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Regioselective intramolecular annulations of ambident β-enamino esters: A diversity-oriented synthesis of nitrogen-containing privileged molecules

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ABSTRACT

Diversity-oriented, regioselective, intramolecular annulation of β-enamino esters is described under solvent-free, calcium-catalysis. 2-aminoaryl ketones and alkyl propiolates undergone a [4+2] annulation to yield substituted quinolines; with an excess of alkyl propiolates, benzodiazepines were formed via a [4+2+1] annulation. We also described a one-pot, 3-component synthesis of quinoline derivatives via a [4+2+2] annulation. Interestingly, 2-aminoaryl ketones undergone a self-condensation [4+4] and gave the dibenzodiazocines.

The small molecules, especially nitrogen-containing heterocyclic compounds have been serving as viable research tools in the drug discovery.[1,2] The major class of current FDA approved drugs are small molecules.[3] Hence the pharmaceutical industries screen a large number of small molecules in a traditional high-throughput screening (HTS) to identify the bioactive molecules and lead compounds for drug discovery.[4,5] The results of HTS iterates the need to have functionally diverse small molecules, and as a consequence, the diversity-oriented synthesis (DOS) has emerged as a new branch of organic synthesis, aimed to fill the chemical space with efficient synthetic strategies.[6] On the other hand, privileged molecules are one of the important concepts in the rationale drug discovery.[7] If one can combine both the concepts together, that is a DOS to make the libraries of privileged molecules, that could be a much more efficient tool for the drug discovery than the individual strategies.

β-enamino esters are versatile intermediates in organic synthesis; they are an integral part of many natural and synthetic bioactive molecules.[8] As depicted in Fig. 1, one can presume the β-enamino esters as ambident substrates due to the reason that they have an electrophilic carbon and also a nucleophilic carbon. Therefore we designed our synthetic plan to explore the ambident reactivity of β-enamino esters for the synthesis of quinolines and benzodiazepines. As part of our research aimed for the development of new synthetic methods towards privileged molecules of medicinal importance,[9] herein we report a diversity-oriented synthesis of nitrogen-containing privileged molecules, such as quinolines, benzodiazepines, and dibenzodiazocines (Fig. 2).

Initially, we planned to synthesize the quinolines and hence chose 2-amniobenzophenone (**1a**) and ethyl propiolate (**2a**) as the model substrates (Table 1).[10] A mixture of **1a**, **2a**, and 10 mol % of $Ca(OTf)_2$ and Bu_4NPF_6 (additive) was refluxed in 1,2-DCE for 24 h to isolate the desired quinoline **3a** in 52% yield (entry 1, Table 1). Encouraged by this result, we screened few other solvents such as acetonitrile (entry 2), ethanol (entry 3) and toluene (entry 4) to see the maximum yield of the reaction. Unfortunately, none of them gave better results. Nevertheless, we were delighted to note that under the solvent-free conditions quinoline **3a** was isolated in 76% yield in 3 h (entry 5). We also confirmed that the combination of catalyst and additive is necessary for the quinoline synthesis (entries 6, 7, and 11 Table 1). Further experiments to minimize the catalyst loadings were unsuccessful. Finally, we found that entry-5 (Table 1) as the best condition for the synthesis of quinoline **3a** in 3 h with 76% yield.

Having the optimum condition in hand for a [4+2] annulation of **1a** and **2a**, we aimed to check the generality of this reaction concerning the two reacting partners, i.e., 2-aminobenzophenone and alkyne (Table 2). Under the standard conditions (Table 1, entry 5) ethyl propiolate reacted with substituted 2-aminoaryl ketones and furnished the respective quinoline derivatives **3b-3d** in good yields. An obvious and similar reactivity was also observed with methyl propiolate and substituted amino ketones while obtaining the quinoline derivatives **3e-3h** (Table 2) in good yields. Encouraged by the reactivity of terminal alkynes, we then treated the 2-amino ketones with internal alkynes, activated on both sides and obtained the fully substituted quinolines **3i-3L**. It is worth to note that the yields of quinoline derivative with the internal-alkynes activated on both sides were better than terminal alkynes.

