Tetrahedron xxx (2018) 1–6

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An expeditious access of 2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone in water

Keshri Nath Tiwari*, S.M. Prabhakaran, Vaneet Kumar, Thakar Snehal Rajendra, Shintu Mathew

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), ITI Compound, Raebareli, 229010, India

ARTICLE INFO

Article history:
Received 21 February 2018
Received in revised form
4 May 2018
Accepted 7 May 2018
Available online xxx

Keywords:
Isatin
Enaminone
Ethyl cyanoacetate
Spirooxindole
Multicomponent reaction

ABSTRACT

We have demonstrated three component reaction of isatin, enaminone and ethyl cyanoacetate leading to sprirooxindole scaffold without catalyst in water. The synthetic protocol has several advantages like wide substrate scope, atom-economy and operationally simple experimental procedures which provides rapid access to library of compounds. The mechanistic details of the reaction has been investigated during the course of study.

1. Introduction

Multicomponent reactions are widely explored as a synthetic tool due to their atom economy, operationally simple procedures and flexible substrate scope.[1] Such reactions create several covalent bonds in one pot and provide a quick access to library of molecules for combinatorial chemistry. These reactions also provide opportunity to create complex molecular structure with several contiguous stereocentres which otherwise require several steps in linear synthesis. There has been major concerns in development of multicomponent reactions with respect to reaction media particularly solvents.

Now a days, much attention is also being paid on the development of synthetic methods using water as a reaction media in view of the fact that many toxic solvents contribute to the environmental pollution.[2] Water is a non-hazardous, non-toxic and inexpensive solvent and despite having certain limitations like poor solubility of organic substrates, many organic reactions have now been widely demonstrated using water as a reaction media.[3] Several metal catalyzed reactions which were initially considered difficult are now also carried out in aqueous media for the synthesis of pharmaceutically active ingredients.[4] It is also considered as near to ideal green solvent due to its recyclability and environmental benign reasons. Therefore, it is highly desirable to develop synthetic processes that can be performed in aqueous media.

The nitrogen containing spirocyclic oxindoles are featured in a number of natural products as well as medicinally active compounds and exhibit a broad spectrum of bioactivities like antimicrobial, antibacterial and anti-inflammatory.[5] Particularly, the six member nitrogen containing spirooxindoles have garnered considerable interest due to their pharmaceutical applications as well as structural complexity.[6]

For example Surugatoxin, having similar spirooxindole have been found as ganglionic blocker of nicotinic acetylcholine receptors and cipargamin (NITD609) is an antimalarial drug belonging to spiroindolone class (Fig. 1).[7]

The reaction of isatin with 1,3-cyclohexadione leading to spirooxindoles[8] has been recently reported. However, the reaction of isatin with enaminones have been shown to yield pyrroloquinolones under cascade conditions.[9] The three component reaction of isatin, enaminone and ethyl cyanoacetate have not been explored so far to the best of our knowledge.

* Corresponding author.
E-mail address: keshri.tiwari@niperraebareli.edu.in (K.N. Tiwari).

https://doi.org/10.1016/j.tet.2018.05.020
0040-4020/

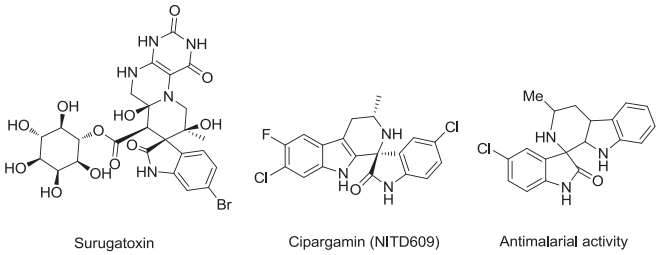


Fig. 1. Some biologically active spirooxindoles.

As a part of our research plan aimed at developing new synthetic methodologies for the creation of biologically important molecules,[10] we inspired to investigate greener protocols for generation of dihydropyridine fused spirooxindoles. Along this line, we wish to report the synthesis of 2,5′-dioxo-5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone using water as a solvent.

2. Results and discussion

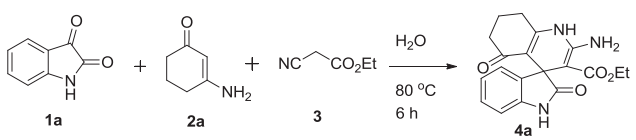
The reaction of isatin (**1a**), enaminone (**2a**) and ethyl cyanoacetate (**3**) was chosen as a model substrate using water as a reaction media. The three substrates in equimolar ratio were heated at 80 °C without catalyst. In the beginning, the colour of reaction mixture was orange but after the few hours of reaction, the light yellow solid precipitated out.

The solid precipitated in small amount was identified as product (**4a**) by TLC. The aqueous layer was extracted with ethyl acetate several times. The precipitated solid was further dissolved in combined organic layer which was evaporated and purified by silica gel column chromatography to afford product (**4a**) in 61% of yield (Scheme 1). On structural characterization by NMR spectral analysis, the product was identified as ethyl 2′-amino-2,5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate (**4a**).

