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$ZnCl_2$-catalyzed three-component domino reactions for the synthesis of pyrano[3,2-*c*]quinolin-5(6*H*)-ones

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ABSTRACT

The $ZnCl_2$-catalyzed three-component synthesis of pyrano[3,2-*c*]quinolin-5(6*H*)-ones from the domino reactions of 4-hydroxy-1-methylquinolin-2(1*H*)-one, nitroketene *N*,*S*-methylacetal, and aromatic aldehydes in ethanol in good yields is described. This domino transformation leads to the formation of one ring by creation of two C–C bonds and one C–O bond in a single synthetic operation.

The pyranoquinolinone scaffold is a privileged sub-structure prevalent in numerous natural products.[1] A variety of bioactive natural products, especially alkaloids such as flindersine, simulenoline, melicobisquinolones (A and B), and huajiaosimuline (Fig. 1) comprise a pyranoquinolinone hybrid moiety as the basic building block.[2] Structures embedded with pyranoquinolinone units display potential medicinal properties such as anti-inflammatory,[3] anti-allergic,[4] antibacterial,[5] antimicrobial,[6] estrogenic, and psychotropic.[7] In particular, simulenoline, huajiaosimuline, and zanthodioline are potent inhibitors of platelet aggregation,[8] while *N*-methylflindersine, isolated from *Orixa japonica*, acts as an insecticide for livestock.[9] Further, pyranoquinolinones often serve as potential synthons for the assembly of natural products such as dimeric quinolone alkaloids[10] and polycyclic heterocycles.[11]

Reported approaches to synthesize/functionalize pyranoquinolinones include: (i) reactions of 4-hydroxy-1-methylquinolin-2(1*H*)-one with 1-aryloxy-4-chloro-but-2-yne in the presence of K_2CO_3 in butanol or intramolecular annulation of propynyl/butynyl ethers of 4-hydroxy-1-alkylquinoline-2*H*-one in chlorobenzene,[12] (ii) reaction of 4-hydroxy-2-quinolin-(1*H*)-one with α,β-unsaturated aldehydes in the presence of Yb(III)triflate/indium(III) chloride in acetonitrile or iodine in dichloromethane,[13] (iii) intramolecular electrophilic annulation of 2-alkynylquinoline-3-carboxaldehydes in the presence of *N*-iodosuccinimide,[14] (iv) domino Knoevenagel condensation/hetero Diels–Alder reactions of 4-hydroxy-1,2-dihydro-2-quinolinones and *o*-prenylated aromatic/aliphatic aldehyde,[15] (v) VCl_3-catalyzed three-component reactions via aza-Diels–Alder reaction of aldimines with dihydropyran,[16] (vi) microwave-mediated three-component reactions of 4-hydroxyquinolin-2(1*H*)-ones, aromatic aldehydes, and ethyl cyanoacetate,[17] (vii) dehydrocyclization of prenyl and vinylquinolones effected by DDQ,[18] and (viii) tandem Knoevenagel condensation of 4-hydroxyquinolin-2(1*H*)-ones with aliphatic aldehyde and

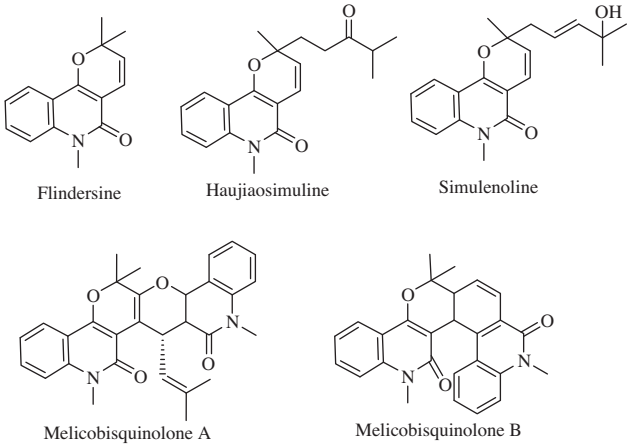

Figure 1. Pyranoquinolinone based natural products.