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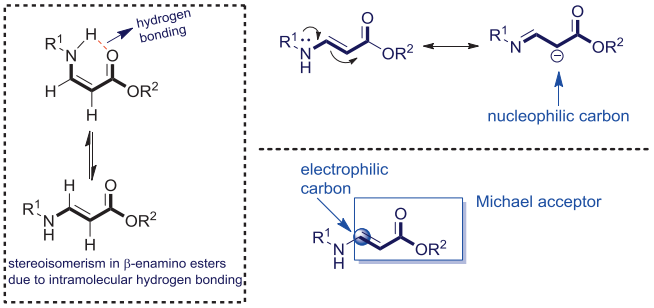


Fig. 1. Ambident reactivity of β-enamino esters.

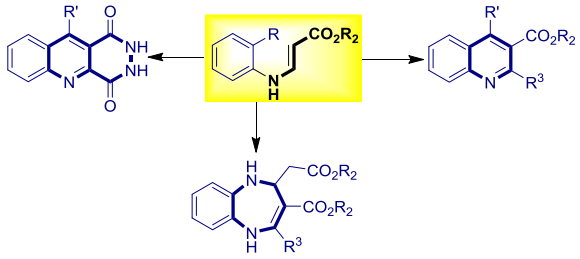
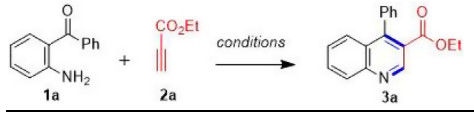


Fig. 2. Exploing ambiden reactiviy of β-enamino esters in a diversity-oriented approach to synthesize quinoline and benzoiazepine derivatives.

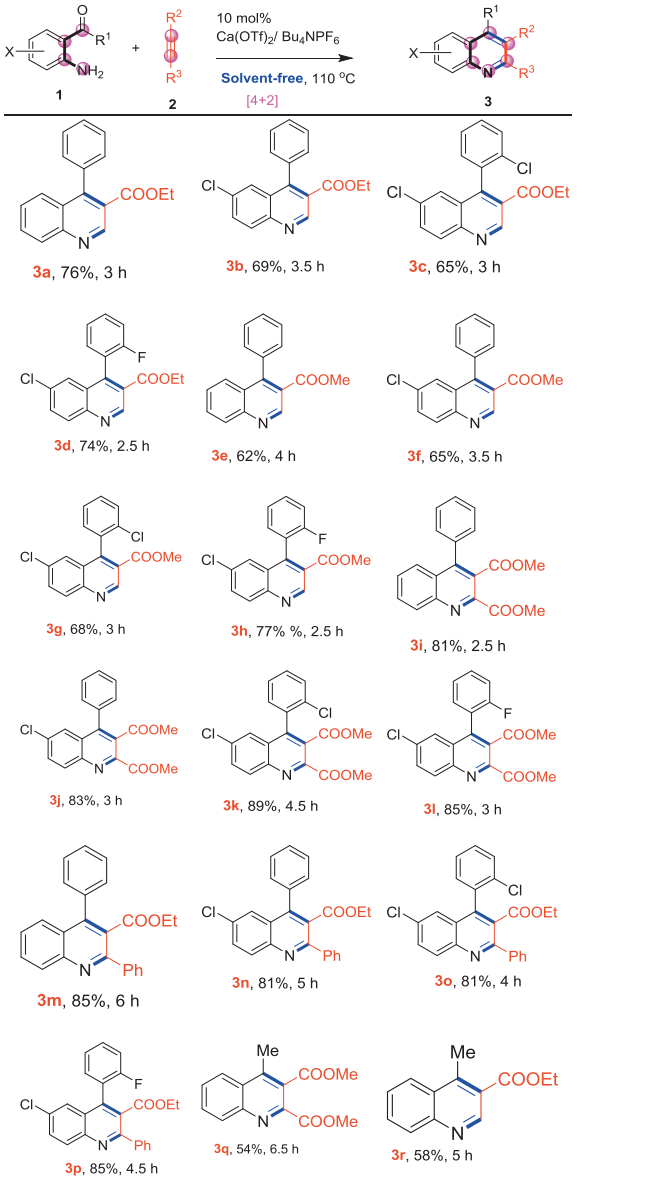
Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst (mol%)	Conditions[b]	Yield (%)[b]
1	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	1,2-DCE, 90 °C, 24 h	52
2	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	CH_3CN, 90 °C, 24 h	30
3	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	EtOH, 90 °C, 8 h	60
4[c]	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Toluene, 110 °C, 24 h	16
5	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Neat, 110 °C, 3 h	76
6	$Ca(OTf)_2$ (10)	Neat, 110 °C, 12 h	15
7	Bu_4NPF_6 (10)	Neat, 110 °C, 12 h	nr
8	$Ca(OTf)_2/Bu_4NPF_6$ (5/5)	Neat, 110 °C, 8 h	62
9	$Ca(OTf)_2/Bu_4NPF_6$ (10/5)	Neat, 110 °C, 8 h	68
10	$Ca(OTf)_2/Bu_4NPF_6$ (5/10)	Neat, 110 °C, 8 h	63
11	–	Neat, 110 °C, 12 h	nr

