NJC

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Cite this: *New J. Chem.*, 2015, 39, 8978

A novel one pot four-component reaction for the efficient synthesis of spiro[indoline-3,4′-pyrano-[2,3-*c*]pyrazole]-3′-carboxylate and trifluoro-methylated spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] derivatives using recyclable PEG-400†

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Received (in Montpellier, France) 8th June 2015,
Accepted 2nd September 2015

DOI: 10.1039/c5nj01448d

www.rsc.org/njc

A novel, simple and efficient synthetic protocol has been developed for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate and trifluoromethylated spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] derivatives *via* a one pot, four-component reaction using recyclable polyethylene glycol (PEG-400). This new protocol produces novel spiro pyranopyrazole derivatives in good to excellent yields, with operational simplicity and recycling of PEG-400. The remarkable features of this methodology are high yields, an easy work-up process, and a greener method that avoids toxic catalyst and hazardous solvents.

Introduction

The design of multicomponent reactions (MCRs) is a significant field of research from the point of view of combinatorial chemistry.[1] Multi-component reactions, involving the intrinsic formation of several bonds in one step, have proven to be an efficient and powerful tool for the rapid formation of complex heterocyclic compounds in recent years.[2] The MCR strategy is an important approach utilized by researchers worldwide to create several libraries of molecules of miscellaneous biological activities and has gained prominence in organic, medicinal and combinatorial chemistry.[3] In most of the cases, a single product is obtained by reacting three or more different substrates in a well-defined manner through MCRs.[4] These time-efficient reactions are environmentally benign and atom economic. MCRs are cost-effective because the expensive purification processes as well as protection–deprotection steps are non-existent.[5] Although the first MCR dates back to the Strecker synthesis[6] of α-amino acid in 1850, the MCR strategy has been successfully utilized in Hantzsch's synthesis of 1,4-dihydropyridines[7] and Robinson's synthesis of alkaloid tropinone.[8] Consequently, rapid development has been observed in three- and four-component reactions.

Polyethylene glycol (PEG), a biologically acceptable polymer used widely in drug delivery and in bioconjugates as a tool for diagnostics, has hitherto not been broadly used as a solvent medium but has been used as a support for various transformations.[9] Polyethylene glycol (PEG) and modified polyethylene glycol derivatives have been admired as efficient alternate reaction media due to their remarkable features, such as non-toxicity, low cost, recoverability, bio-degradability and bio-compatibility, when compared to other "neoteric solvents" such as ionic liquids, super-critical fluids and micellar systems.[10] PEG is most commonly employed as a phase-transfer catalyst in various organic transformations.[11] PEG is also used as a recyclable reaction medium in various substitution reactions,[12] oxidation and reduction reactions,[13] asymmetric dihydroxylation,[14] Heck reaction,[15] Wacker reaction,[16] Suzuki cross-coupling reaction,[17] and partial reduction of alkynes.[18]

Potential biological activities and widespread synthetic utilities of spirocyclic compounds have led to their identification as a class of heterocyclic compounds, which has created considerable interest in the pharmaceutical industry and in the diversified field of organic synthesis due to the steric strain associated with their quaternary carbon atom.[19] Moreover, increased potentiality is generally observed when two or more different heterocyclic moieties exist in a single molecule.[20] Isatin based spiro compounds or spirooxindoles are important core structures found in many natural alkaloids as well as synthetic pharmaceuticals[21] such as spirotryprostatin (A and B), NTD609, pteropodine and strychnofoline (Fig. 1).[22] Recent developments of new protocols for the construction of spirocyclic compounds is an interesting

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† Electronic supplementary information (ESI) available. CCDC 982356. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5nj01448d

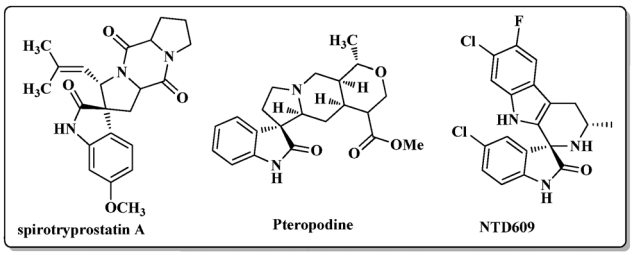
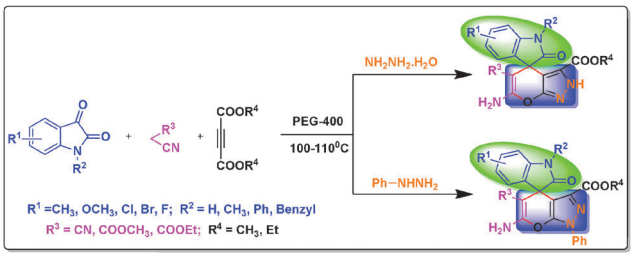


Fig. 1 Some important biologically active molecules containing the spirooxindole motif.



