

# Synthetic Applications of the Blaise Reaction

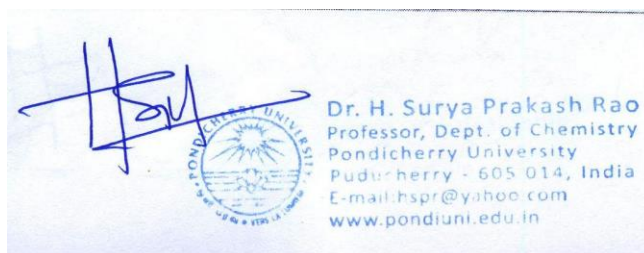
FINAL REPORT OF THE PROJECT SUBMITTED TO  
UNIVERSITY GRANTS COMMISSION (UGC), NEW DELHI

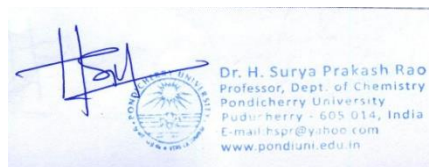
(Ref: F.No.43-191/2014(SR), Dated 29.12.2015)  
(UGC FILE NO.F. MRP-MAJOR-CHEM-2013-20349; Duration of the project: 2015-2018)



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June 2018





Annexure -VIII

**PONDICHERRY UNIVERSITY**  
**PUDUCHERRY – 605 014**

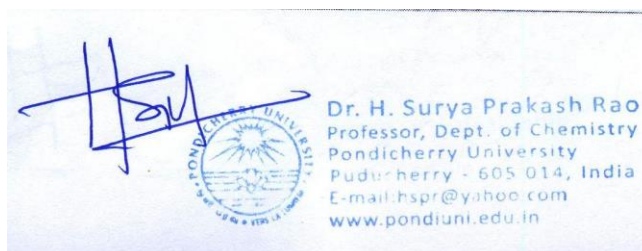
**FINAL REPORT OF THE WORK DONE ON THE MAJOR RESEARCH PROJECT**

(Report to be submitted within 6 weeks after completion of each year)

1. Project report No. 1st /2nd /3rd/Final Final
2. UGC Reference F. No. MRP-MAJOR-CHEM-2013-20349 Dated 29.12.2015
3. Period of report: 2015-2018
4. Title of research project Synthetic Applications of the Blaise Reactions
5. (a) Name of the Principal Investigator H. Surya Prakash Rao
- (b) Deptt. Department of Chemistry
- (c) University where work has progressed Pondicherry University
6. Effective date of starting of the project 29-12-2015
7. Grant approved and expenditure incurred during the period of the report:
  - a. Total amount approved Rs.15,03,600/- (Released: 8,10,600/-)
  - b. Total expenditure Rs. 5,89,86/-
  - c. Report of the work done: (Please attach a separate sheet)

**i. Brief objective of the project**

Objective of the present proposal is the studies on the Blaise reaction. the Blaise reaction is a classical reaction, but less explored. It has, however, enormous scope. Hitherto, the studies were restricted



to the use of  $\alpha$ -bromo esters. We proposed in the project to widen the scope to include  $\alpha$ -acyl bromides of many kinds. Reaction of each one of them with aliphatic / aromatic / benzyl /benzoyl aceto nitriles is expected to provide easy access to 1,3-dicarbonyl / 1,3,5-tricarbonyl / acyl  $\beta$ -keto esters.

**ii. Work done so far and results achieved and publications, if any, resulting from the work**  
(Give details of the papers and names of the journals in which it has been published or accepted for publication)

Two scholarly papers emanated from the work as given below. For details see the attachment

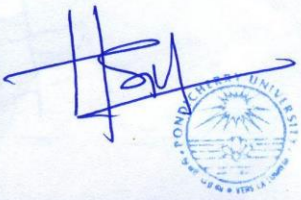
(1) Variations on the Blaise Reaction: Synthesis of 3,5-Dioxopentanoates and 3-Amino-5-oxopent-3-enoates H. Surya Prakash Rao,\*Nandurka Muthanna *SYNLETT* **2016**, 27, 2014–2018.