[a] 1 equiv. of **1a** and 1.2 equiv. of **2a** were used.
[b] Isolated yields.
[c] Optimum conditions. nr = no reaction.

Table 2
Substrate scope of calcium-catalyzed cascade synthesis of quinoline from 1-(2-aminophenyl)ketones under solvent-free condition.

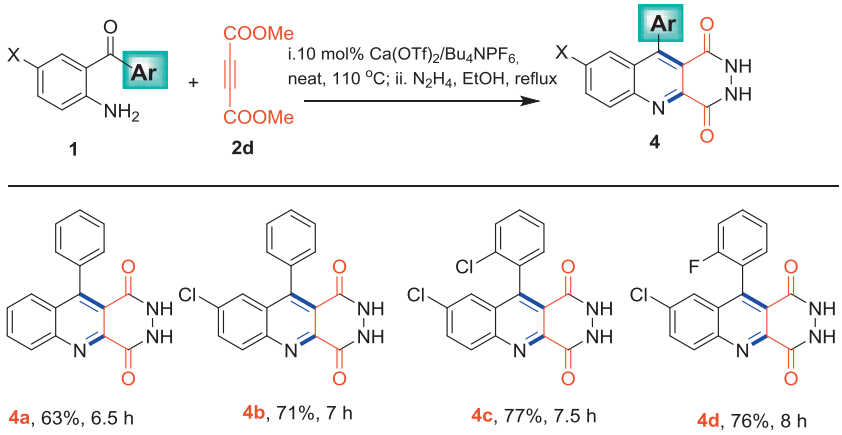


Reaction conditions: 1 equiv. of **1**, 1.2 equiv. of **2**, 10 mol% of $Ca(OTf)_2$ and 10 mol% Bu_4NPF_6 were heated at 110 °C for specified time.

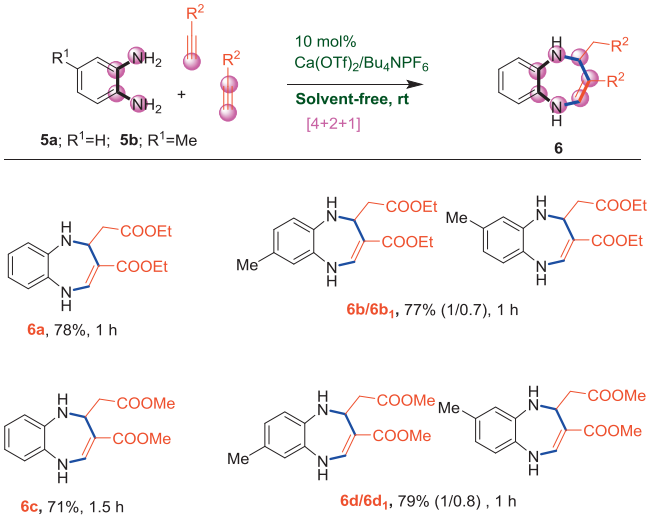
Ethyl 3-phenylpropiolate also participated in the intramolecular annulation/aromatization cascade and furnished the quinolines **3m**-**3p** in excellent yields. The reaction of 2-amino acetophenone with dimethylacetylenedicarboxylate and ethyl propiolate was also investigated. In this case, the reaction took relatively long time with moderate yields of **3q** and **3r** (Table 2).