Scheme 1 Synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate derivatives using PEG-400.

and challenging task in organic synthesis. Moreover, the dihydropyrano[2,3-*c*]pyrazole skeleton is an important core unit known to exhibit a wide range of biological activities such as anti-inflammatory, antimicrobial, anticancer and molluscicidal activities.[23]

It is well known that the fluorine containing heterocyclic compounds often result in a dramatic modification in physical, chemical and biological properties by introduction of fluorine to simple heterocyclic compounds.[24] In particular, the trifluoromethyl group is a key structural unit in many fluorinated compounds of biological and pharmaceutical significance. As a result, trifluoromethyl substituted organic molecules exhibit interesting biological activities with potential applications in medicinal and agricultural fields.[25] Due to their significant and diverse biological activities, the design and expansion of the scope of novel methods for the construction of trifluoromethylated compounds are challenging tasks for researchers involved in this particular field.

Herein, we sought to develop a single structural framework by combining spirooxindole, pyran, and pyrazole motifs for emergent interest in the design of novel polycyclic heterocycles by combining various structurally diverse motifs. Recently, Choudhury *et al.* developed spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate derivatives in the presence of triethylamine and ethanol.[26] Song *et al.* synthesized trifluoromethylated spiro pyranopyrazole derivatives from isatin, malononitrile, hydrazine hydrate and ethyl 4,4,4-trifluoroacetoacetate as starting materials.[27] Very recently, Pore *et al.* reported novel spiro pyranopyrazole derivatives from isatin, malononitrile, hydrazine hydrate and dialkyl acetylenedicarboxylates in the presence of an ethanol and water mixture.[28]

Despite the importance of these reported protocols, many suffer from drawbacks such as the use of expensive reagents, prolonged reaction times, harsh reaction conditions, cumbersome product isolation procedures, and low yields. Sustainable chemistry has attracted prominence recently due to its environmental compatibility. To explore a mild, efficient and environmentally benign recyclable synthetic protocol, we have demonstrated the synthesis of pyrazolo[3,4-*b*]quinoline derivatives in the presence of PEG-400.[29] In our continued quest for the development of eco-friendly protocols[30] and considering the significant biological activities of spirooxindoles, herein, we report a one-pot, four-component reaction for the synthesis of novel spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate derivatives using recyclable PEG-400 as a reaction medium (Scheme 1).

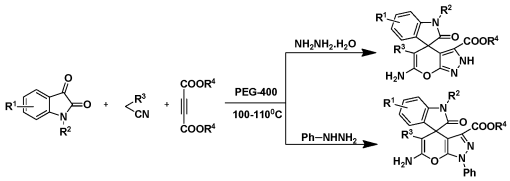
Results and discussion

Initially, a model reaction was conducted by taking isatin (1.0 mmol), malononitrile (1.0 mmol), dimethyl acetylenedicarboxylate (DMAD) (1.0 mmol) and hydrazine hydrate (1.0 mmol) at 40–50 °C and the desired product was obtained in 30% yield, along with the unreacted starting materials, even after a prolonged reaction time (24 h). To explore the ideal reaction conditions to obtain the maximum product yield, several reactions were conducted. During this optimization study, it was observed that 100–110 °C is the ideal temperature for the reaction. After optimizing the experimental conditions, 5-methoxy isatin (1.0 mmol), malononitrile (1.0 mmol) dimethyl acetylene dicarboxylate (DMAD) (1.0 mmol) and hydrazine hydrate (1.0 mmol) were reacted in the presence of recyclable polyethylene glycol (PEG)-400, resulting in the formation of the desired spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate derivative in excellent yield (Table 1, entry 1). To expand the scope of this protocol, different experiments were conducted with various substituted isatins and these results are tabulated in Table 1. It was observed that this protocol was also effective with *N*-substituted isatins such as *N*-CH_3, *N*-Ph, *N*-benzyl isatins, resulting in good yields. Apart from malononitrile, reactions with methyl cyanoacetate and ethyl cyanoacetates were also conducted resulting in the corresponding spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate derivatives in a moderate yield. The scope of the protocol was also extended with diethyl acetylenedicarboxylate under similar reaction conditions and the results are summarized in Table 1. This protocol was also extended a step further, using phenyl hydrazine in the place of hydrazine, providing the desired spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate derivatives in a good yield.