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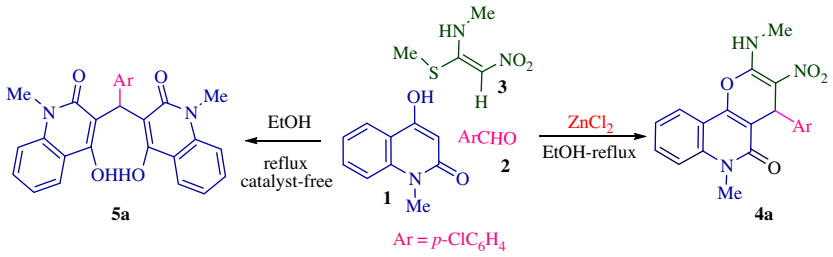
Table 1
Screening of catalysts, solvents, and reaction conditions for the synthesis of **4a**



Entry	Catalyst[a]	Solvent	Time (h)	Yield (%)	
				5a[b]	**4a**[b]
1	—	Solvent-free	10	—[c]	63
2	—	Water	13	—[c]	—[c]
3	—	Ethanol	7	—[c]	35
4	—	Acetonitrile	9	—[c]	20
5	Et_3N	Ethanol	8	—[c]	73
6	Pyrrolidine	Acetonitrile	6	—[c]	67
7	Pyrrolidine	Ethanol	7	—[c]	68
8	NH_4OAc	Acetonitrile	7	—[c]	50
9	NH_4OAc	Ethanol	6	—[c]	67
10	$Yb(OTf)_3$	Ethanol	7	—[c]	65
11	$Yb(OTf)_3$	Acetonitrile	5	—[c]	40
12	$ZnCl_2$	Water	8	—[c]	—[c]
13	$ZnCl_2$ (100)	Ethanol	3	92	—[c]
14	$ZnCl_2$ (30)	Ethanol	4	92	—[c]
15	$ZnCl_2$ (20)	Ethanol	7	78	—[c]
16	$ZnCl_2$ (10)	Ethanol	10	60	—[c]
14	$ZnCl_2$	Acetonitrile	7	73	4
15	$ZnCl_2$	THF	9	56	29
16	$ZnCl_2$	Dioxane	14	35	11
17	$CuBr_2$	Acetonitrile	9	40	4
18	$CuBr_2$	Ethanol	6	70	10
19	$CuCl_2$	Ethanol	9	55	5
20	$CuCl_2$	Acetonitrile	8	45	7

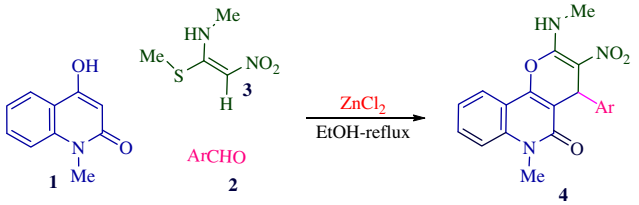
[a] 100 mol % of catalysts employed unless stated in parenthesis.
[b] Yield of isolated product.
[c] Product not obtained.

Michael-type 1,4-addition of enamine, derived from aldehyde and diethylamine, to quinone methide.[19] These methods, however, suffer from one or more disadvantages such as low/inconsistent yields, tedious work up, the need for column chromatographic purification, etc.

Under this context, we now report an expedient, three-component protocol for the synthesis in good yields of novel pyrano[3,2-*c*]quinolin-5(6*H*)-ones from the reaction of 4-hydroxy-1-methylquinolin-2(1*H*)-one **1**, aromatic aldehydes **2**, and nitroketene *N*,*S*-methylacetal **3** in the presence of anhydrous $ZnCl_2$ in ethanol (Tables 1 and 2).

The nitroketene *N*,*S*-methylacetal[20] **3** is a versatile synthon with an electron-releasing MeNH and an electron-withdrawing NO_2, besides having a nucleofuge (MeS). These functionalities enable this unique synthon to display nucleophilic and electrophilic character at the adjacent olefinic carbons (Fig. 2) and to be a good Michael acceptor, facilitating the incorporation of diverse nucleophiles by addition–elimination mechanism at the carbon bearing the amino

Table 2
Synthesis of 4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-ones **4**



Entry	Compd	Ar	Time (h)	Yield of **4** (%)
1	**4a**	4-ClC_6H_4	4	92
2	**4b**	4-MeC_6H_4	6	91
3	**4c**	4-$MeOC_6H_4$	5	85
4	**4d**	4-$Pr^iC_6H_4$	8	90
5	**4e**	2-MeC_6H_4	4	89
6	**4f**	C_6H_5	7	90
7	**4g**	4-FC_6H_4	7	93
8	**4h**	2-ClC_6H_4	8	89
9	**4i**	3-FC_6H_4	7	87
10	**4j**	3-BrC_6H_4	6	88
11	**4k**	4-$O_2NC_6H_4$	6	92
12	**4l**	1-Naphthyl	4	92
13	**4m**	2,3-$Cl_2C_6H_3$	6	89
14	**4n**	2,4-$Cl_2C_6H_3$	5	91
15	**4o**	2,5-$(MeO)_2C_6H_3$	8	88

