c**	H	Br	**5c**	65	82
4	**4d**	H	Methyl	**5d**	65	81
5	**4e**	Allyl	H	**5e**	65	81
6	**4f**	Benzyl	H	**5f**	65	80
7	**4g**	Propargyl	H	**5g**	65	78
8	**4h**	Methyl	H	**5h**	65	81

[a] The products were characterized by spectral and elemental analysis.
[b] Isolated yield by recrystallization.

in situ to give spiro-piperidinoisoquinoline **3**.[9] The dimer **3** adds on to isatin keto carbonyl group **4a** to yield 3-hydroxyoxindole **3a** in presence of triethyl amine. The intermediate **3a** cyclizes intramolecularly via the nucleophilic attack of the –OH group on the cyano triple bond resulting in the formation of imine intermediate **3b**. The intermediate **3b** involves proton transfer to afford product **5a**.

The promising results prompted us to extend the protocol by replacing cyclic ketones with aromatic aldehydes (**12a–h**) under identical conditions (Scheme 6). The dimer **3** formed in situ from *N*-methyl-4-piperidone **1** and malononitrile **2** undergoes nucleophilic addition with aromatic aldehydes (**12a–h**) to furnish 3-aryl-3*H*-spiro[piperidine-4',7-pyrano[3,4,5-*de*]isoquinoline] derivatives (**13a–h**) in good yields (76–82%) (Table 3).

With a view to explore the generality of the reaction, various derivatives of isatylidene malononitrile (**14a–h**) as Michael acceptor and dimer **3** were exploited to synthesize a library of spiro-oxindoles containing spiro piperidine rings (**15a–h**) under optimized conditions (Scheme 7).

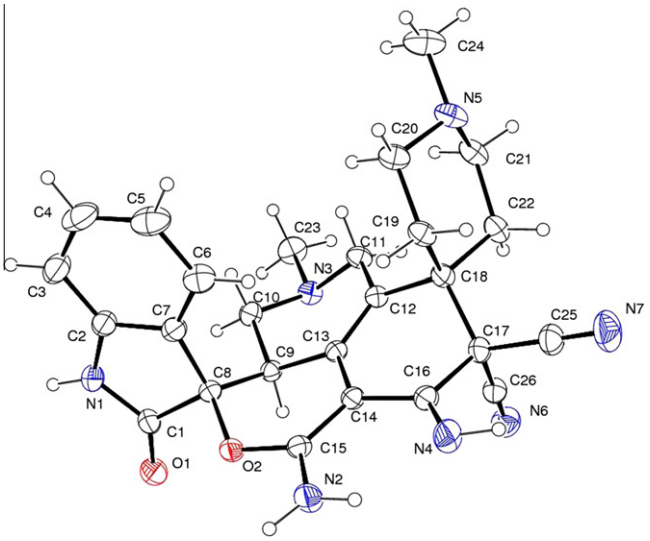
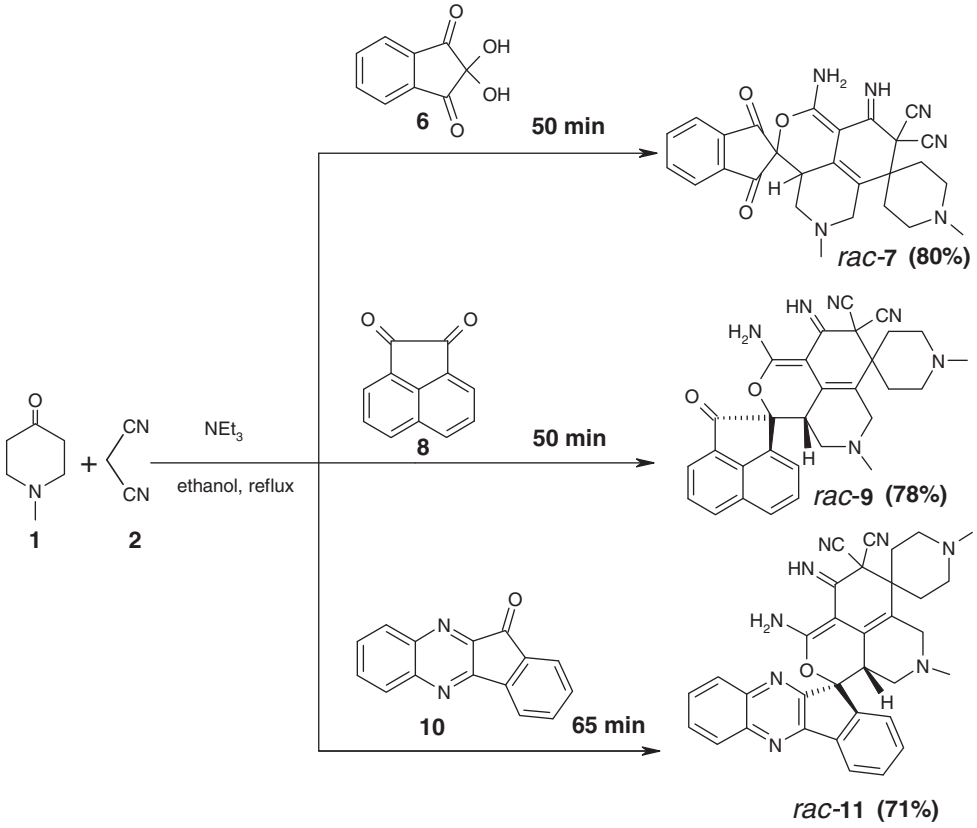