(2) Vinylogous Blaise reaction: Conceptually new synthesis of 2-pyridones, H. Surya Prakash Rao,\*Nandurka Muthanna and Ashiq Hussain Padder *SYNLETT* **2018**, 29, 000

**iii. Has the progress been according to original plan of work and towards achieving the objective? If not, state reasons**

Yes. As per the plan we have achieved a facile and convenient synthesis of a variety of 3,5-diketopentanoates (3,5-diketo esters) and 3-amino-5-oxopent-3-enoates from zinc mediated condensation of readily available 3-oxopropanenitriles ( $\alpha$ -cyano ketones) with ethyl bromoacetate. The reaction is a variation of the classical Blaise reaction tuned to synthesis of tri-functional compounds having 3,5-diketo ester or 3-enamino 5-keto ester functional groups. Our studies revealed that the Blaise reaction on nitrile works ahead of the Reformatsky reaction on the neighbouring ketone when the two functional groups are located in germinal position as found in  $\alpha$ -cyano ketones, possibly due to zinc complexation leading to increased electrophilicity of the nitrile. This work has been published in *SYNLETT*, a prestigious journal in Organic Chemistry. Reference: *SYNLETT* **2016**, 27, 2014–2018.

In continuation of the above work we have discovered and elaborated a new method for the synthesis of 2-pyridones by employing the vinylogous version of the Blaise reaction. Present method constitutes a new pyridine ring synthesis, generated by  $[C_4 + CN]$  assembly. The vinylogous Blaise reaction with ethyl bromobut-2-enoate on a variety of nitriles furnished C(6) substituted 2-pyridones.



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This work has been accepted for publication in the prestigious journal *SYNLETT* and is due to appear any time. Reference: *SYNLETT* **2018**, 27, 000.

**iv. Please indicate the difficulties, if any, experienced in implementing the project**

We did not get second installment of the project although we submitted UC. On enquiry we were told – orally – that second installment will be released only if 80% of the fund from first installment has been utilized. Since we had difficulty in employing project assistant, we fell short of 80% fund utilization. If PIs were clearly informed on this aspect, it would have been better.

We had encountered difficulties in recruitment of Project Fellow. Mr. Muthanna who was employed as project fellow received Ph.D. degree and left Pondicherry University. We could not find a replacement after his exit. So the project suffered. However, work was continued by Mr. Ashiq Hussain Padder another Ph.D. scholar and we were able to publish second paper in the prestigious journal.

**v. If project has not been completed, please indicate the approximate time by which it is likely to be completed.** A summary of the work done for the period (Annual basis) may please be sent to the Commission on a separate sheet.

The work is complete. We will, however, continue to work on the scientific problem and hope to contribute to the field.

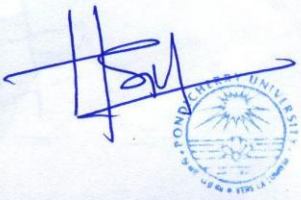
**vi. If the project has been completed, please enclose a summary of the findings of the study.** One bound copy of the final report of work done may also be sent to University Grants Commission.

Enclosed herewith.

**vii. Any other information which would help in evaluation of work done on the project.** At the completion of the project, the first report should indicate the output, such as

(a) Manpower trained:

Mr. N. Muthanna was trained as a competent research scholar by utilizing the project funds. He could carry out difficult work of finding right reaction conditions for transformation of readily available fine chemicals like acyl acetonitriles, alpha bromoesters into value added diketo esters using ordinary zinc.



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(b) Ph. D. awarded:

Mr. N. Muthanna was awarded Ph.D. degree

(c) Publication of results:

Two papers were published in leading organic chemistry journal namely SYNLETT (reprints enclosed)

(d) Other impact, if any:

We have developed conceptually new synthesis of pyridine ring by [C4 + CN] assembly has been developed by applying vinylogous version of the classical Blaise reaction. The zinc mediated reaction of aryl/heteroaryl/alkyl nitriles with ethyl-4-bromocrotonate provided a variety of C(6) substituted 2-pyridones in a single-step.