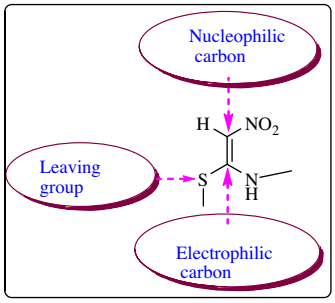


Figure 2. Unique structural features of nitroketene *N*,*S*-methylacetal **3**.

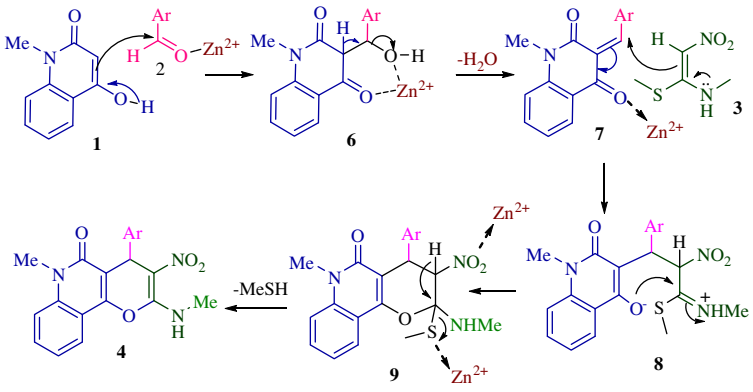
and sulfanyl groups, while the alkenic carbon bearing the nitro group can function as a nucleophilic center. This intramolecular polarization can be advantageously employed for the assembly of novel heterocyclic ring systems by reaction with an electrophilic as well as a nucleophilic reactant together in a one pot multicomponent domino reaction.[21]

It is pertinent to note that domino reactions have emerged as a powerful synthetic tool from the perspective of green chemistry and atom economy,[22] as they provide a rapid, convergent, and elegant synthesis of complex organic molecules without isolation and/or purification of intermediates. In particular, the development of domino reactions for the construction of medicinally relevant heterocycles has been a fertile research area in organic synthesis,[23] besides being an important goal in combinatorial chemistry. The present work stems as a part of our continued exploratory research on the construction of novel structurally diverse heterocycles[24] employing tandem/domino/sequential processes and green transformations.

We have initiated our study by performing the model reaction of equimolar amounts of 4-hydroxy-1-methylquinolin-2(1*H*)-one **1**, 4-chlorobenzaldehyde **2**, and nitroketene *N*,*S*-methylacetal **3** in the absence of any catalyst under solvent-free conditions, in water, ethanol, and acetonitrile (Table 1). No reaction was found to occur in water, while the reaction in ethanol, acetonitrile, and solvent-free conditions led to the formation of **5a** arising from the reaction of two molecules of 4-hydroxy-1-methylquinolin-2(1*H*)-one with one molecule of 4-chlorobenzaldeyde, leaving nitroketene *N*,*S*-methylacetal and 50% of 4-chlorobenzaldehyde unreacted (Table 1). The above reaction in the presence of triethylamine, pyrrolidine, ammonium acetate, or $Yb(OTf)_3$ as catalysts also furnished only **5a** (Table 1, entries 5–11), while the reaction in the presence of $CuBr_2$ and $CuCl_2$ furnished the desired product, **4a** along with **5a** (Table 1, entries 17–20). It is gratifying to find that the reaction in the presence of $ZnCl_2$ led exclusively to the formation of 4-(4-chlorophenyl)-6-methyl-2-(methylamino)-3-nitro-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one **4a** (Table 1) in 92% yield. The maximum yield in the shortest reaction time was obtained when the $ZnCl_2$–ethanol combination was employed (Table 1, entry 13).