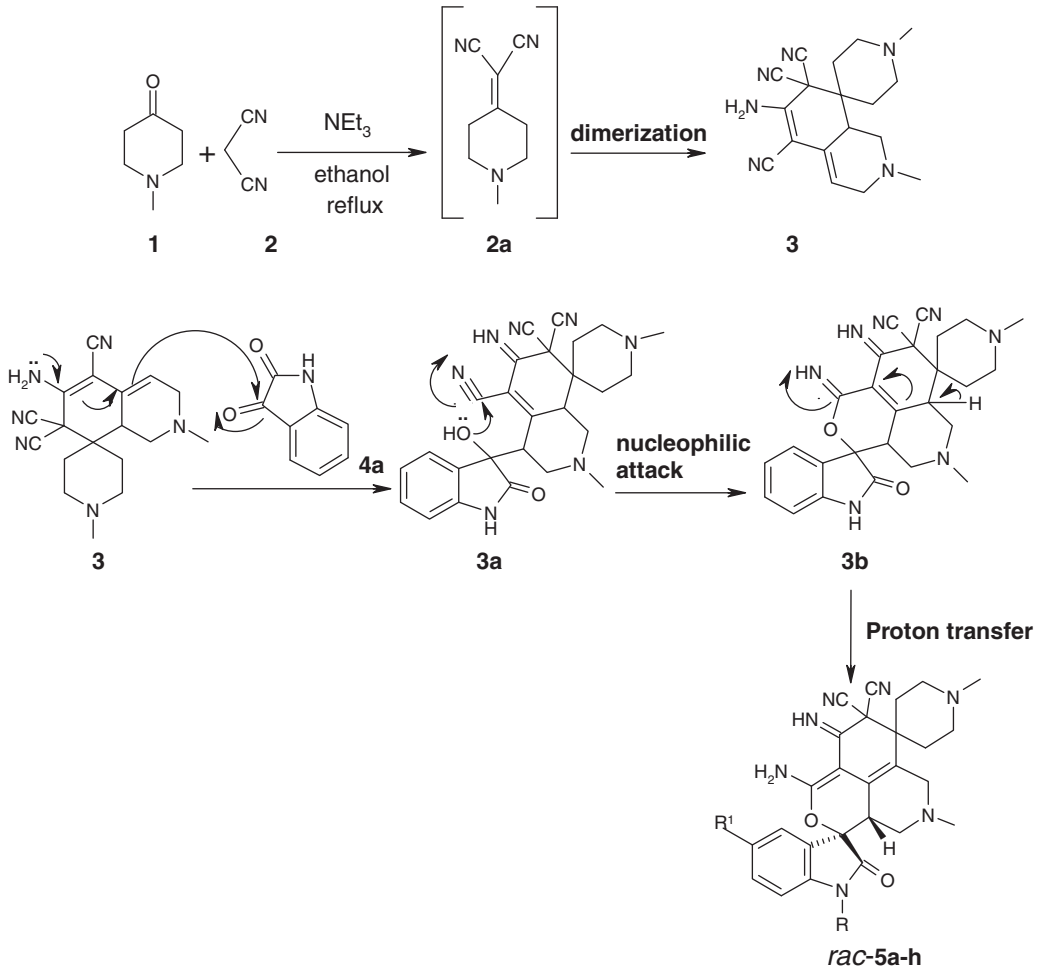
Figure 1. ORTEP diagram of compound **5a**.

The dimer **3** undergoes Michael addition with derivatives of isatylidene malononitrile (**14a–h**) instead of nucleophilic addition as in Scheme 5 to provide spiro-oxindoles (**15a–h**) in good yields (72–78%) (Table 4). The reaction is diastereoselective since only one diastereomer was formed in all the reactions.