## FINAL REPORT OF THE WORK DONE ON THE MAJOR RESEARCH PROJECT

Name of PI: Dr. H. Surya Prakash Rao

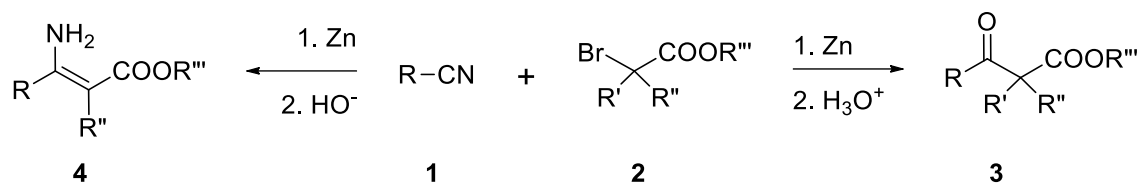
UGC MRP No. MRP-MAJOR-CHEM-2013-20349 Dated 29.12.2015

### Introduction

The project is on “Synthetic Applications on the Blaise Reactions”. Development in the methodologies for the construction of the C-C bonds in the synthesis of complex non-natural and natural products have taken place in an incremental manner through pioneering studies made by eminent organic chemists for more than the past 150 years. Such reactions discovered, described and explored –in are generally named after their discoverers, e.g., Grignard reaction, Wittig reaction, Diels-Alder reaction, Friedel-Crafts acylation, etc<sup>1</sup> On such named reaction is the Blaise reaction discovered by Blaise in 1902.<sup>2</sup> In this reaction, a nitrile **1** is reacted with the zinc enolate of ethyl bromoacetate (or 2-alkyl-2-bromoacetates) **2** to yield the corresponding  $\beta$ -keto ester **3** (Scheme 1). The Blaise intermediate could provide either the  $\beta$ -keto esters **3** or enamionitriles **4** depending on the hydrolytic conditions employed. While acidic hydrolysis leads to  $\beta$ -keto esters **3** basic hydrolysis provide enanionitriles **4**.



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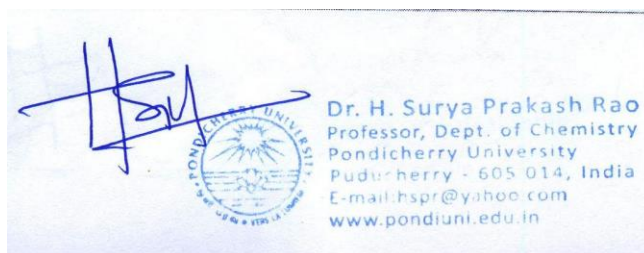


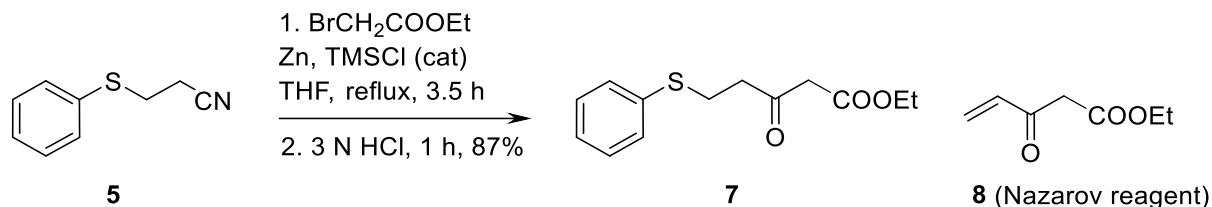
**Scheme 1.** The Blaise reaction leading to formation of  $\beta$ -keto ester **3** or enaminonitriles **4**.

The Blaise reaction closely resembles the Reformatsky reaction in which the zinc enolate of an  $\alpha$ -halo ester is reacted with a carbonyl compound to give the corresponding  $\beta$ -keto esters.<sup>3</sup> Unlike the relatively more well-known Reformatsky reaction, the Blaise reaction has found little application in organic synthesis, due to problems of low yield and competing side reactions. Recent developments in organometallic chemistry, however, have rekindled interest in developing this reaction as a formidable tool for synthetic organic chemists, particularly because the starting materials like 2-bromoacetates and nitriles are easy to prepare are commercially available and the  $\beta$ -keto ester functional group in the product **3** is highly versatile for further transformation.<sup>4</sup> Moreover, the Blaise reaction can be truncated to produce  $\beta$ -amino- $\alpha,\beta$ -unsaturated esters **4**, which are useful for the synthesis of heterocycles and  $\beta$ -amino acids. Overall, the Blaise conversion of nitriles **1** into the corresponding  $\beta$ -keto esters **3** or  $\beta$ -amino acrylates **4** constitutes a two-carbon homologation. To improve efficacy of the Blaise reaction, activation of zinc was necessary and it could be achieved by 3*N* HCl,<sup>5</sup> ultrasound,<sup>6</sup> methanesulfonic acid<sup>7</sup> or trimethylsilyl chloride<sup>8</sup>.