The study of the effect of catalyst loading on the model reaction leading to **4a** with different amounts of $ZnCl_2$ in ethanol (Table 1, entries 13–16) show that the yield remains almost the same, when 30 or 100 mol % of $ZnCl_2$ was employed, while lower amounts diminished the yield significantly. Although this $ZnCl_2$-catalyzed reaction failed to proceed in water as the sole reaction medium (Table 1, entry 12), the release of 1 M equiv of water into the ethanol medium during the course of the reaction apparently does not impede the reaction significantly as evident from the formation of a high yield of the product. However, the yield of the product **4a** dropped significantly to 78%, when 10% water–90% ethanol (v/v) mixture was employed, compared to 92% yield of **4a** when absolute ethanol was used. Consequently, for all subsequent reactions, 30 mol % of $ZnCl_2$ was employed in absolute ethanol at reflux temperature. Interestingly, the products precipitated from the reaction mixtures and could be brought to high purity by a single recrystallization from dichloromethane, thus avoiding the need for extraction and chromatographic purification stages. These are important characteristics of our method, since it is well known that waste generation from synthetic operations is mostly due to the isolation and purification stages. The fact that $ZnCl_2$ has emerged as the most suitable catalyst for this transformation, renders the protocol attractive, as $ZnCl_2$ is an abundant and inexpensive Lewis acid. For all these reactions absolute ethanol was employed.

Presumably, $ZnCl_2$ can activate both aldehyde **2** and nitroketene *N*,*S*-methylacetal **3** as well as intermediates involved in complexa-



Scheme 1. Plausible mechanism for $ZnCl_2$-catalyzed formation of 4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-ones **4**.

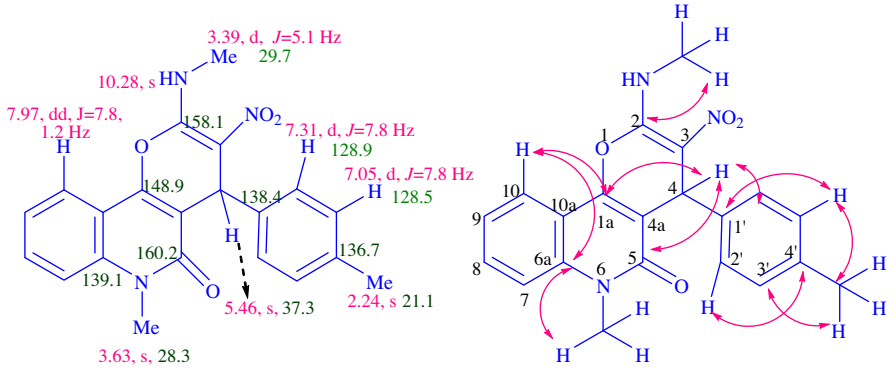


Figure 3. HMB correlations of compound **4b**.

tion, thereby catalyzing the reaction (Scheme 1). It is pertinent to note that $ZnCl_2$ catalyzes diverse organic reactions such as tandem/domino coupling of enones[25] and Mukaiyama aldol lactonization[26] and enables the synthesis of pyrimidines,[27] pyridines,[28] 1,2,4-oxadiazoles,[29] benzofurans/indoles,[30] 3-aminopyrazinones,[31] etc.

With the above results in hand, the scope of the reaction was investigated under the optimal conditions established above (Table 2) with a series of substituted aromatic aldehydes. Typically, the reaction of a mixture 4-hydroxy-1-methylquinolin-2(1*H*)-one **1** (1 mmol), aromatic aldehydes **2** (1 mmol), and nitroketene *N*,*S*-methylacetal **3** (1 mmol) in ethanol (15 ml) at reflux for 4–8 h afforded a library of novel 4-aryl-6-methyl-2-(methylamino)-3-nitro-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-ones **4** in 85–93% yields.[32]

The structure of compounds **4** is in accord with elemental analysis and NMR spectroscopic (^1H, ^{13}C, and 2D NMR) data as illustrated for a representative example **4b** (Fig. 3).[33] In the ^1H NMR spectrum of **4b**, the methyl hydrogens of the NCH_3 group attached to the pyran ring give a doublet at 3.39 ppm (J = 5.1 Hz), which shows HMBCs with C-2 at 158.1 ppm, while the N–CH_3 hydrogens of the quinolinone ring appear at 3.63 ppm and show HMBC with C-6a. The benzylic hydrogen, H-4 appears as a singlet at 5.46 ppm and displays HMBCs with C-2′, C-5, and C-1a at 128.9, 160.2, and 148.9 ppm, respectively. The H-10 gives a doublet of doublets at 7.97 ppm (J = 7.8 Hz), which shows HMBCs with C-6a and C-1a at 139.1 and 148.9 ppm, respectively. The *p*-tolyl methyl hydrogens appearing as a singlet at 2.24 ppm show HMBCs with the signal at 128.5 ppm assignable to C-3′. The H-3′ gives a doublet at 7.05 ppm (J = 7.8 Hz), which shows HMBCs with the signals of C-1′ and methyl carbon of the tolyl group at 138.4 and 21.1 ppm, respectively. Similarly, the H-2′ gives a doublet at 7.31 ppm (J = 7.8 Hz), which shows HMBCs with C-4′ at 136.7 ppm. The ^{13}C signals of hydrogen bearing carbons have been assigned from C,H-COSY correlations. The mass spectrum of **4b** has a M^+ peak at 378.20, in accord with the proposed structure and gives correct combustion micro analytical data.