We further synthesized a variety of trifluoromethylated spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] derivatives (Scheme 2) using ethyl 4,4,4-trifluoroacetoacetate in the place of dialkyl acetylenedicarboxylate, affording the desired products in good yields. In continuation of further explorations of this method, several reactions were also conducted with various substituted isatins and these results are tabulated in Table 2. All these products were characterized by spectroscopic and analytical methods.

A plausible mechanism was proposed for the general synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylates using this present protocol (Scheme 3). Initially, a Knoevenagel condensation occurs between isatin and malononitrile, forming adduct (A), which reacts with the pyrazolone intermediate (B) formed by the

Table 1 Synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate derivatives using PEG-400[a]



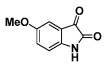
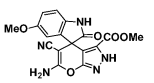
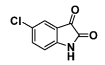
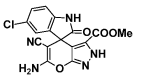
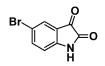
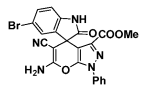
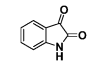
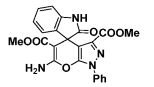
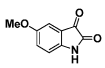
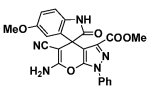
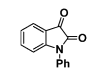
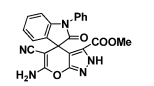
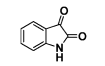
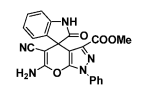
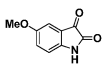
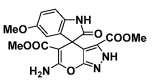
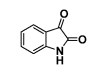
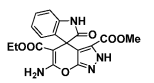
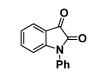
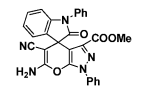
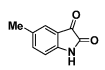
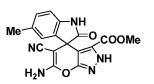
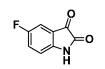
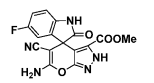
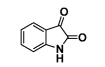
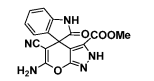
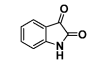
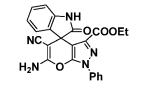
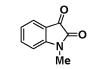
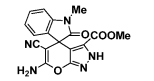
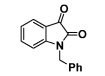
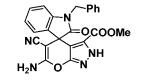
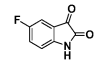
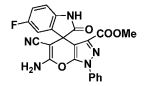
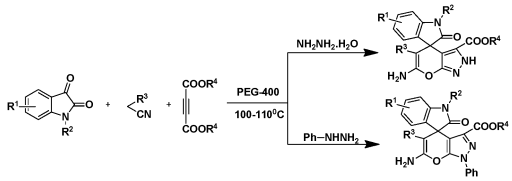
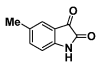
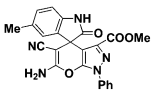
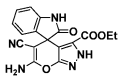
S. no.	1	R^3	3	R^4	Product	Time (h)	Yield[b] (%)
1		CN	$NH_2NH_2{\cdot}H_2O$	Me		3	92
2		CN	$NH_2NH_2{\cdot}H_2O$	Me		3.5	87
3		CN	$Ph–NH_2NH_2$	Me		3.5	83
4		COOMe	$Ph–NH_2NH_2$	Me		3	84
5		CN	$Ph–NH_2NH_2$	Me		3	88
6		CN	$NH_2NH_2{\cdot}H_2O$	Me		3	82
7		CN	$Ph–NH_2NH_2$	Me		3	80
8		COOMe	$NH_2NH_2{\cdot}H_2O$	Me		3	86
9		COOEt	$NH_2NH_2{\cdot}H_2O$	Me		3	84
10		CN	$Ph–NH_2NH_2$	Me		3	79
11		CN	$NH_2NH_2{\cdot}H_2O$	Me		3	85
12		CN	$NH_2NH_2{\cdot}H_2O$	Me		3.5	87
13		CN	$NH_2NH_2{\cdot}H_2O$	Me		3	86
14		CN	$Ph–NH_2NH_2$	Et		3	82
15		CN	$NH_2NH_2{\cdot}H_2O$	Me		3	83
16		CN	$NH_2NH_2{\cdot}H_2O$	Me		3	81
17		CN	$Ph–NH_2NH_2$	Me		3.5	78

