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PAPER

A Novel One pot four-component reaction for the efficient 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 recyclable PEG-400

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

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, easy work-up process, and a greener method by avoiding 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 efficient and a powerful tool for the rapid formation of complex heterocyclic compounds in recent years.[2] 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 was obtained from three or more different substrates by reacting in a well-defined manner through MCRs.[4] These time-efficient reactions are environmentally benign and atom economic. MCRs are cost-effective since 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 utilized successfully in Hantsch's synthesis of 1,4-dihydropyridines[7] and Robinson's synthesis of alkaloid tropinone.[8] Consequently, rapid development is observed in three- and four-component reactions.

Polyethylene glycol (PEG), a biologically acceptable polymer used widely in drug delivery and in bioconjugates as 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 like 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 reductions of alkynes.[18]

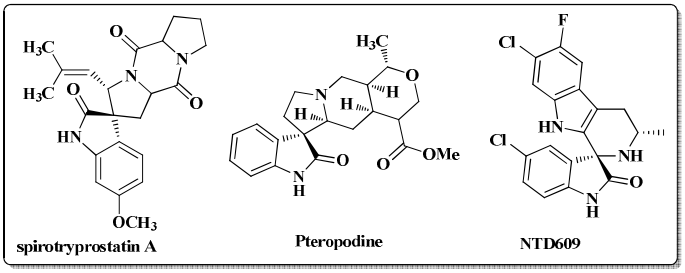

Fig. 1 Some biologically active important molecules containing Spirooxindole motif.

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 their steric strain associated with the quaternary carbon.[19] Moreover, increased

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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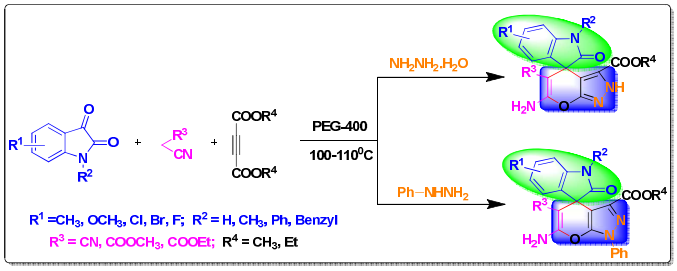
DOI: 10.1039/C5NJ01448D

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 & B), NTD609, Pteropodine and strychnofoline,[22] (**Fig.1**). Recent development of new protocols for the construction of spirocyclic compounds is an interesting and challenging task in organic synthesis. Moreover, dihydropyrano[2,3-c]pyrazole skeleton is an important core unit 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 hetero-cyclic compounds often results in dramatic modification of their physical, chemical and biological properties.[24] Especially, 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 for applications in the medicinal and agricultural fields.[25] Due to their significant and diverse biological activities design and widening the scope of novel methods for the construction of trifluoromethylated compounds are the challenging task 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 designing 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 a 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 ethanol and water mixture.[28]

Despite the importance of these reported protocols, many suffer from drawbacks such as use of expensive reagents, prolonged reaction times, harsh reaction conditions, cumbersome product isolation procedures, and low yields. Sustainable chemistry has gained 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**).



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

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 ^{0}C and the desired product was obtained in 30% yield, along with the unreacted starting materials, even after prolonged reaction time (24 h). To explore the ideal reaction conditions to get maximum product yield several reactions were conducted. During this optimization study, it was observed that 100-110 ^{0}C is ideal temperature for the reaction. After optimizing the experimental conditions, 5-methoxy isatin (1.0 mmol), malononitrile (1.0 mmol) dimethy 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 were 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 corresponding spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-3'-carboxylate derivatives in moderate yield. 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 place of hydrazine component, providing the desired spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-3'-carboxylate derivatives in good yield.

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

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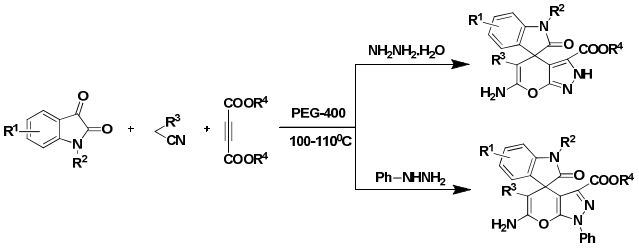
We further synthesized a variety of trifluoromethylated spiro[indole-3,4'-pyrano[2,3-*c*]pyrazole] derivatives (**Scheme 2**) using ethyl 4,4,4-trifluoroacetoacetate in place of dialkyl acetylenedicarboxylate affording products in good yields. In continuation of further explorations of this method, several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