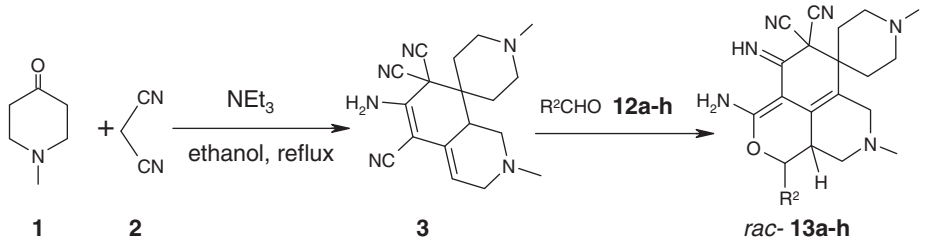
The spiro-oxindoles **15a–h** were confirmed by spectral and elemental analysis. The IR spectrum of compound **15a** showed peaks at 2232 and 1695 cm^{-1} for cyano and amide functional groups. The ^1H NMR spectrum of compound **15a** exhibited four characteristic singlets at δ 2.04, 2.21, 7.12, and 8.30 ppm for two –NCH_3 protons,



Scheme 4. Synthesis of spiroframeworks containing spiropiperidine rings **7**, **9** and **11**.



Scheme 5. Plausible mechanism for the synthesis of spiro-oxindoles containing spiropiperidine ring **5a**–**h**.



Scheme 6. Synthesis of 3-aryl-3*H*-spiro[piperidine-4',7-pyrano[3,4,5-*de*]isoquinoline] derivatives **13a**–**h**.

–NH_2 protons and –N*H* proton of imine group (D_2O exchangeable) respectively. A broad singlet at δ 10.67 ppm indicates the presence of –N*H* proton of oxindole ring (D_2O exchangeable).

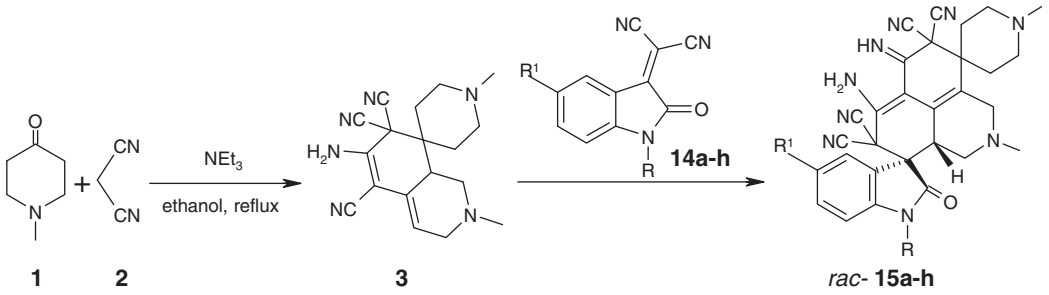
The amide carbonyl carbon atom of oxindole ring showed a signal at δ 166.3 ppm in ^{13}C NMR spectrum. A distinguishing peak was observed at *m*/*z* 518.43 in the mass spectrum. The stereochemistry of the products **15a–h** was assigned by analogy of compound **5a**.

In summary, we have demonstrated a simple, facile, and novel reaction for the synthesis of spiro-frameworks containing spiropiperidine ring from cyclic ketones such as isatin, ninhydrin, acenaphthenequinone, and indeno[1,2-*b*]quinoxalin-11-one. The Knoevenagel condensation product of *N*-methyl-4-piperidone and malononitrile was dimerized to form spiro-piperidinoisoquinoline which attacks cyclic ketones and aromatic aldehydes to provide a

Table 3
Synthesis of 3-aryl-3*H*-spiro[piperidine-4',7-pyrano [3,4,5-*de*]isoquinoline] derivatives **13a**–**h**

Entry	R^2CHO (**12a**–**h**)	R^2	Product (**13**)[a]	Time (min)	Yield[b] (%)
1	**12a**	C_6H_5	**13a**	70	76
2	**12b**	1-Napthyl	**13b**	70	78
3	**12c**	2-Napthyl	**13c**	70	78
4	**12d**	4-ClC_6H_4	**13d**	70	80
5	**12e**	4-BrC_6H_4	**13e**	70	82
6	**12f**	4-$CH_3C_6H_4$	**13f**	70	78
7	**12g**	4-$OCH_3C_6H_4$	**13g**	70	76
8	**12h**	4-FC_6H_4	**13h**	70	76

[a] The products were characterized by spectral and elemental analysis.
[b] Isolated yield by recrystallization.