Table 1 (*continued*)



S. no.	1	R^3	3	R^4	Product	Time (h)	Yield[b] (%)
18		CN	$Ph–NH_2NH_2$	Me		3	84
19		CN	$NH_2NH_2{\cdot}H_2O$	Et		3	87
20		COOMe	$NH_2NH_2{\cdot}H_2O$	Me		3	86

[a] Reaction conditions: isatin (1.0 mmol), malononitrile (1.0 mmol), dialkyl acetylene dicarboxylate (1.0 mmol), hydrazine hydrate (1.0 mmol) and PEG-400 at the temperature of 100–110 °C. [b] Isolated yields.

Scheme 2 Synthesis of trifluoromethylated spiro[indoline-3,4′-pyrano-[2,3-*c*]pyrazole] derivatives using PEG-400.

condensation of dialkyl acetylene dicarboxylate and hydrazine hydrate. This crucial step involves the Michael addition of B onto intermediate (A), followed by enolization and ring closure to provide the desired product (C), as reported in the literature; this was further supported by X-ray crystallography (Fig. 2).[31]

Conclusions

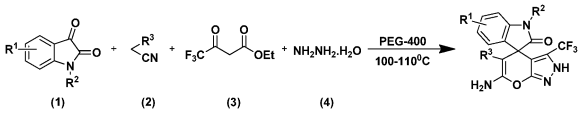
In conclusion, we have developed a simple and highly efficient greener approach for the one-pot, four-component synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate and trifluoromethylated spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] derivatives using PEG-400 as an inexpensive, biodegradable, and reusable reaction medium. This novel protocol generates five new bonds in one sequence. The salient features of this methodology are efficiency, environmentally benign nature and high yield, wider scope of substrate choice, ease of product purification, and no involvement of hazardous catalysts or toxic solvents.

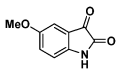
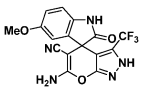
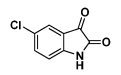
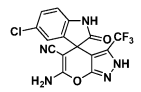
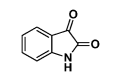
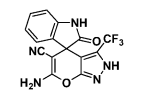
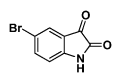
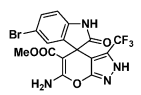
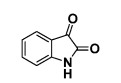
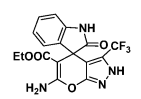
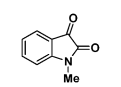
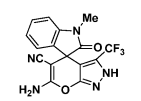
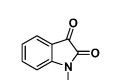
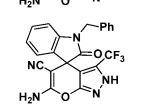
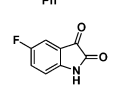
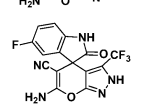
Experimental section

General procedure for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate/trifluoromethylated spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] derivatives

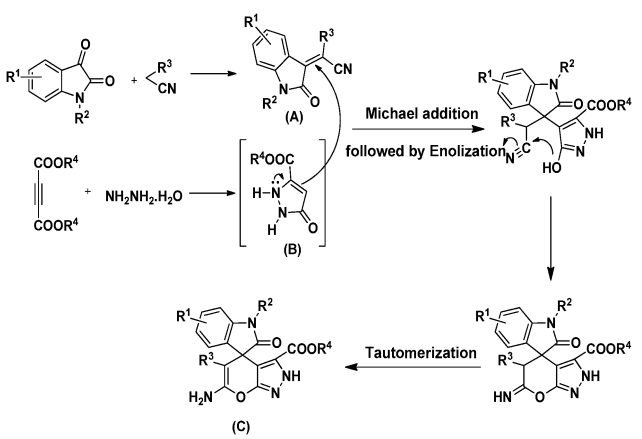
To a stirred solution of polyethylene glycol (PEG)-400 (5 mL), isatin (1.0 mmol), and malononitrile (1.0 mmol) were added

Table 2 Synthesis of trifluoromethylated spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives using PEG-400[a]



S. no.	1	2	Product	Time (h)	Yield[b] (%)
1				3.5	93
2				4	89
3				3.5	90
4				4	87
5				4	86
6				3	88
7				3	85
8				4	86

[a] Reaction conditions: isatin (1.0 mmol), malononitrile (1.0 mmol), ethyl 4,4,4-trifluoroacetoacetate (1.0 mmol), hydrazine hydrate (1.0 mmol) and PEG-400 at the temperature of 100–110 °C. [b] Isolated yields.