When we looked at the products obtained from acetylene dicarboxylates and 2-aminoaryl ketones (Table 2, entries **3i**-**3L**), we thought of a condensation reaction between these quinoline diesters and hydrazine. Interestingly these compounds were known to show antibacterial activity.[11] However, the reported synthesis of these compounds was not a straightforward,[11] hence we decided to extend our two component synthesis of quinolines to a one-pot, 3-component synthesis (Scheme 1). Therefore, 2-aminoaryl ketones were treated with $Ca(OTf)_2$ and dimethyl acetylenedicarboxylate under neat conditions at 110 °C. After the formation of corresponding quinoline diesters (monitored by TLC) the reaction temperature was brought to 90 °C and then added ethanol and hydrazine to obtain the desired tricyclic quinoline derivatives **4a**-**4d** in good yields as depicted in the Scheme 1.

After the suceessful substantiation of our synthetic protocol towards synthesis of quinolines (Table 2) and tricyclic-quinoline derivatives (Scheme 1) from 1-(2-aminophenyl)ketones, we further elaborated the diversity of this methodology to explore the synthesis of another privileged class of N-heterocyclic molecules, benzodiazepines (Scheme 2).[12,13] Interestingly, the [4+2+1] annulation of o-phenyldiamine with ethyl propiolate (2 equiv.) was catalyzed by calciumtriflate at room temperature under solvent-free conditions to furnish the respective benzodiazepine **6a** in 78% yield. Similarly, methylpropiolate gave **6c** in 71% yield. In case of the annulation between 4-methylbenzene-1,2-diamine and ethyl propiolate, the reaction yielded the regioisomeric benzodiazepines



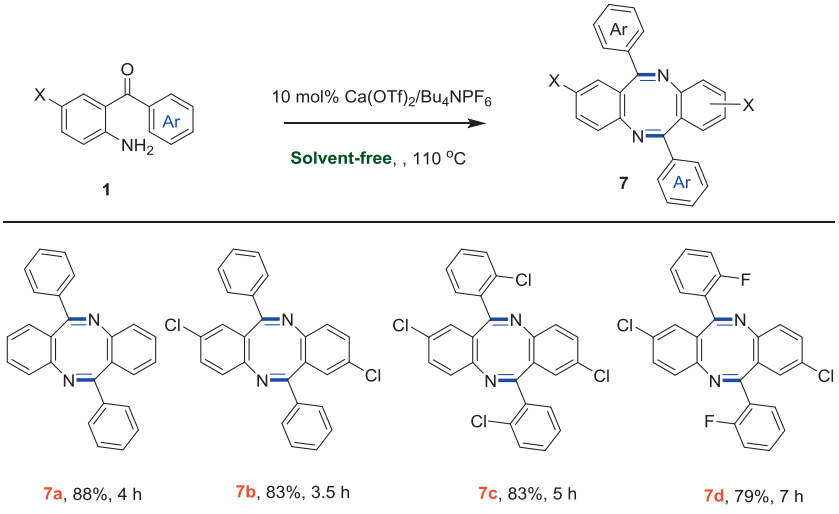
Scheme 1. Calcium (II)-catalyzed, one-pot, 3-omponent synthesis of 10-phenyl-2,3-ihydropyridazino [4,5-b]quinoline-1,4-diones.



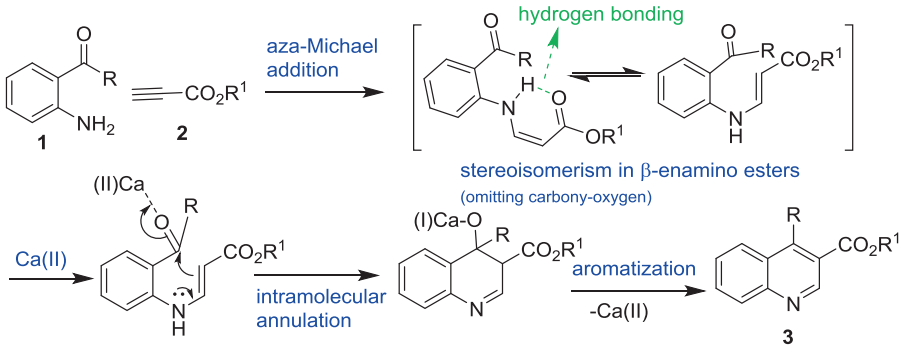
Scheme 2. Synthesis of benzodiazepines hrough a calcium-catalyzed [4+2+1] annulation.