The reaction provided the expected product in good yield with relatively shorter duration. To obtain the optimized conditions, the reaction was screened in different solvents using model substrate. It is quite evident from Table 1 that water acts as better solvent in comparison to organic solvents like MeOH, EtOH, THF, CH_3CN etc. for this reaction. The yield of the reaction was found maximum in water as compared to other solvents after six hours of reaction. The reactions in other solvents were continued for even longer hours (up to 24 h) but either reaction was not completed or degradation happened. The yield is based on isolation of expected product after 6 h of reaction. The temperature of reaction was fixed based on reflux temperature of particular solvent in order to keep optimal conditions as at higher temperature decomposition was observed.

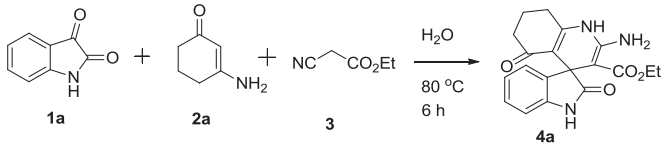
To investigate further, the scope of reaction was explored with different substituted isatin and enaminone. Firstly, the scope of isatin substitution was examined on the course of reaction and to our happiness all the isatins were found reactive towards the optimized reaction conditions to provide good to excellent yield of products (Scheme 2).

To extend the synthetic strategy, the scope of enaminone was



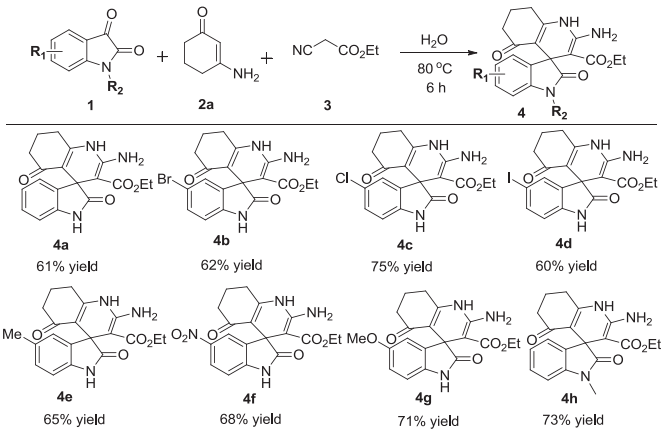
Scheme 1. Three component reaction of isatin, enaminone and ethyl cyanoacetate.

Table 1
Optimization of condition[a].



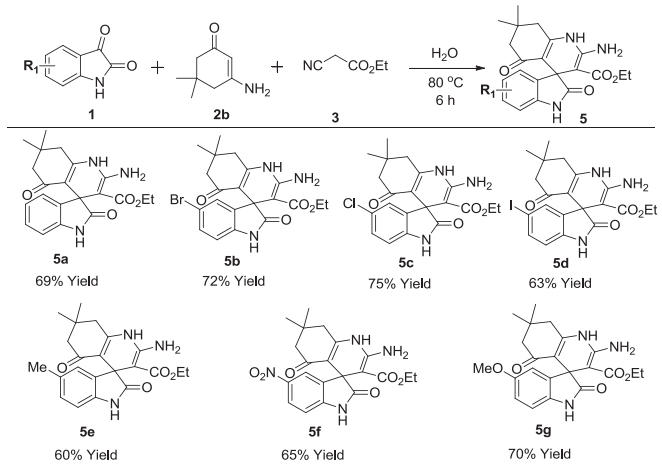
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	MeOH	65	6	30
2	EtOH	75	6	35
3	DCE	80	6	20
4	CH_3CN	80	6	45
5	DMF	120	6	50
6	H_2O	80	6	61
7	Toluene	100	6	35
8	THF	60	6	50

[a] Reaction conditions Isatin (1.36 mmol), Enaminone (1.36 mmol), ECA (1.36 mmol).
[b] Isolated yield after silica gel chromatography.



Scheme 2. Examples of three component reaction with **2a**.

next studied. The enaminone with dimedone was prepared by our recently developed protocol in water.[10c] Consequently, the two enaminones **2a** (Scheme 2) and **2b** (Scheme 3) were found compatible with several isatins and provided expected product



Scheme 3. Examples of three component reaction with **2b**.

Please cite this article in press as: Tiwari KN, et al., An expeditious access of 2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone in water, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.020

with good yield (up to 75%).

Further to diversify the scope of reaction with enaminone, the acetylacetone derived enaminone (**2c)** was also allowed to react with isatin (**1a**) and ethylcyanoacetate (**3**) but unfortunately it provided ethyl 2-cyano-2-(oxoindolin-3-ylidene) acetate (**7**) as only product (Scheme 4).

Similarly, when isatin (**1a**) was allowed to react with 3-aminocyclopent-2-en-1-one (**2d**), synthesized from 1,3-cyclopentadione and ammonium acetate, and ethyl cyanoacetate (**3**) which provided the expected product **(6)** with yield of 55% (Scheme 5). In order to attempt reaction with 3-aminocyclohept-2-enone, several attempts were made for the synthesis of 3-aminocyclohept-2-enone but unfortunately no desired product was isolated.

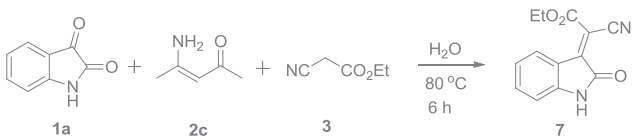
Accordingly, two new series of ethyl 2′-amino-2,5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate **4** (**a**–**h**) and ethyl 2′-amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate **5** (**a**–**g**) were synthesized and their structure were deduced by respective spectral analysis (^{1}H NMR, ^{13}C NMR and HRMS). The structure of the one representative compounds **4b** was further confirmed by X-ray analysis (Fig. 2).[11]

The versatility of this method is that it is being performed in sustainable reaction media like water without any catalyst. Most of the developed synthetic methods for these kind of reactions although use green solvent but the application of metal catalysts in the reaction limits the scope and make an impact on environment. This synthetic process also follows atom-economy principle as all the substrates are incorporated into product with only loss of water.