Scheme 3 Plausible mechanism for the general synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-3′-carboxylates.

and stirred at 100–110 °C for 20 min. Then, a solution of hydrazine hydrate (1.0 mmol) and dialkyl acetylenedicarboxylate/ethyl 4,4,4-trifluoroacetoacetate (1.0 mmol) in PEG-400 was added to the reaction mixture. The whole reaction mixture was stirred

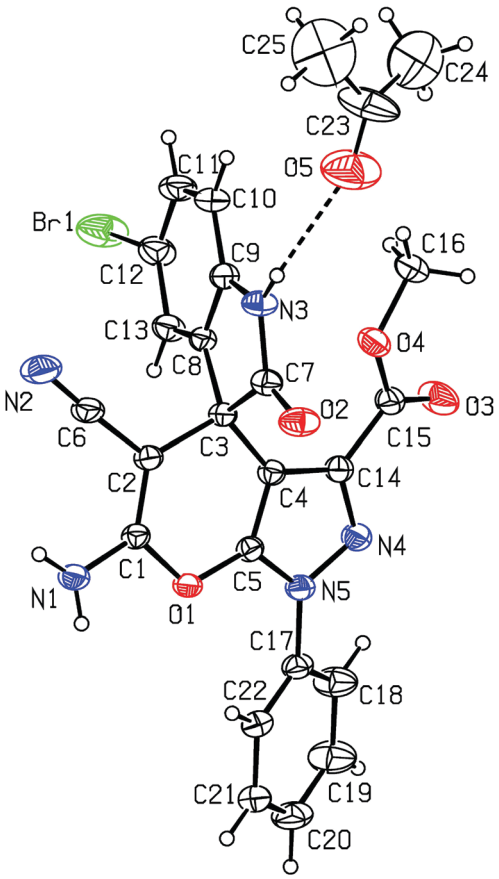


Fig. 2 ORTEP diagram of compound mentioned in Table 1, entry 3, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and the H atoms are shown as small spheres of arbitrary radii. The solvent of crystallization acetone was also included in the crystal lattice. The asymmetric unit containing a 1:1 stoichiometric ratio of compound and acetone is shown. Only the major component of the disordered atoms is shown for clarity.

until the reaction was complete, as indicated by TLC. After completion of the reaction, ether (5 mL) was added and stirred for 5–10 minutes and cooled to −50 °C. At this temperature, PEG became solid and the ether layer saturated with product was separated and evaporated. The crude product obtained was purified by column chromatography, using hexane and EtOAc as the eluent to obtain the title compound. The recovered PEG was reused for further cycles. For NMR spectroscopic analysis, the title compound was dissolved in the NMR solvents, acetone-d_6 and DMSO-d_6 in the ratio of 4:1.

Characterization of selected compounds

Methyl-6′-amino-5′-cyano-5-methoxy-2-oxo-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate (Table 1, entry 1). IR (KBr) 3445, 3275, 3185, 2933, 2192, 1710, 1635, 1494, 1222, 1089 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6 + DMSO-d_6) δ = 9.83 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.80–6.76 (m, 1H), 6.74–6.70 (m, 1H), 6.67 (s, 2H), 3.69 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C NMR (75 MHz, acetone-d_6 + DMSO-d_6) δ = 177.3, 161.3, 158.0, 155.9, 135.8, 135.3, 129.2, 128.7, 117.5, 113.4, 110.6, 109.7, 101.1, 58.7, 55.0, 51.0, 48.3 ppm. ESI-MS: 368 $(M + H)^+$; $C_{17}H_{14}N_5O_5$.