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



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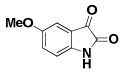
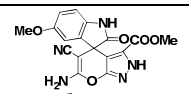
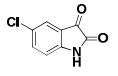
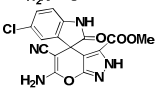
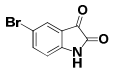
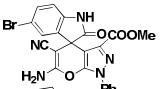
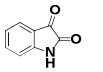
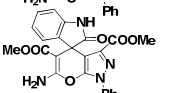
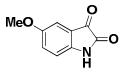
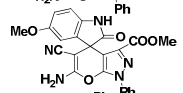
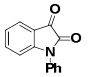
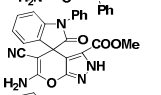
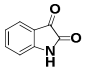
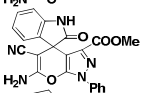
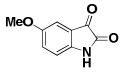
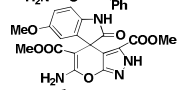
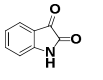
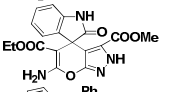
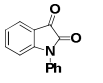
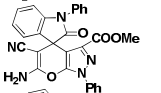
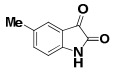
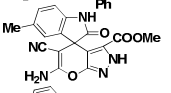
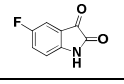
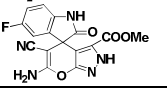
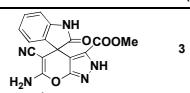
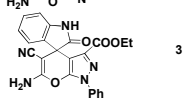
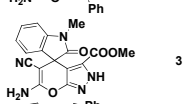
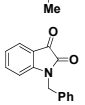
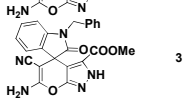
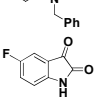
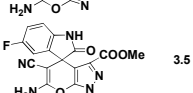
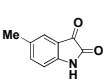
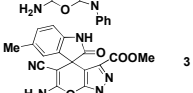
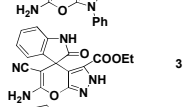
1		CN	$NH_2NH_2.H_2O$	Me		3	92
2		CN	$NH_2NH_2.H_2O$	Me		3.5	87
3		CN	Ph–NHNH$_2$	Me		3.5	83
4		COOMe	Ph–NHNH$_2$	Me		3	84
5		CN	Ph–NHNH$_2$	Me		3	88
6		CN	$NH_2NH_2.H_2O$	Me		3	82
7		CN	Ph–NHNH$_2$	Me		3	80
8		COOMe	$NH_2NH_2.H_2O$	Me		3	86
9		COOEt	$NH_2NH_2.H_2O$	Me		3	84
10		CN	Ph–NHNH$_2$	Me		3	79
11		CN	$NH_2NH_2.H_2O$	Me		3	85
12		CN	$NH_2NH_2.H_2O$	Me		3.5	87
13		CN	$NH_2NH_2.H_2O$	Me		3	86
14		CN	Ph–NHNH$_2$	Et		3	82
15		CN	$NH_2NH_2.H_2O$	Me		3	83
16		CN	$NH_2NH_2.H_2O$	Me		3	81
17		CN	Ph–NHNH$_2$	Me		3.5	78
18		CN	Ph–NHNH$_2$	Me		3	84
19		CN	$NH_2NH_2.H_2O$	Et		3	87
20		COOMe	$NH_2NH_2.H_2O$	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 110-110 ^{0}C. [b] Isolated yields.

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

(1) (2) (3) (4)

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 110-110 ^{0}C. [b] Isolated yields.

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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 in scheme 3. Initially, Knoevenagel condensation occurs between isatin and malononitrile, forming the adduct (A), which reacts with the pyrazolone intermediate (B) formed by the condensation of dialkyl acetylene dicarboxylate and hydrazine hydrate. This crucial step involves Michael addition of B onto intermediate (A), followed by enolization and ring closure providing the desired product (C) as reported in the literature and it was further supported by X-ray crystallography [31] (**Figure 2**).