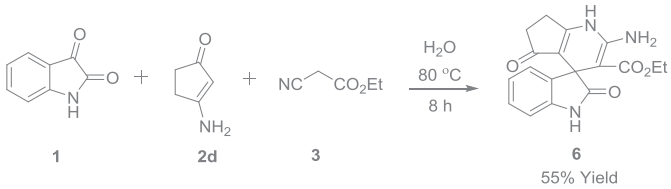
After conducting entire experimental executions and taking product structure into consideration, a plausible mechanism of product formation is outlined in Scheme 6. There could be two possible pathways for product formation. In first mechanism, the Knoevenagel condensation happens between isatin (**1a**) and ethyl cyanoacetate (**3**) to gives ethyl 2-cyano-2-(oxoindolin-3-ylidene) acetate (**8**). Further, the enaminone (**2a**) attacks on double bond of **8** preferably from less hindered side. The internal nucleophilic attack of amine on carbon of nitrile gives spiro annulation to form product **4a**. In second mechanism, isatin (**1a**) and enaminone (**2a**) reacts to provide 3-sunstituted-3-hydroxyindoline-2-ones (**7**) which is then reacted with ethyl cyanoacetate (**3**) to give product **4a**.

To support both the mechanism, we carried out set of different control experiments. For first set of reaction, isatin (**1c**) was treated with enaminone (**2b**) in water under similar conditions which provided 3-sunstituted-3-hydroxyindoline-2-ones (**7**) as a single product which is otherwise known to give pyrrolo-quinolone in presence of catalyst as discussed earlier. When **7** was allowed to react with ethyl cyanoacetate (**3**) in water it cleanly provided **5c** as a sole product.

In the next set of experiment, the isatin (**1a**) was treated with ethyl cyanoacetate (**3**) in water under similar conditions which yielded ethyl 2-cyano-2-(oxoindolin-3-ylidene) acetate (**8**). The enaminone (**2b**) was then allowed to react with ethyl 2-cyano-2-(oxoindolin-3-ylidene) acetate (**8**) which provided **5a** in 69% yield (Scheme 7). This two set of experiments clearly indicates that the reaction follows both the proposed pathway as in Scheme 6.



Scheme 4. Three component reaction with **2c**.



Scheme 5. Three component reaction with **2d**.

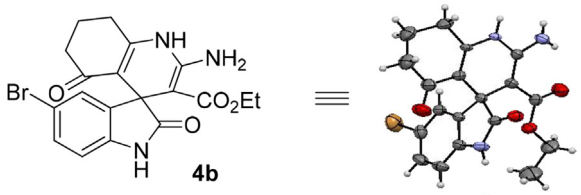
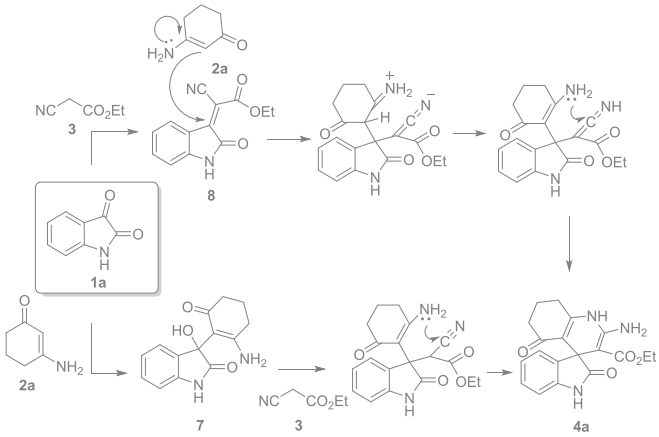
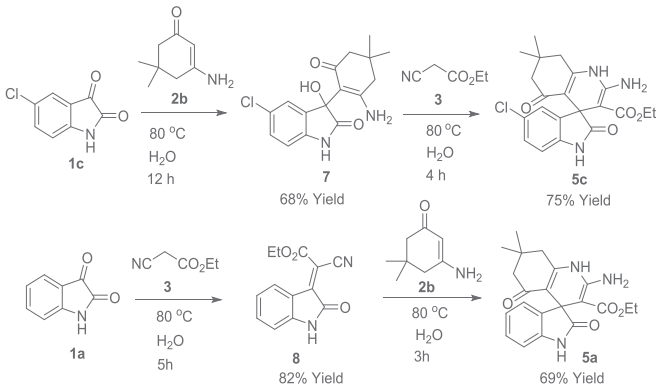


Fig. 2. ORTEP diagram of **4b**.



Scheme 6. Plausible mechanism for formation of **4a**.



Scheme 7. Control reaction of isatin, enaminone, and ethyl cyanoacetate.

However, it is significant to note that the first pathway is faster than second one.