Methyl-6′-amino-5-chloro-5′-cyano-2-oxo-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate (Table 1, entry 2). IR (KBr) 3442, 3275, 3180, 2933, 2185, 1710, 1622, 1494, 1222, 1089 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6 + DMSO-d_6) δ = 10.60 (s, 1H), 7.26–7.23 (m, 1H), 7.10–7.14 (m, 3H), 6.97 (d, J = 8.3 Hz, 1H), 3.55 (s, 3H) ppm. ^{13}C NMR (75 MHz, acetone-d_6 + DMSO-d_6) δ = 177.2, 161.2, 157.9, 156.3, 141.5, 136.1, 128.9, 128.4, 126.3, 124.1, 117.6, 110.7, 100.3, 57.1, 51.2, 48.0 ppm. ESI-MS: 372 $(M + H)^+$; $C_{16}H_{11}ClN_5O_4$.

Methyl-6′-amino-5-bromo-5′-cyano-2-oxo-1′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate (Table 1, entry 3). IR (KBr) 3444, 3273, 3180, 2930, 2182, 1715, 1622, 1494, 1220, 1085 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6 + DMSO-d_6) δ = 10.34 (s, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.64 (t, J = 8.1 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.19–7.16 (m, 3H), 7.10 (d, J = 7.1 Hz, 1H), 6.98–6.92 (m, 2H), 3.48 (s, 3H) ppm. ^{13}C NMR (75 MHz, acetone-d_6 + DMSO-d_6) δ = 177.8, 160.6, 159.0, 142.4, 138.3, 137.5, 134.0, 129.5, 128.7, 128.1, 125.4, 124.0, 122.4, 122.0, 121.8, 117.2, 109.5, 59.2, 51.0, 48.5 ppm. ESI-MS: 492 $(M + H)^+$; $C_{22}H_{15}BrN_5O_4$.

Methyl-6′-amino-5′-cyano-5-methoxy-2-oxo-1′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-3′-carboxylate (Table 1, entry 5). IR (KBr) 3440, 3278, 3180, 2933, 2185, 1710, 1622, 1494, 1222, 1089 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6 + DMSO-d_6) δ = 9.93 (s, 1H), 7.43 (m, 3H), 7.28 (m, 2H), 6.91 (d, J = 8.4 Hz, 1H), 6.82–6.79 (m, 1H), 6.74–6.70 (m, 1H), 6.64 (s, 2H), 3.71 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C NMR (75 MHz, acetone-d_6 + DMSO-d_6) δ = 177.2, 160.4, 159.9, 155.5, 146.3, 138.0, 137.0, 135.8, 135.0, 129.3, 127.9, 121.6, 117.1, 113.2, 110.7, 109.6, 99.1, 59.0, 55.0, 50.6, 48.6 ppm. ESI-MS: 444 $(M + H)^+$; $C_{23}H_{18}N_5O_5$.

6′-Amino-5-methoxy-2-oxo-3′-(trifluoromethyl)-2′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (Table 2, entry 1). IR (KBr) 3470, 3311, 3175, 3105, 2205, 1711, 1648, 1501, 1402, 1336, 1146, 1018 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ = 9.51 (s, 1H), 6.94–6.83 (m, 3H), 6.66 (s, 2H), 3.72 (s, 3H) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ = 49.6, 56.9, 60.6, 112.1, 113.2, 116.3, 118.6, 123.2, 130.5, 135.6, 136.7, 136.8, 158.1, 163.0, 178.7 ppm. ESI-MS: 378 $(M + H)^+$; $C_{16}H_{11}F_3N_5O_3$.

Acknowledgements

We thank CSIR, New Delhi, India, for fellowships to K.K, K.H.V.R, B.S.P, K. D. and UGC for fellowship to K.R.

References

1 (*a*) L. Weber, K. Illegen and M. Almstetter, *Synlett*, 1999, 366; (*b*) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123.

2 (*a*) B. Jiang, T. Rajale, W. Wever, S.-J. Tu and G. Li, *Chem. – Asian J.*, 2010, **5**, 2318; (*b*) S. Maiti, S. Biswas and U. Jana, *J. Org. Chem.*, 2010, **75**, 1674; (*c*) L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinhein, 2006; (*d*) A. de Meijere, P. von Zezschwitz and S. Brase, *Acc. Chem. Res.*, 2005, **38**, 413, and references cited therein.

3 (*a*) H. Bienayme, C. Hulme, G. Oddon and P. Schmitt, *Chem. – Eur. J.*, 2000, **6**, 3321–3329; (*b*) G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem.*, 2003, 4101–4111; (*c*) S. Brase, C. Gil and K. Knepper, *Bioorg. Med. Chem.*, 2002, **10**, 2415–2437; (*d*) A. Domling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168–3210.