6b/6b$_1$ in 1/0.7 ratio with a 77% combined yield.[14] A similar observation was made with methyl propiolate (**6d**/**6d$_1$** = 1:0.8).

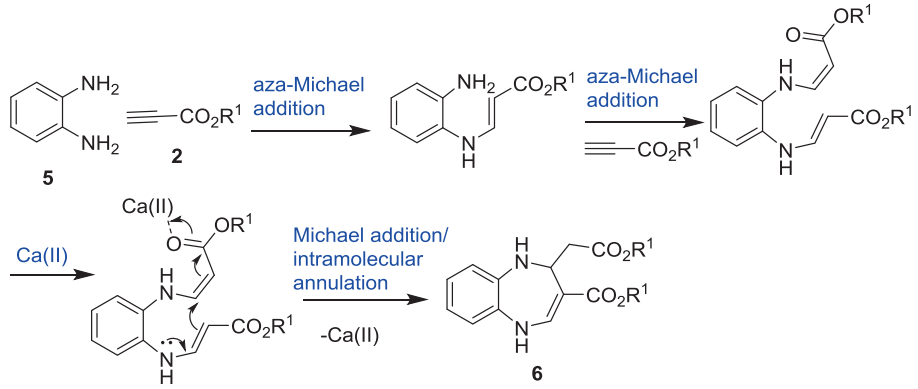
While synthesizing the quinolines through an intramolecular annulation of β-enamino esters (Scheme 1), we treated 2-aminobenzophenone and diphenyl acetylene under standard conditions to get the 2,3,4-triaryl quinoline. However, the reaction did not give the desired product but gave [1,5]-dibenzodiazceine **7a** (Scheme 3). Since the alkyne is not activated, β-enamino ester intermediate was not formed. But 2-aminobenzophenone underwent an intermolecular condensation to yield **7a** with Ca(II) under neat conditions. A thorough literature survey suggested that owing to the pharmacological and material applications;[15] few approaches have been developed for the synthesis of dibenzo[1,5]-diazecines. The most common approach is the condensation of 2-aminoaryl ketone in the presence of a suitable catalyst.[16] When compared to the existing methods, we felt that it would be useful to develop a method under solvent-free conditions using an environmentally benign catalyst ($Ca(OTf)_2$). Therefore a suitable 2-aminoaryl ketone was heated at 110 °C in neat with 10 mol% of Ca(II) and obtained the dibenzo[1,5]diazacines **7a**-**7d** in good yields (Scheme 3).



Scheme 3. Calcium catalyzed homodimerization of 2-aminoaryl ketones to dibenzodiazocines.



Scheme 4. (i). Possible mechanism for quinoline synthesis



Scheme 4. (i) Possible mechanism for quinoline synthesis. (ii) Possible mechanism for benzodiazepine synthesis.

The possible mechanism for the intramolecular annulation of β-enamino esters to quinolines and benzodiazepines is described in the Scheme 4. Initially aza-Michael addition of 2-aminoaryl ketone and activated alkyne takes place to furnish the β-enamino ester, where exists stereoisomerism due to the presence of intramolecular hydrogen bonding.[17] Whenever the trans isomer activated by the Lewis acid, then an intramolecular annulation takes place (here β-enamino ester behaves as carbon nucleophile and adds to the carbonyl carbon), followed by a subsequent elimination/aromatization results the quinoline molecule **3** (Scheme 4 (i)). Similarly, o-phenyldiamine undergoes aza-Michael addition twice with two moles of activated alkyne to furnish the bis-β-enaminoester. A Ca(II)-mediated intramolecular annulation (one of the β-enamino ester acts as carbon nucleophile and adds to another β-enamino ester via a Michael addition) yields the benzodiazepine **6**.