3. Conclusions

To conclude, we have developed a novel and efficient one-pot three component protocol for the synthesis of ethyl 2′-amino-2,5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-

Please cite this article in press as: Tiwari KN, et al., An expeditious access of 2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone in water, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.020

carboxylate, ethyl 2′-amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate and ethyl 2-amino-2′,5-dioxo-1,5,6,7-tetrahydrospiro [cyclopenta [b] pyridine-4,3′-indoline]-3-carboxylate without any catalyst in water. Operationally simple procedures, high yield and environmental benign conditions make this protocol attractive and useful. The mechanistic postulations have also been rationalized based on set of control experiments. This method provides an easy entry into pharmaceutically active spirooxindole derivatives for combinatorial purpose. The further exploration of synthetic method and mechanistic studies is currently underway and will be reported with due course.

4. Experimental

4.1. Typical procedure for synthesis of **4a-4h**

A solution of 200 mg (1.36 mmol) of isatin (**1a**), 151 mg of 3-aminocyclohex-2-enone (**2a**) (1.36 mmol) and 0.144 mL (1.36 mmol) of ethyl cyanoacetate (**3**) was heated to 80 °C in H_2O for 6 h. After the TLC indicated the complete consumption of isatin, the reaction mixture was extracted with ethyl acetate three times. With few isatins, solid precipitate was obtained in reaction mixture in small amount which was found as expected product by TLC. The precipitated solid was dissolved in combined organic layer which was evaporated to provide light yellow solid and purified by silica gel column chromatography using hexane:ethyl acetate (6:4) as an eluent to provide **4a** as white solid (295 mg).

4.1.1. Ethyl 2′-amino-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate (**4a**)

White solid, 61%, m.p.: 216–218 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.12 (s, 1H) 7.83 (br s, 2H) 7.06–7.01 (m, 1H) 6.85–6.83 (m, 1H) 6.77–6.73 (m, 1H) 6.66 (br d, J = 7.36 Hz, 1H) 3.71–3.68 (m, 2H) 2.64–2.62 (m, 2H) 2.24–2.14 (m, 2H) 1.87 (br s, 2H) 0.79 (br t, J = 6.99 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.74, 179.83, 167.64, 164.15, 158.97, 144.01, 136.09, 127.08, 122.39, 120.47, 114.23, 107.99, 76.39, 58.79, 46.71, 37.08, 26.92, 19.63, 13.07 HRMS (ESI) *m/z* for $C_{19}H_{19}N_3O_4$ $[M + H]^+$, calcd, 354.1453, found, 355.1271.

4.1.2. Ethyl 2′-amino-5-bromo-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**4b**)

White solid, 62%, m.p.:222–224 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.29 (s, 1H) 7.91 (br s, 2H) 7.23–7.20 (dd, J = 8.21, 1.98 Hz, 1H) 7.03 (s, 1H) 6.64–6.62 (d, J = 8.12 Hz, 1H) 3.74–3.71 (m, 2H) 2.66–2.62 (m, 2H) 2.23–2.19 (m, 2H) 1.91–1.86 (m, 2H) 0.82 (t, J = 7.18 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.95, 179.45, 167.42, 164.75, 159.04, 143.49, 138.60, 129.77, 125.23, 113.58, 112.04, 109.88, 75.77, 58.93, 46.93, 36.97, 28.95, 26.93, 13.10HRMS (ESI) *m/z* for $C_{19}H_{18}BrN_3O_4$ $[M + H]^+$, calcd, 432.0558, found: 433.0375.

4.1.3. Ethyl 2′-amino-5-chloro-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**4c**)

White solid, 75%, m.p.:218–220 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.29 (s, 1H) 7.91 (s, 2H) 7.11–7.07 (dd, J = 8.12, 2.27 Hz, 1H) 6.94–6.93 (d, J = 2.08 Hz, 1H) 6.68–6.66 (d, J = 8.12 Hz, 1H) 3.76–3.70 (m, 2H) 2.67–2.63 (m, 2H) 2.21–2.19 (m, 2H) 1.92–1.89 (m, 2H) 0.83 (t, J = 7.18 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.94, 179.58, 167.43, 164.71, 159.04, 143.08, 138.20, 126.90, 124.35, 122.58, 113.58, 109.25, 75.76, 58.92, 46.97, 36.98, 26.93, 19.54, 13.1010HRMS (ESI) *m/z* for $C_{19}H_{18}ClN_3O_4$ $[M + H]^+$, calcd, 388.1064, found: 389.0891.

4.1.4. Ethyl 2′-amino-5-iodo-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**4d**)

White solid, 60%, m.p.:220–222 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.27 (s, 1H) 7.90 (br s, 2H) 7.39–7.36 (m, 1H) 7.15 (s, 1H) 6.54–6.52 (d, J = 7.93 Hz, 1H) 3.74–3.71 (m, 2H) 2.66–2.62 (m, 2H) 2.20–2.19 (m, 3H) 1.90–1.86 (m, 2H) 0.82 (br t, J = 7.08 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.96, 179.24, 167.42, 164.70, 159.02, 143.97, 138.87, 135.67, 130.59, 113.63, 110.58, 82.90, 75.83, 58.93, 46.72, 36.98, 26.92, 19.53, 13.10 HRMS (ESI) *m/z* for $C_{19}H_{18}IN_3O_4$ $[M + H]^+$, calcd, 480.0420, found: 481.0242.