The Blaise reaction found use in the total synthesis of a few natural products,<sup>9</sup> industrial chemicals,<sup>10</sup> and some monosaccharide  $\beta$ -amino acid hybrids.<sup>11</sup> We have published first review of literature on the Blaise reaction and its application for the construction of complex molecules of biological interest.<sup>12</sup>

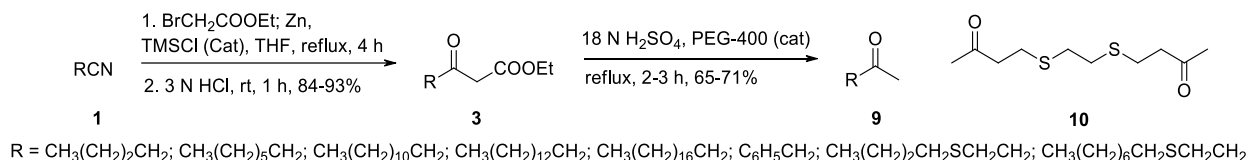
By working on the synthetic applications of the Blaise reaction, we have developed a facile, efficient and high yielding two-step synthesis of 3-oxo-5-arylthiopentanoates **7** - the precursors for the Nazarov reagent **8** - from low-cost bench top chemicals like thiophenols, acrylonitrile, zinc and ethyl bromoacetate (Scheme 2). This synthesis went through the nitrile **5**, which was generated from thiophenol and acrylonitrile. In this work we discovered that trimethylsilyl chloride is an efficient catalyst for cleaning zinc and thus promoting the Blaise reaction.





**Scheme 2.** Synthesis for precursor of the Nazarov reagent.

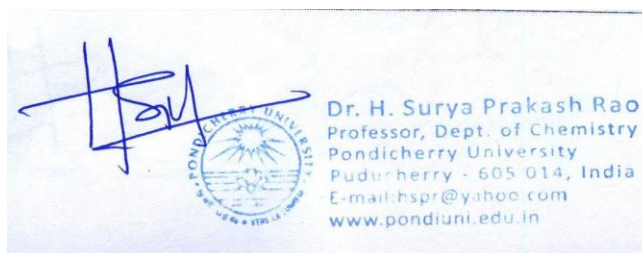
Continuing our work on the Blaise reaction we have described a facile two-step synthesis of methyl ketones **9** via the Blaise conversion of nitriles **1** into  $\beta$ -keto esters **3** followed by acid mediated hydrolysis followed by decarboxylation (Scheme 3).<sup>13</sup> In this way double Blaise reaction could be conducted to prepare diketone **10**.

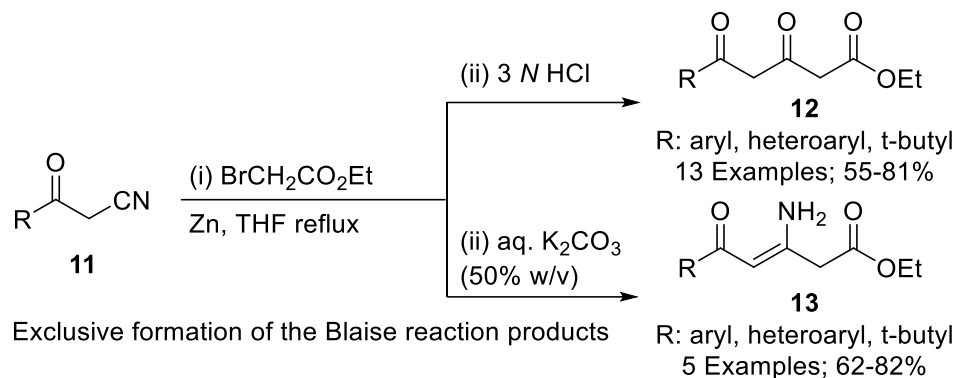


**Scheme 3.** Synthesis of methyl ketones via the Blaise reaction

## Results and Discussion

By continuing our efforts to broaden the scope of the Blaise reaction, we demonstrated that the zinc mediated condensation of 3-oxo-3-aryl propanenitriles **11** with ethyl bromoacetate furnish 3,5-diketo esters **12**.<sup>14</sup> This reaction is a useful variant for two-carbon homologation of readily available  $\alpha$ -keto nitriles into a range of 3,5-diketo pentanoates **12** incorporating aromatic and heteroaromatic and aliphatic groups at C(5) position. While acidic workup of the reaction broth provides 3,5-diketo pentanoates, the basic workup provides ethyl (Z)-3-amino-5-oxo-5-pent-3-enoates **13**. This method allows direct and regioselective synthesis of enamines of 3,5-diketo pentanoates at C(3) position. Mechanistic probing revealed that the Blaise reaction is preferred when the keto and nitrile functional groups are at vicinal position and if there is a possibility of enolization.