A plausible mechanism for the formation of 4-aryl-6-methyl-2-(methylamino)-3-nitro-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-ones **4** is depicted in Scheme 1. Presumably, this transformation occurs via α,β-unsaturated heterocyclic ketone **7** formation, Michael addition, annulation, and elimination of methanethiol sequence. The unique catalytic efficacy of $ZnCl_2$ in this transformation presumably arises from its multiple catalytic roles by expediting (i) the formation of hydroxydiketone **6** by enhancing the electrophilicity of the aromatic aldehyde, (ii) the dehydration of **6** leading to the Michael acceptor **7**, and (iii) Michael addition of **3**–**7** forming intermediate **8**, which subsequently undergoes intramolecular annulation to afford intermediate **9**. Finally, elimination of methanethiol from intermediate **9** leads to the formation of the product **4** (Scheme 1). Thus, this protocol proceeds via one pot three-component domino reactions with operational simplicity and in excellent yields.

In conclusion, we have developed an expedient three-component protocol for the synthesis of novel 4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-ones in good yields from the reaction of 4-hydroxy-1-methylquinolin-2(1*H*)-one, aromatic aldehydes, and nitroketene *N*,*S*-methylacetal in the presence of $ZnCl_2$, an inexpensive catalyst, in refluxing ethanol, without the need for extraction or chromatography. This one-pot transformation presumably occurs via a domino sequence of reactions involving the formation of two C–C bonds and one C–O bond in a single synthetic operation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.022.