4.1.5. Ethyl 2′-amino-5-methyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**4e**)

White solid, 65%, m.p.:206–208 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.01 (s, 1H) 7.82 (s, 2H) 6.85–6.82 (m, 1H) 6.66 (s, 1H) 6.56–6.54 (d, J = 7.74 Hz, 1H) 3.74–3.66 (q, J = 7.18 Hz, 2H) 2.66–2.62 (m, 2H) 2.15 (s, 3H) 1.91–1.86 (m, 2 H) 1.24–1.15 (m, 2H) 0.82 (t, J = 7.18 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.71, 179.79, 167.68, 164.05, 158.93, 141.60, 136.11, 128.99, 127.32, 123.12, 114.34, 107.74, 76.52, 58.81, 46.74, 37.11, 28.95, 20.62, 19.61, 13.05 HRMS (ESI) *m/z* for $C_{20}H_{21}N_3O_4$ $[M + H]^+$, calcd, 368.1610, found: 369.1435.

4.1.6. Ethyl 2′-amino-5-nitro-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**4f**)

White solid, 68%, m.p.:222–224 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.95 (s, 1 H) 8.10–8.06 (m, 1H) 8.00 (s, 2H) 7.80 (d, J = 2.46 Hz, 1H) 6.87 (d, J = 8.69 Hz, 1H) 3.73 (q, J = 7.11 Hz, 2H) 2.69–2.67 (m, 2H) 2.21–2.19 (m, 2H) 1.91–1.89 (m, 2H) 0.82 (t, J = 7.18 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 195.27, 170.27, 167.14, 165.43, 159.21, 150.83, 141.53, 137.20, 125.05, 117.99, 113.08, 107.98, 75.13, 59.70, 46.73, 36.78, 28.94, 20.70, 14.03HRMS (ESI) *m/z* for $C_{19}H_{18}N_4O_6$ $[M + H]^+$, calcd, 399.1304, found: 400.1155.

4.1.7. Ethyl 2′-amino-5-methoxy-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**4g**)

White solid, 71%, m.p.:208–210 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.95 (s, 1 H) 7.83 (br s, 2 H) 6.63–6.60 (m, 1H) 6.59–6.54 (m, 1H) 6.47–6.46 (m, 1H) 3.74–3.68 (q, J = 7.11 Hz, 2H) 3.62 (s, 3H) 2.63–2.61 (m, 2H) 2.21–2.12 (m, 2H) 1.89–1.86 (m, 2H) 0.82 (br t, J = 6.99 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.71, 179.65, 167.68, 164.12, 158.92, 154.24, 137.63, 137.41, 114.15, 111.12, 110.01, 108.01, 76.40, 58.82, 55.22, 47.19, 37.12, 26.95, 19.60, 13.07 HRMS (ESI) *m/z* for $C_{20}H_{21}N_3O_5$ $[M + H]^+$, calcd, 384.1559, found: 385.1376.

4.1.8. Ethyl 2′-amino-1-methyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**4h**)

White solid, 73%, m.p.:214–216 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.89 (br s, 2H) 7.18–7.15 (m, 1H) 7.13–7.12 (m, 1H) 6.93–6.91 (m, 1H) 6.87–6.82 (m, 1H) 3.69–3.63 (dt, J = 10.65, 3.66 Hz, 2H) 3.10 (s, 3 H) 2.66–2.62 (m, 2H) 2.17–2.12 (m, 2H) 1.89–1.85 (m, 2H) 0.72 (t, J = 7.08 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.82, 178.20, 167.48, 164.35, 159.12, 145.22, 135.13, 127.38, 122.20, 121.26, 114.13, 106.72, 75.94, 58.69, 36.98, 26.87, 26.04, 19.59, 13.4707 HRMS (ESI) *m/z* for $C_{20}H_{21}N_3O_4$ $[M + H]^+$, calcd, 368.1610, found: 369.1439.

4.2. Typical procedure for synthesis of **5a-5g**

A solution of 200 mg (1.36 mmol) of isatin (**1a**), 190 mg (1.36 mmol) of 3-amino-5,5-dimethylcyclohex-2-enone (**2b**) and 0.144 mL (1.36 mmol) of ethyl cyanoacetate (**3**) was heated to 80 °C in H_2O for 6 h. After the TLC indicated the complete consumption of isatin (**1a**), the reaction mixture was extracted with ethyl acetate

Please cite this article in press as: Tiwari KN, et al., An expeditious access of 2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone in water, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.020

three times. With few isatins, solid precipitate was obtained in reaction mixture in small amount which was found as expected product by TLC. The precipitated solid was dissolved in combined organic layer which was evaporated to provide light yellow solid and purified by silica gel column chromatography using hexane:ethyl acetate (6:4) as an eluent to provide **5a** as white solid (353 mg).

4.2.1. Ethyl 2′-amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**5a**)

White solid, 69%, m.p.:214–216 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.12 (s, 1H) 7.84 (s, 2H) 7.06–7.01 (td, J = 7.55, 1.32 Hz, 1H) 6.85–6.81 (m, 1H) 6.78–6.75 (m, 1H) 6.68–6.66 (m, 1H) 3.72–3.69 (m, 2H) 2.18–2.12 (d, J = 14.73 Hz, 2H) 1.24 (s, 2H) 1.01 (s, 3H) 0.95 (s, 3H) 0.80 (t, J = 7.08 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.57, 179.74, 167.62, 162.34, 159.09, 144.01, 127.12, 122.18, 120.48, 113.09, 108.09, 76.34, 58.79, 50.63, 46.60, 31.49, 27.75, 26.85, 13.07 HRMS (ESI) m/z for $C_{21}H_{23}N_3O_4$ [M + H]$^+$, calcd, 382.1766, found: 383.1596.