4 (*a*) P. A. Tempest, *Curr. Opin. Drug Discovery Dev.*, 2005, **8**, 776; (*b*) H. Fujioka, K. Murai, O. Kubo, Y. Ohba and Y. Kita, *Org. Lett.*, 2007, **9**, 1687; (*c*) N. M. Evdokimov, A. S. Kireev, A. A. Yakovenko, M. Y. Antipin, I. V. Magedov and A. Kornienko, *J. Org. Chem.*, 2007, **72**, 3443; (*d*) X. S. Wang, Q. Li, J. R. Wu, Y. L. Li, C. S. Yao and S. J. Tu, *Synthesis*, 2008, 1902.

5 (*a*) B. M. Trost, *Angew. Chem., Int. Ed.*, 1995, **34**, 259; (*b*) P. A. Wender, S. T. Handy and D. L. Wright, *Chem. Ind.*, 1997, 765.

6 A. Strecker, *Liebigs Ann. Chem.*, 1850, **75**, 27.

7 A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **215**, 1.

8 R. Robinson, *J. Chem. Soc.*, 1917, **111**, 876.

9 (*a*) V. N. Vasudevan and S. V. Rajender, *Green Chem.*, 2001, **3**, 146–148; (*b*) A. Haimov and R. Neumann, *Chem. Commun.*, 2002, 876–877; (*c*) L. Heiss and H. J. Gais, *Tetrahedron Lett.*, 1995, **36**, 3833–3836; (*d*) T. J. Dickerson, N. N. Reed and K. D. Janda, *Chem. Rev.*, 2002, **102**, 3325–3344.

10 J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64.

11 K. Z. Andrade and L. M. Alves, *Curr. Org. Chem.*, 2005, **9**, 195.

12 P. Ferravoschi, A. Fiecchi, P. Grisenti, E. Santaniello and S. Trave, *Synth. Commun.*, 1987, 1569.

13 J. R. Blanton, *Synth. Commun.*, 1997, **27**, 2093.

14 S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. K. Reddy, *Chem. Commun.*, 2003, 1716.

15 S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. K. Reddy, *Org. Lett.*, 2002, **4**, 4399.

16 A. Haimov and R. Neumann, *Chem. Commun.*, 2002, 876.

17 V. V. Namboodiri and R. S. Varama, *Green Chem.*, 2001, **3**, 146.

18 S. Chandrasekhar, Ch. Narsihmulu, G. Chandrasekhar and T. Shyamsundar, *Tetrahedron Lett.*, 2004, **45**, 2421.

19 S. T. Hilton, T. C. T. Ho, G. Pljevalijcic and K. Jones, *Org. Lett.*, 2000, **17**, 2639.

20 R. Balini, G. Bosica, M. Conforti, R. Magi, A. Mazzacannt, P. Righi and G. Sarton, *Tetrahedron*, 2001, **57**, 1395.

21 (*a*) T. H. Kang, K. Matsumoto, Y. Murakami, H. Takayama, M. Kitajima, N. Aimi and H. Watanabe, *Eur. J. Pharmacol.*, 2002, **444**, 39; (*b*) S. Edmondson, S. Danishefsky, L. Sepp-lorenzinol and N. Rosen, *J. Am. Chem. Soc.*, 1999, **121**, 2147.

22 (*a*) C. B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, **52**, 12651–12666; (*b*) C. B. Cui, H. Kakeya and H. Osada, *J. Antibiot.*, 1996, **49**, 832–835; (*c*) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175–1180; (*d*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758.

23 (*a*) M. E. A. Zaki, H. A. Soliman, O. A. Hiekal and A. E. Z. Rashad, *Naturforscher*, 2006, **61**, 1–5; (*b*) E. H. El-Tamany, F. A. El-Shahed and B. H. Mohamed, *J. Serb. Chem. Soc.*, 1999, **64**, 9–18; (*c*) J. L. Wang, D. Liu, Z. J. Zhang, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri and Z. Huang, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 7124–7129; (*d*) F. M. Abdelrazek, P. Metz, N. H. Metwally and S. F. El-Mahrouky, *Arch. Pharm.*, 2006, **339**, 456–460; (*e*) F. M. Abdelrazek, P. Metz, O. Kataeva, A. Jaeger and S. F. El-Mahrouky, *Arch. Pharm.*, 2007, **340**, 543–548.