In summary, we have developed an efficient, diversity-oriented approach for the synthesis of privileged-nitrogen containing heterocyclic molecules such as quinolines, dihydropyridazino-quinolines, benzodiazepines and dibenzo[1,5]diazocines. All these reactions were promoted by $Ca(OTf)_2$ as the sustainable Lewis acid catalyst and most of them are performed under solvent-free conditions. The synthesis of quinoline derivatives and benzodiazepines proceeded through the formation of ambident β-enamino esters as key intermediates followed by the regioselective intramolecular annulation. Further exploration of this ambident nature of β-enamino esters is currently under progress.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.064.

References

1. Strausberg RL, Schreiber SL. *Science*. 2003;300:294.
2. O'Connor CJ, Laraia L, Spring DR. *Chem Soc Rev*. 2011;40:4332.
3. (a) Lacana E, Amur S, Mummanneni P, Zhao H, Frueh FW. *Clin Pharmacol Ther*. 2007;82:466;
   (b) Nelson AL, Dhimolea E, Reichert JM. *Nat Rev Drug Discovery*. 2010;9:767.
4. (a) Lehar J, Stockwell BR, Giaever G, Nislow C. *Nat Chem Biol*. 2008;4:674;
   (b) Spring DR. *Chem Soc Rev*. 2005;34:472.
5. (a) Macarron R, Banks MN, Bojanic D, et al. *Nat Rev Drug Discovery*. 2011;10:188;
   (b) Ricardo M. *Drug Discovery Today*. 2006;11:277.
6. (a) Schreiber SL. *Science*. 2000;287:1964;
   (b) Galloway WRJD, Isidro-Llobet A, Spring DR. *Nat Commun*. 2010;1:80;
   (c) Spring DR. *Org Biomol Chem*. 2003;1:3867;
   (d) Tan DS. *Nat Chem Biol*. 2005;1:74.
7. (a) Ramstrong O, Lehn JM. *Nat Rev Drug Disc*. 2002;1:26;
   (b) Hochgürtel M, Niesinger R, Kroth H, et al. *J Med Chem*. 2003;46:356;
   (c) Sindeler M, Lutz TA, Petrera M, Wanner KT. *J Med Chem*. 2013;56:1323.
8. (a) Salaheldin AM, Al-Sheikh MA. *Molecules*. 2010;15:4359;
   (b) Elassar AZA, El-Khair AA. *Tetrahedron*. 2003;59:8463;
   (c) David O, Fargeau-Bellassoued MC, Lhommet G. *Tetrahedron Lett*. 2002;43:3471;
   (d) Aumann R, Gottker-Schnetmann I, Frohlich R, Saarenketo P, Holst C. *J Chem Eur*. 2001;7:711;
   (e) Abelman MM, Curtis JK, James DR. *Tetrahedron Lett*. 2003;44:6527;
   (f) Russowsky D, Silveira Neto BA. *Tetrahedron Lett*. 2003;44:2923;
   (g) Revial G, Lim S, Viossat B, et al. *J Org Chem*. 2000;65:4593;
   (h) Foster JE, Nicholson JM, Butcher R, et al. *Bioorg Med Chem*. 1999;7:2415;
   (i) Scott KR, Rankin GO, Stables JS, et al. *J Med Chem*. 1995;38:4033;
   (j) Yaragorla S, Saini PL, Pareek, Almansour AI, Arumugam A. *Tetrahedron Lett*. 2016;57:2034;
   (k) Yaragorla S, Dada R. *ACS Omega*. 2017;2:4859.
9. (a) Yaragorla S, Dada R, Singh S, Pareek A, Rana M, Sharma AK. *Chemistry Select*. 2016;1:6902;
   (b) Pareek A, Dada R, Rana M, Sharma AK, Yaragorla S. *RSC Adv*. 2016;6:89732;