4.2.2. Ethyl 2′-amino-5-bromo-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**5b**)

White solid, 72%, m.p.:218–220 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.29 (s, 1H) 7.91 (s, 2H) 7.24–7.20 (dd, J = 8.12, 2.08 Hz, 1H) 7.00 (d, J = 2.08 Hz, 1H) 6.65–6.63 (d, J = 8.12 Hz, 1H) 3.77–3.69 (m, 2H) 2.11–2.08 (m, 2H) 1.23–1.15 (m, 2H) 1.01 (s, 3H) 0.97 (s, 3H) 0.82 (t, J = 7.15 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.80, 179.35, 167.41, 162.86, 159.17, 143.52, 138.49, 129.81, 125.02, 112.48, 109.97, 75.68, 58.94, 50.56, 46.84, 31.53, 27.38, 27.09, 13.11 HRMS (ESI) m/z for $C_{21}H_{22}BrN_3O_4$ [M + H]$^+$, calcd, 460.0871, found: 461.0700.

4.2.3. Ethyl 2′-amino-5-chloro-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**5c**)

White solid, 75%, m.p.:212–214 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.29 (s, 1H) 7.91 (s, 2H) 7.11–7.07 (dd, J = 8.12, 2.27 Hz, 1H) 6.91–6.89 (m, 1H) 6.69 (d, J = 8.12 Hz, 1H) 3.77–3.69 (m, 2H) 2.12–2.08 (m, 2H) 1.23–1.14 (m, 2H) 1.01 (s, 3H) 0.98 (br s, 3H) 0.82 (t, J = 7.08 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.79, 179.49, 167.43, 162.85, 159.19, 154.42, 143.13, 138.11, 126.96, 124.38, 122.36, 109.35, 75.70, 58.93, 50.57, 46.90, 31.52, 27.41, 27.08, 13.11 HRMS (ESI) m/z for $C_{21}H_{22}ClN_3O_4$ [M + H]$^+$, calcd, 416.1377, found: 417.1198.

4.2.4. Ethyl 2′-amino-5-iodo-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**5d**)

White solid, 63%, m.p.:220–222 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.28 (s, 1H) 7.91 (s, 2H) 7.40–7.37 (dd, J = 8.03, 1.79 Hz, 1H) 7.12 (d, J = 1.70 Hz, 1H) 6.53 (d, J = 7.93 Hz, 1H) 3.77–3.69 (m, 2H) 2.11–2.10 (m, 2H) 1.26–1.17 (m, 2H) 1.01 (s, 3H) 0.97 (s, 3H) 0.82 (t, J = 7.08 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.80, 179.14, 167.41, 162.82, 159.14, 143.99, 138.76, 135.70, 130.47, 112.54, 110.67, 82.79, 75.74, 58.94, 50.56, 46.62, 31.53, 27.39, 27.04, 13.10 HRMS (ESI) m/z for $C_{21}H_{22}IN_3O_4$ [M + H]$^+$, calcd, 508.0733, found: 509.0551.

4.2.5. Ethyl 2′-amino-5-methyl-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**5e**)

Isolated as a white solid, 60%, m.p.:216–218 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.01 (s, 1H) 7.83 (s, 2H) 6.85–6.82 (m, 1H) 6.64 (s, 1H) 6.57–6.54 (m, 1H) 3.74–3.67 (q, J = 7.18 Hz, 2H) 2.15–2.11 (m, 2H) 2.05–1.98 (m, 3H) 1.23 (s, 2H) 1.01 (s, 3H) 0.96 (s, 3H) 0.82 (t, J = 7.18 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.56, 179.71, 167.67, 162.23, 159.05, 141.63, 136.02, 129.02, 127.36, 113.19, 107.81, 76.46, 58.83, 50.67, 46.65, 31.51, 27.63, 26.84, 20.62, 13.06 HRMS (ESI) m/z for $C_{22}H_{25}N_3O_4$ [M + H]$^+$, calcd, 396.1923, found: 397.1750.

4.2.6. Ethyl 2′-amino-5-nitro -7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**5f**)

White solid, 65%, m.p.:218–220 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.96 (s, 1H) 8.10–8.07 (m, 1H) 8.01 (s, 2H) 7.76–7.75 (m, 1H) 6.89 (d, J = 8.69 Hz, 1H) 3.77–3.70 (q, J = 7.18 Hz, 2H) 2.12–2.11 (m, 2H) 1.23 (s, 2H) 1.01 (s, 3H) 0.97 (s, 3H) 0.82 (t, J = 7.08 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 189.14, 180.38, 167.13, 163.53, 159.35, 150.88, 141.53, 137.12, 125.12, 117.66, 112.03, 108.09, 75.04, 59.71, 59.10, 50.38, 46.64, 31.59, 28.95, 27.21, 13.14 HRMS (ESI) m/z for $C_{21}H_{22}N_4O_6$ [M + H]$^+$, calcd, 427.1617, found: 428.1428.