24 R. E. Bank, *Organofluorine Chemistry: Principles and Commercial Application*, Plenum and Elsevier, New York, 1994; R. E. Filler, *Organic Chemistry in Medicinal Chemistry and Biochemical Applications*, Plenum and Elsevier, Amsterdam, 1993(*a*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3–11; (*b*) N. Iwai, R. Sakai, S. Tsuchida, M. Kitazume and T. Kitazume, *J. Fluorine Chem.*, 2009, **130**, 434–437; (*c*) W. R. Dolbier Jr., *J. Fluorine Chem.*, 2005, **126**, 157–163.

25 (*a*) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123–3197; (*b*) M. Frezza, D. Balestrino, L. Soulère, S. Reverchon, Y. Queneau, C. Forestier and A. Doutheau, *Eur. J. Org. Chem.*, 2006, 4731–4736; (*c*) F. Leroux, O. Lefebvre and M. Schlosser, *Eur. J. Org. Chem.*, 2006, 3147–3151.

26 S. Pal, Md. N. Khan, S. Karamthulla, S. J. Abbas and L. H. Choudhury, *Tetrahedron Lett.*, 2013, **54**, 5434.

27 X. Liu, X. Xu, X. Wang, W. Yang, Q. Qian, M. Zhang, L. Song, H. Deng and M. Shao, *Tetrahedron Lett.*, 2013, **54**, 4451.

28 D. M. Pore, P. B. Patil, D. S. Gaikwad, P. G. Hegade, J. D. Patil and K. A. Undale, *Tetrahedron Lett.*, 2013, **54**, 5876.

29 K. Karnakar, S. N. Murthy, K. Ramesh, G. Satish, N. Jagadeesh Babu and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2012, **53**, 2897.

30 (*a*) K. Karnakar, A. V. Kumar, S. N. Murthy, K. Ramesh and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2012, **53**, 4613; (*b*) K. Karnakar, S. N. Murthy, K. Ramesh, K. H. V. Reddy, Y. V. D. Nageswar, U. Chandrakala, B. L. A. Prabhavathi Devi and R. B. N. Prasad, *Tetrahedron Lett.*, 2012, **53**, 3497; (*c*) K. Karnakar, S. N. Murthy, K. Ramesh, Y. V. D. Nageswar, T. V. K. Reddy, B. L. A. Prabhavathi Devi and R. B. N. Prasad, *Tetrahedron Lett.*, 2012, **53**, 1968; (*d*) J. Shankar, K. Karnakar, B. Srinivas and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2010, **51**, 3938; (*e*) K. Karnakar, J. Shankar, S. N. Murthy, K. Ramesh and Y. V. D. Nageswar, *Synlett*, 2010, 5252; (*f*) K. Ramesh, K. Karnakar, G. Satish, K. H. V. Reddy and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2012, **53**, 6095; (*g*) B. S. P. Anil Kumar, B. Madhav, K. H. V. Reddy and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2011, **52**, 2862.

31 Crystal data for Table 1 entry 3: the compound was crystallized from acetone using the slow evaporation method. Acetone was included in the crystal lattice. The asymmetric unit contains the compound and acetone in a 1 : 1 ratio. Molecular formula, $C_{22}H_{14}BrN_5O_4{\cdot}C_3H_6O$, M = 550.37, colourless block, 0.42 × 0.38 × 0.29 mm^3, triclinic, space group $P\bar{1}$ (No. 2), a = 10.107(3) Å, b = 11.058(3) Å, c = 12.667(3) Å, α = 71.325(4)°, β = 71.161(4)°, γ = 78.620(4)°, V = 1262.4(6) Å^3, Z = 2, D_c = 1.448 g cm^{-3}, F_{000} = 560, CCD area detector, MoKα radiation, λ = 0.71073 Å, T = 293(2) K, $2\theta_{max}$ = 56.56°, 14 880 reflections obtained, 5935 unique (R_{int} = 0.022), final GooF = 1.038, R_1 = 0.0468, wR_2 = 0.1409, R indices based on 4013 reflections with $I > 2\sigma(I)$ (refinement on F^2), 378 parameters, 34 restraints, μ = 1.673 mm^{-1}, minimum and maximum residual density, −0.24 and 0.67 e Å^{-3}. CCDC 982356.