References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 697; (b) Brader, G.; Bacher, M.; Greger, H.; Hofer, O. *Phytochemistry* **1996**, *42*, 881; (c) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 77; (d) Grundon, M. F. In *The Alkaloid: Quinoline Alkaloids Related to Anthranilic Acids*; Academic: London, 1988; Vol. 32, p 341.
2. (a) Barr, S. A.; Neville, C. F.; Grundon, M. F.; Boyd, D. R.; Malone, J. F.; Evans, T. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 445; (b) Mitaku, S.; Skaltsounis, A. L.; Tillequin, F.; Koch, M.; Pusset, J.; Chauviere, G. *J. Nat. Prod.* **1985**, *48*, 772; (c) Ahmad, S. *J. Nat. Prod.* **1985**, *47*, 391; (d) Ulubelen, A.; Meric, I. A.; Meric, I. F.; Kaya, U. *Phytochemistry* **1994**, *35*, 1600; (e) Shwu, J. W.; Ih, S. C. *Phytochemistry* **1993**, *34*, 1659.
3. Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177.
4. Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211.
5. Johnson, J. V.; Rauckman, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942.
6. Nadaraj, V.; Thamarai Selvi, S.; Bai, H. P.; Mohan, S.; Thangadurai, T. D. *Med. Chem. Res.* **2012**, *21*, 2902.
7. (a) Abd, E.; Hisham, A. *Pharmazie* **1997**, *52*, 28; (b) Mohmed, E. A. *Chem. Pap.* **1994**, *48*, 261.
8. Chen, I. S.; Wu, S. J.; Tsai, I. J.; Wu, T. S.; Pezzuto, J. M.; Lu, M. C.; Chai, H.; Suh, N.; Teng, C. M. *J. Nat. Prod.* **1994**, *57*, 1206.
9. (a) Funayama, S.; Murata, K.; Nozoe, S. *Phytochemistry* **1994**, *36*, 525; (b) Huffman, J. W.; Hsu, T. M. *Tetrahedron Lett.* **1972**, *13*, 141.
10. (a) Clark, E. A.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. 1* **1964**, 438; (b) Grundon, M. F. *Tetrahedron* **1978**, *34*, 143; (c) Barr, S. A.; Neville, C. F.; Grundon, M. F.; Boyd, D. R.; Malone, J. F.; Evans, T. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 445; (d) Ngadjui, B. T.; Ayafor, J. F.; Bilon, A. E. N.; Sondengam, B. L.; Conolly, J. D.; Rycroft, D. S. *Tetrahedron* **1992**, *48*, 8711.
11. Asherson, J. L.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 512.
12. (a) Majumdar, K. C.; Choudhury, P. K. *Synth. Commun.* **1993**, *23*, 108; (b) Majumdar, K. C.; Ghosh, M.; Jana, M.; Saha, D. *Tetrahedron Lett.* **2002**, *43*, 2111.
13. (a) Lee, R.; Kweon, H. I.; Koh, W. S.; Min, K. R.; Kim, Y.; Lee, S. H. *Synthesis* **2001**, *1851*, 12; (b) Lee, R.; Kim, D. H.; Shim, J. J.; Kim, S. K.; Park, J. H.; Cha, J. S.; Lee, C. S. *Bull. Korean Chem. Soc.* **2002**, *23*, 998; (c) Jung, E. J.; Lee, Y. R.; Lee, H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2835.
14. Singh, B.; Chandra, A.; Singh, S.; Singh, R. M. *Tetrahedron* **2011**, *67*, 505.
15. Manikandan, S.; Shanmugasundaram, M.; Raghunathan, R. *Tetrahedron* **2002**, *58*, 8957.
16. Sabitha, G.; Kumar Reddy, M. S.; Arundhathi, K.; Yadav, J. S. *ARKIVOC* **2006**, *6*, 153.
17. Nadaraj, V.; Thamarai Selvi, S.; Bai, H. P.; Mohan, S.; Thangadurai, T. D. *Med. Chem. Res.* **2012**, *21*, 2902.
18. Ramesh, M.; Mohan, P. S.; Shanmugam, P. *Tetrahedron* **1984**, *40*, 4041.
19. Ye, J. H.; Ling, K. Q.; Zhang, Y.; Li, N.; Xu, J. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2017.
20. (a) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Academic Press: New York, 1994; (b) Kolb, M. *Synthesis* **1990**, 171; (c) Tominaga, Y.; Matsuda, Y. *J. Heterocycl. Chem.* **1985**, *22*, 937; (d) Ila, H.; Junjappa, H.; Mohanta, P. K. In *Progress in Heterocyclic Chemistry III*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon Press: Oxford, 2001; Vol. 13, pp 1–24; (e) Prakash Rao, H. S.; Geetha, K. *Tetrahedron Lett.* **2009**, *50*, 3836.
21. (a) Wen, L. R.; Li, Z. R.; Li, M.; Cao, H. *Green Chem.* **2012**, *14*, 707; (b) Chowdhury, S.; Nandi, G. C.; Samai, S.; Singh, M. S. *Org. Lett.* **2011**, *13*, 3762; (c) Verma, R. K.; Verma, G. K.; Shukla, G.; Nagaraju, A.; Singh, M. S. *ACS Comb. Sci.* **2012**, *14*, 224; (d) Singh, M. S.; Nandi, G. C.; Samai, S. *Green Chem.* **2012**, *14*, 447.
22. (a) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463; (b) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072; (c) Domling, A. *Chem. Rev.* **2006**, *106*, 17; (d) De Souza, D. M.; Muller, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1095; (e) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546.
23. (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (b) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (c) Guo, H. C.; Ma, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (d) Nicholau, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed* **2006**, *45*, 7134; (e) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861; (f) Gondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.
24. (a) Gunasekaran, P.; Indumathi, S.; Perumal, S. *RSC Adv.* **in press**, doi: http://dx.doi.org/10.1039/C3RA00136A.; (b) Prasanna, P.; Perumal, S.; Menéndez, J. C. *Green Chem.* **in press**, doi: http://dx.doi.org/10.1039/C3GC37128J.; (c) Perumal, S.; Menéndez, J. C. In *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry, 2011; Vol. 15, pp 402–422; (d) Gunasekaran, P.; Balamurugan, K.; Sivakumar, S.; Perumal, S.; Menéndez, J. C.; Almansour, A. I. *Green Chem.* **2012**, *14*, 750; (e) Prasanna, P.; Balamurugan, K.; Perumal, S.; Menéndez, J. C. *Green Chem.* **2011**, *13*, 2123; (f) Michael Rajesh, S.; Devi Bala, B.; Perumal, S.; Menéndez, J. C. *Green Chem.* **2011**, *13*, 3248; (g) Indumathi, S.; Perumal, S.; Menéndez, J. C. *Tetrahedron* **2011**, *67*, 7101.