Scheme 7. Synthesis of spiro-oxindoles containing spiropiperidine ring derivatives **15a–h**.

Table 4
Synthesis of spiro-oxindoles having spiropiperidine rings **15a–h**

Entry	(**14a–h**)	R	R^1	Product (**15**)[a]	Time (min)	Yield[b] (%)
1	**14a**	H	H	**15a**	85	75
2	**14b**	H	Cl	**15b**	85	78
3	**14c**	H	Br	**15c**	85	78
4	**14d**	H	Methyl	**15d**	95	78
5	**14e**	Allyl	H	**15e**	95	76
6	**14f**	Benzyl	H	**15f**	95	75
7	**14g**	Propargyl	H	**15g**	95	72
8	**14h**	Methyl	H	**15h**	95	72

[a] The products were characterized by spectral and elemental analysis.
[b] Isolated yield by recrystallization.

series of spiropiperidine derivatives. Moreover a further delineation to replace isatin by isatylidene malononitrile as Michael acceptor to synthesize spiro-oxindoles containing spiro piperidine rings is also discussed. The simplicity of the approach makes this strategy useful for the synthesis of novel spiro frameworks. Further studies to delineate the scope and limitations of the present methodology are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.129.

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10. *Spectral data of compound* **3**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.46–1.49 (m, 1H), 1.61–1.64 (m, 1H), 2.00 (s, 3H, -NCH_3), 2.11–2.12 (m, 3H), 2.14–2.16 (m, 1H), 2,2 (s, 3H, -NCH_3), 2.42–2.44 (m, 1H), 2.66–2.68 (m, 2H), 2.77 (d, 1H, J = 7.0 Hz), 2.92–2.95 (m, 1H), 3.10–3.12 (m, 1H), 3.19–3.21 (m, 1H), 5.68 (t, 1H, J = 2.5 Hz), 7.27 (s, 2H, –NH_2, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6): 26.6, 33.2, 43.8, 45.7, 46.1, 50.9, 51.8, 53.1, 53.3, 54.6, 55.3, 81.0, 113.2, 113.3, 116.1, 120.2, 126.7, 142.9. MS (EI): (m/z) 323.12 [M+H]$^+$.
11. Typical experimental procedure for **5a**: A mixture of *N*-methyl-4-piperidone **1** (1.0 mmol), malononitrile **2** (1.0 mmol) in the presence of triethyl amine was refluxed in ethanol for 5 min. After that, isatin **4a** (1.0 mmol) was added and was refluxed for 40 min and cooled to room temperature. The solid formed in the reaction mixture was filtered and dried under vacuum. The crude solid product was purified by recrystallization in ethanol to obtain the pure product **5a** in good yield (85%).
12. *Spectral data of compound 5a* (Table 1, entry 1): White solid. mp 284–286 °C. R_f 0.25 (50% EtOAc/Petroleum ether); ν_{max} (KBr): 3449, 3314, 2943, 2797, 2249, 1742, 1635, 1583, 1471, 1323, 1211, 1123, 1082, 791, 749 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14 (t, 1H, J = 10.7 Hz), 1.61 (t, 1H, J = 11.45 Hz), 1.86–1.89 (m, 2H), 1.94–1.96 (m, 1H), 2.02–2.04 (m, 1H), 2.13 (s, 3H, –NCH_3), 2.17 (s, 3H, –NCH_3), 2.50–2.52 (m, 1H), 2.69–2.72 (m, 2H), 2.81–2.83 (m, 1H), 3.07–3.09 (m, 1H), 3.31–3.33 (m, 2H), 6.77 (d, 1H, J = 7.65 Hz, Ar-*H*), 6.90–6.93 (m, 2H, Ar-*H*), 7.29 (t, 1H, J = 7.65 Hz, Ar-*H*), 8.29 (s, 2H, –NH_2, D_2O exchangeable), 9.07 (br s, 1H, –N*H*, D_2O exchangeable), 10.02 (br s, 1H, –N*H*, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6): 31.2, 31.9, 37.9, 43.7, 45.6, 46.0, 51.3, 52.7, 55.3, 58.3, 81.2, 81.3, 111.2, 114.0, 119.4, 122.9, 123.2, 124.9, 125.6, 131.7, 142.7, 160.0, 172.6. MS (EI): (m/z) 470.20 [M+H]$^+$. Anal. Calcd for $C_{26}H_{27}N_7O_2$: C 66.51; H 5.80; N 20.88. Found: C 66.54; H 5.78; N 20.93.
13. Crystallographic data for compound **5a** in this paper have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no. CCDC-833093. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).