4.2.7. Ethyl 2′-amino-5-methoxy-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate (**5g**)

White solid, 70%, m.p.:214–216 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.95 (s, 1H) 7.84 (s, 2H) 6.63–6.61 (m, 1H) 6.65–6.60 (m, 1H) 6.45 (d, J = 2.27 Hz, 1H) 3.75–3.68 (m, 2H) 3.61 (s, 3H) 2.20–2.12 (m, 2H) 1.23–1.15 (m, 2H) 1.01 (s, 3H) 0.96 (s, 3H) 0.82 (t, J = 7.26 Hz, 3 H) ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 194.56, 179.57, 167.67, 162.32, 159.05, 154.27, 137.65, 137.31, 113.04, 111.27, 109.73, 108.13, 76.35, 58.83, 55.23, 50.68, 47.10, 31.49, 27.74, 26.72, 13.08 HRMS (ESI) m/z for $C_{22}H_{25}N_3O_5$ [M + H]$^+$, calcd, 412.1872, found: 413.1727.

4.3. Typical procedure for synthesis of **6**

A solution of 200 mg (1.36 mmol) of isatin (**1a**), 132 mg (1.36 mmol) of 3-aminocyclopent-2-en-1-one (**2d**) and 0.144 mL (1.36 mmol) of ethyl cyanoacetate (**3**) was heated to 80 °C in H_2O for 8 h. After the TLC indicated the complete consumption of isatin (**1a**), the reaction mixture was extracted with ethyl acetate three times and the combined organic layer was dried and evaporated to provide brown solid. The reaction mixture was purified by silica gel column chromatography using hexane:ethyl acetate (4:6) as an eluent to provide **6** as white solid (253 mg).

4.3.1. Ethyl 2-amino-2′,5-dioxo-1,5,6,7-tetrahydrospiro[cyclopenta[b]pyridine-4,3′-indoline]-3-carboxylate (**6**)

White solid, 55%, m.p.:204–206 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.31 (s, 1H) 8.05 (br s, 2H) 7.11–7.07 (m, 1H) 6.98–6.97 (m, 1H) 6.82–6.79 (m, 1H) 6.74–6.73 (m, 1H) 3.73 (q, J = 7.11 Hz, 2H) 2.92–2.88 (m, 2H) 2.09–2.05 (m, 2H) 0.73 (t, J = 7.03 Hz, 3H) ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 200.06, 176.22, 169.42, 168.17, 143.65, 135.20, 127.98, 123.20, 121.44, 117.46, 108.93, 75.48, 59.37, 49.32, 33.60, 31.75, 13.53. HRMS (ESI) m/z for $C_{18}H_{17}N_3O_4$ [M + H]$^+$, calcd., 340.1297, found:340.1294.

4.4. Typical procedure for synthesis of **7**

A solution of 200 mg (1.10 mmol) of 5-chloroisatin (**1c**), 153 mg (1.10 mmol) of 3-amino-5,5-dimethylcyclohex-2-enone (**2b**) was heated to 80 °C in H_2O for 6 h. After the TLC indicated the complete consumption of 5-chloroisatin (**1c**), the reaction mixture was extracted with ethyl acetate three times. The combined organic layer was dried over Na_2SO_4 and evaporated on rotatory evaporator to provide light yellow solid which was purified by silica gel column chromatography using hexane:ethyl acetate (2:8) as an eluent to provide **7** as white solid (239 mg).

4.4.1. 3-(2-amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-chloro-3-hydroxyindolin-2-one (**7**)

White solid, 68%, m.p.:174–176 °C. ^{1}H NMR (300 MHz, MeOH-

Please cite this article in press as: Tiwari KN, et al., An expeditious access of 2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone in water, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.020

d_4) δ ppm 7.18–7.17 (m, 1H) 7.15–7.14 (m, 1H) 6.82–6.80 (m, 1H) 2.54–2.48 (m, 1H) 2.38–2.28 (m, 1H) 2.18–2.12 (m, 2H) 1.99–1.92 (m, 1H) 1.09 (s, 3H) 0.99 (s, 3H).^{13}C NMR (75 MHz, MeOH-d_4) δ ppm 195.24, 168.25, 142.55, 136.88, 129.92, 128.15, 124.76, 112.19, 106.34, 79.79, 50.90, 45.74, 33.29, 29.04, 27.50.HRMS (ESI) *m/z* for $C_{16}H_{17}ClN_2O_3$ $[M+H]^+$, calcd., 321.1005, found: 321.1003.

4.5. Typical procedure for synthesis of **8**

A solution of 200 mg (1.36 mmol) of isatin (**1a)** and 0.144 mL (1.36 mmol) of ethyl cyanoacetate (**3**) was heated to 80 °C in H_2O for 5 h. After the TLC indicated the complete consumption of isatin (**1a)**, the reaction mixture was extracted with ethyl acetate three times. The combined organic layer was dried over Na_2SO_4 and evaporated on rotatory evaporator to provide red solid which was purified by silica gel column chromatography using hexane:ethyl acetate (7:3) as an eluent to provide **8** as a red solid (269 mg).

4.5.1. (E)-ethyl 2-cyano-2-(2-oxoindolin-3-ylidene) acetate **(8)**

White solid, 82%, m.p.:174–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.31 (d, J = 8 Hz, 1H) 8.12 (br, s 1H) 7.42 (t, J = 8 Hz, 1H) 7.03 (t, J = 8 Hz, 1 H) 6.90 (d, J = 8 Hz, 1 H) 4.46 (dd, J = 4 Hz, 8 Hz, 2 H) 1.43 (t, J = 8.25 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.48, 156.24, 144.75, 143.81, 130.86, 130.29, 123.26, 119.30, 113.99, 110.72, 63.46, 13.99. HRMS (ESI) *m/z* for $C_{13}H_{10}N_2O_3$ $[M + H]^+$, calcd., 243.0769, found:243.0764.