25. Ikeda, S.; Sanuki, R.; Miyachi, H.; Miyashita, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* **2004**, *126*, 10331.
26. Zhao, C.; Mitchell, T. A.; Vallakati, R.; Pérez, L. M.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 3084.
27. Sasada, T.; Kobayashi, F.; Sakai, N.; Konakahara, T. *Org. Lett.* **2009**, *11*, 2161.
28. Sridhar, M.; Ramanaiah, B. C.; Narsaiah, C.; Mahesh, B.; Kumaraswamy, M.; Mallu, K. K. R.; Ankathi, V. M.; Rao, P. S. *Tetrahedron Lett.* **2009**, *50*, 3897.
29. Augustine, J. K.; Akabote, V.; Hegde, S. G.; Alagarsamy, P. *J. Org. Chem.* **2009**, *74*, 5640.
30. Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803.
31. Chung, J. Y. L.; Cvetovich, R. J.; Tsay, F.; Dormer, P. G.; DiMichele, L.; Mathre, D. J.; Chilenski, J. R.; Mao, B.; Wenslow, R. *J. Org. Chem.* **2003**, *68*, 8838.
32. *General procedure for the synthesis of 4H-pyrano[3,2-c]quinolin-5(6H)-ones 4:* a mixture of 4-hydroxy-1-methylquinolin-2(1*H*)-one **1** (1 mmol), aromatic aldehydes **2** (1 mmol), and nitroketene *N,S*-methylacetal **3** (1 mmol) in the presence of $ZnCl_2$ (30 mol %) in ethanol (15 ml) was stirred at reflux for the time given in Table 3. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and the resulting solid was filtered off and recrystallized from dichloromethane to obtain pure products **4**.
33. *The spectroscopic data for representative compounds* ***4a*** *and* ***4b****:* 4-(4-chlorophenyl)-6-methyl-2-(methylamino)-3-nitro-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one (**4a**). Yellow solid; yield 92%; mp 325 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.42 (d, 3H, *J* = 3.0 Hz, $NHCH_3$), 3.65 (s, 3H, NCH_3), 5.46 (s, 1H, CH), 7.19–7.24 (m, 2H, Ar-H), 7.34–7.42 (m, 4H, Ar-H), 7.67 (td, 1H, *J* = 7.8 Hz, 0.9 Hz, Ar-H), 7.98 (d, 1H, *J* = 7.2 Hz, Ar-H), 10.28 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 27.7, 28.9, 36.5, 108.0, 111.9, 113.8, 121.4, 121.9, 127.2, 129.1, 131.1, 131.5, 139.5, 157.0, 159.2. ESI-MS *m*/*z* calcd for $C_{20}H_{16}ClN_3O_4$ $[M+H]^+$ 398.08, found 398.28. Anal. Calcd for $C_{20}H_{16}ClN_3O_4$: C, 60.38; H, 4.05; N, 10.56. Found: C, 60.44; H, 4.12; N, 10.64.
6-Methyl-2-(methylamino)-3-nitro-4-*p*-tolyl-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one (**4b**). Yellow solid; yield 91%; mp 320 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.24 (s, 3H), 3.39 (d, 3H, *J* = 5.1 Hz, $NHCH_3$), 3.65 (s, 3H, NCH_3), 5.46 (s, 1H, CH), 7.05 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.29–7.40 (m, 4H, Ar-H), 7.65 (td, 1H, *J* = 8.1 Hz, 1.5 Hz, Ar-H), 7.97 (dd, 1H, *J* = 7.8 Hz, 1.2 Hz, Ar-H), 10.28 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.1, 28.3, 29.8, 37.3, 109.0, 112.8, 113.0, 114.5, 122.1, 122.5, 128.5, 128.9, 131.6, 136.7, 138.4, 139.1, 148.9, 158.1, 160.3. ESI-MS *m*/*z* calcd for $C_{21}H_{19}N_3O_4$ $[M+H]^+$ 377.18, found 378.20. Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.98; H, 5.19; N, 11.27.