(c) Yaragorla S, Dada R, Pareek A, Singh G. *RSC Adv*. 2016;6:28865;
(d) Yaragorla S, Pareek A, Dada R, Saini PL. *Eur J Org Chem*. 2017;4600;
(e) Yaragorla S, Pareek A, Dada R. *Adv Synth Catal*.. 2017;359:3068;
(f) Yaragorla S, Pareek A, Dada R. *Tetrahedron lett*.. 2017;58:4642.
10. Synthesis of quinolines from β-enamino esters (a): Venkanna A, Swapna K, Rao PV. *RSC Adv*. 2014;4:15154;
(b) Bagdi AK, Santra S, Rahman M, Majee A, Hajra A. *RSC Adv*. 2013;3:24034;
(c) Pandit RP, Lee YR. *RSC Adv*. 2013;3:22039;
(d) Chanda T, Verma RK, Singh MS. *Chem Asian J*. 2012;7:778;
(e) Patil DR, Salunkhe SM, Deshmukh MB, Anbhule PV. *J Heterocyclic Chem*. 2011;48:1414;
(f) Gao WY, Leng K, Cash L, Chrzanowski M, Stackhouse CA, Sun Y, Ma S. *Chem Commun*. 2015;51:4827.
11. Sambavekar PP, Aitawade MM, Patil DR, Kolekar GB, Deshmukh MB, Anbhule PV. *Indian J Chem B*. 2013;52B:1521.
12. (a) Cortés EC, Ana LVC, Olivia GM. *J Heterocycl Chem*. 2007;44:183;
(b) Makaron L, Moran CA, Namjoshi O, Rallapalli S, Cook JM, Rowlett JK. *Pharmacol Biochem Behav*. 2013;104:62;
(c) Kumar R, Chaudhary P, Nimesh S, Verma AK, Chandra R. *Green Chem*. 2006;8:519;
(d) Michelini S, Cassano GB, Frare F, Perugi G. *Pharmacopsychiatry*. 1996;29:127;
(e) Ookura R, Kito K, Ooi T, Namikoshi M, Kusumi T. *J Org Chem*. 2008;73:4245;
(f) Naeimi H, Foroughi H. *New J Chem*. 2015;39:1228.
13. (a) Wang L, Pan XQ, Cai JJ, Zou JP. *Bopuxue Zazhi*. 2011;28:383;
(b) Wu H, Yang J, Wang L. *Chin J Chem*. 2011;29:1721;
(c) Li J, Li S, Li C, Liu Y, Jia X. *Adv Synth Catal*. 2010;352:336;
(d) Jiang YJ, Cai JJ, Zou JP, Zhang W. *Tetrahedron Lett*. 2010;51:471.
14. Regioisomeric ration was determined by 1H NMR of the mixture.
15. (a) Jozsef R, Ivan B, Csaba K, Imre H, Miklos N. (Gyar, E. Gy. T. G.) German Offen. Patent 2 608 186, 1976; Chem. Abstr. 1976;85:192593v; (b) D'Amico JJ (Monsanto Co.) Br. Patent 1 167 084, 1967; Chem. Abstr. 1970;72:12603y; (c) Tadashi O, Tsuyosmi K, Hisao Y. (Sumitomo Chemical Co., Ltd.) Jpn. 75 01 276, 1975; Chem. Abstr. 1975;83:43213c; (d) Arnold B, Benjamin P, Sheldon S. (Hoffmann-La Roche, F., and Co., A.-G.) German Offen. Patent 2 353 062;1974, Chem. Abstr. 1974;81:37487n; (e) Casadio S, Pala G, Crescenzi E, Uberti EM, Coppi G, Turba C. *J Med Chem*. 1968;11:97.
16. (a) Bovenkerk M, Esser B. *Eur J Org Chem*. 2015;775;
(b) Pettersson B, Bergman J, Svensson PH. *Tetrahedron*. 2013;69:2647;
(c) Zhao N, Qiu L, Wang X, Li J, Jiang Y, Wan X. *Tetrahedron*. 2012;68:9665;
(d) Wang X, Li J, Zhao N, Wan X. *Org Lett*.. 2011;13:709;
(e) Jung DI, Song JH, Lee EJ, et al. *Tetrahedron Lett*. 2009;50:5805.
17. Zhang LL, Sun J, Yan CG. *Tetrahedron Lett*. 2012;53:6965.

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