Acknowledgments

The authors are thankful to Dr. S. J. S. Flora, Director for his generous support and help in carrying out this research project. The authors (P.S.M., V.K., S.T., and S.M.) would like to acknowledge the financial support from Department of Pharmaceuticals, Ministry of Chemicals & Fertilizers, Govt. of India. Thanks are due to SAIF, CSIR-CDRI, Lucknow for the spectral and single crystal X-ray data. NIPER-R/Communication/033.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.05.020.

References

1. (a) Domling A, Ugi I. *Angew Chem Int Ed*. 2000;39:3168–3210;
(b) Sunderhaus JD, Martin SF. *Chem Eur J*. 2009;15:1300–1308;
(c) Domling A, Wang W, Wang K. *Chem Rev*. 2012;112:3083–3135.
2. (a) Kobayashi S, Manabe K. *Acc Chem Res*. 2002;35:209–217;
(b) Butler RN, Coyne AG. *Chem Rev*. 2010;110:6302–6337;
(c) Simon MO, Li CJ. *Chem Soc Rev*. 2012;41:1415–1427;
(d) Mlynarski J, Bas S. *Chem Soc Rev*. 2014;43:577–587.
3. (a) Tiwari S, Kumar A. *Angew Chem Int Ed*. 2006;45:4942–4943.
4. (a) Wei C, Li CJ. *J Am Chem Soc*. 2003;125:9584–9585;
(b) Fu XP, Lu L, Wang D, Chen YJ, Li CJ. *Green Chem*. 2011;13:549–553.
5. (a) Kumar R, Senthilkumar SP, Yogeeswari P, Sriram D. *J Med Chem*. 2008;51:5731–5735;
(b) Bhaskar G, Arun Y, Balachandran C, Saikumar C, Perumal PT. *Eur J Med Chem*. 2012;51:79–91;
(c) Rajnarendar E, Ramakrishna S, Reddy KG, Nagaraju D, Reddy YN. *Bioorg Med Chem Lett*. 2013;23:3954–3958;
(d) Mali PR, Rao LC, Bangade VM, et al. *New J Chem*. 2016;40:2225–2232.
6. (a) Dabiri M, Azimi SC, Khavasi HR, Bazgir A. *Tetrahedron*. 2008;64:7307–7311;
(b) Jadidi K, Ghahremanzadeh R, Bazgir A. *Tetrahedron*. 2009;65:2005–2009;
(c) Ahadi S, Ghahremanzadeh R, Mirzaei P, Bazgir A. *Tetrahedron*. 2009;65:9316–9321;
(d) Ghahremanzadeh R, Sayyafi M, Ahadi S, Bazgir A. *J Comb Chem*. 2009;11:393–396;
(e) Chen H, Shi D. *J Comb Chem*. 2010;12:571–576;
(f) Chen T, Ping X, Ji S. *J Comb Chem*. 2010;12:659–663.
7. Zheng H, Liu X, Xu C, Xia Y, Lin L, Feng X. *Angew Chem Int Ed*. 2015;54:10958–10962.
8. (a) Ming L, Chao SD, Ya QY, Da Z. *Dyes Pigments*. 2018;150:202–216;
(b) Aizi N, Dezfooli S, Hashemi MM. *J Mol Liq*. 2014;194:62–67;
(c) Karmakar B, Nayak A, Banerji J. *Tetrahedron Lett*. 2012;53:5004–5007;
(d) Wang Z, Xu H, Yan L, Li Q, Rong L. *Mol Divers*. 2017;21:985–987;
(e) Gajaganti S, Bajpal S, Srivastava V, Singh S. *Can J Chem*. 2017;95:1296–1302;
(f) Alizadeh A, Moafi L. *Helv Chim Acta*. 2015;98:546–551.
9. (a) Yu F, Yan S, Hu L, Wang Y, Lin J. *Org Lett*. 2011;13:4782–4785;
(b) Wang H, Li L, Lin W, Xu P, Huang Z, Shi D. *Org Lett*. 2012;14:4598–4601;
(c) Jiang B, Wang X, Xu HW, Tu MS, Tu SJ, Li G. *Org Lett*. 2013;15:1540–1543;
(d) Yu FC, Zhou B, Xu H, et al. *Tetrahedron*. 2015;71:1036–1044;
(e) Xu H, Zhou B, Zhou P, et al. *Chem Commun*. 2016;52:8002–8005.
10. (a) Tiwari KN, Pandurang TP, Pant S, Kumar R. *Tetrahedron Lett*. 2016;57:2286–2289;
(b) Tiwari KN, Bora D, Chauhan G, et al. *Synth Commun*. 2016;46:620–625;
(c) Tiwari KN, Uttam MR, Kumari P, Vatsa P, Prabhakaran SM. *Synth Commun*. 2017;47:1013–1019.
11. Crystal data for product 4b (CCDC 1585453, Fig. 1) C19 H18 Br N3O4, CH3O crystallized in the monoclinic space group P 21/c with the following unit cell parameters: a = 8.002(2) A, Alpha= 90o, b= 19.662(6)A, beta= 90.168(5)o, c= 12.667(4)A, gamma= 90o (MeOH was trapped).