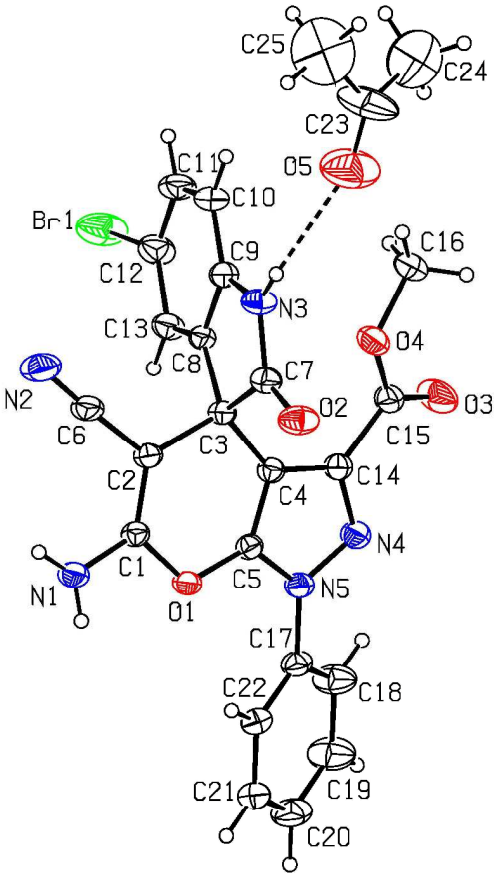
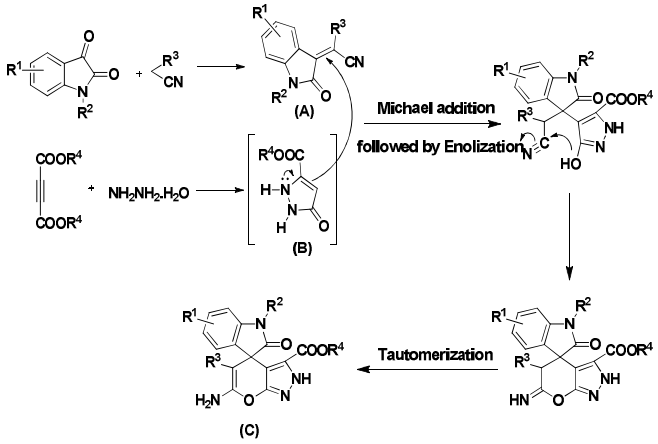


Figure 2. ORTEP diagram of compound Table 1 Entry 3 with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The solvent of crystallization acetone was also included in the crystal lattice. The asymmetric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



Scheme 3: Plausible mechanism

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 by using PEG-400 as 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, non-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 and stirred at 100 - 110 °C for 20 min. Then a solution of hydrazine hydrate (1.0 mmol) and dialkyl acetylenedicrboxylate / ethyl 4,4,4-trifluoroacetoacetate (1.0 mmol) in PEG-400 was added to it. The whole reaction mixture was stirred until the reaction was complete as indicated by TLC. After completion of the reaction, ether (5mL) was added and stirred for a 5-10 mins and cooled to -50 ^{o} C. At this temperature PEG became solid and the ether layer saturated with product was separated and evaporated. The crude product was purified by column chromatography, using hexane and EtOAc as eluent to provide the title compound. The recovered PEG was reused for further cycles. For the NMR spectroscopic analysis the title compound was dissolved in the ratio of solvents Acetone-d_6 and DMSO-d_6 is 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}; ^{1}H NMR (300 MHz, Acetone-

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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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}. ^{1}H 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 $(M+H)^{+}$; $C_{16}H_{11}F_3N_5O_3$.

Acknowledgments

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.

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31. **Crystal data for Table 1 Entry 3**: The compound was crystallized from acetone solvent using the slow evaporation method. The acetone was included in the crystal lattice. The asymmetric unit contains the compound and acetone in 1:1 ratio. Molecular formula, $C_{22}H_{14}BrN_5O_4 \cdot C_3H_6O$, M = 550.37, colourless block, 0.42 x 0.38 x 0.29 mm^3, triclinic, space group $P\bar{1}$ (No. 2), a = 10.107(3), b = 11.058(3), 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, Dc = 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°, 14880 reflections collected, 5935 unique (R_{int} = 0.022), Final GooF = 1.038, $R1$ = 0.0468, $wR2$ = 0.1409, R indices based on 4013 reflections with I >2σ(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 contains supplementary crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk. The full details of crystal data collection and refinement was provided in supporting information.

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DOI: 10.1039/C5NJ01448D

Graphical Abstract

A Novel One pot four-component reaction for the efficient 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 recyclable PEG-400.

K. Karnakar, K. Ramesh, K. Harsha Vardhan Reddy, B. S. P. Anil Kumar, Jagadeesh Babu Nanubonula and Y. V. D. Nageswar*

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 PEG-400.