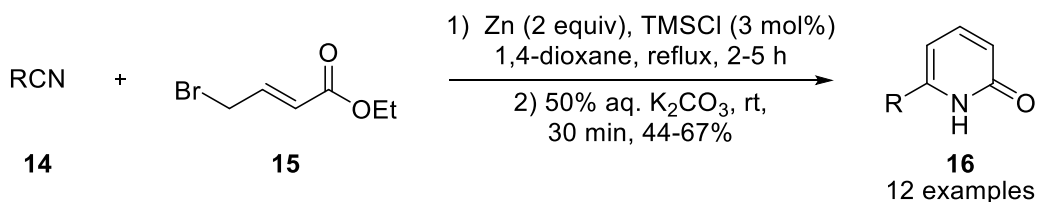




**Scheme 4.** Synthesis of 3,5-diketoesters and enaminoesters by extending the scope of the Blaise reaction.

The pyridine ring is a fundamental heterocycle,<sup>15</sup> and known for over 170 years.<sup>16</sup> The structural element of pyridine is present in many primary and secondary metabolites and such natural products play an extremely important role in biological processes.<sup>17</sup> In the pyridine family, 2-pyridone or its tautomer 2-hydroxypyridine is a very important molecule and its motif is well represented as a structural unit among alkaloids, many of which display useful biological activities.<sup>18</sup>

There are many reports in literature on pyridine ring synthesis.<sup>19</sup> Among them, some have become legendary name reactions (Scheme 1). They include Krohnke [C<sub>5</sub>+N],<sup>20</sup> Guareschi-Thorpe [C<sub>3</sub>+C<sub>2</sub>+N],<sup>21</sup> Hantzsch [C<sub>3</sub>+C<sub>2</sub>+N],<sup>22</sup> Chichibabin [C<sub>3</sub>+C<sub>2</sub>+N],<sup>23</sup> and Petrenko-Kritschenko [C<sub>3</sub>+C<sub>2</sub>+N]<sup>24</sup> reactions. We have designed a conceptually new method in which [C<sub>5</sub>N] of 2-pyridone ring is assembled through the combination of [C<sub>4</sub>+CN] strategy as given in Scheme 5.



**Scheme 5.** Synthesis of pyridones **16** from nitrile **14** and ethyl 4-bromocrotonate **15**.

We have achieved this transformation for synthesis of a variety of C(6) substituted 2-pyridones where R = Ar, benzyl, alkyl etc. (12 examples). The Vinylogous Blaise reaction works efficiently in the presence of table top zinc. Present work constitutes new pyridine ring synthesis by [C<sub>4</sub> + CN] assembly. We have demonstrated an application of the method for a facile synthesis of an analogue of agomelatine an antidepressant drug.

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## Summary

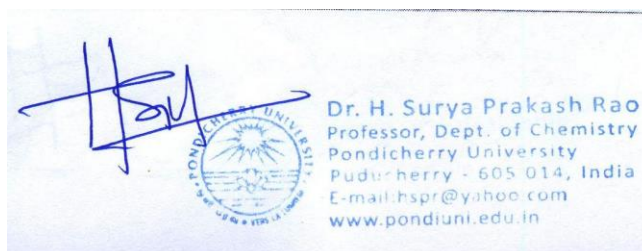
In summary, we have well utilized project funds to (i) publish papers which has made contributions to field of synthetic organic chemistry and heterocyclic chemistry, (ii) trained manpower towards Ph.D. and at least four students towards their project, (iii) contributed to academic enrichment of Pondicherry University. We anticipate that the work done will be highly cited and will become routine laboratory practice.

## Acknowledgement

We thank UGC for funding, Pondicherry University for facilities, and organizations. HSP thanks all the scholars and students who contributed to the project.

## References

- <sup>1</sup> a) Hassner, A.; Stumer, C. *Organic Synthesis Based on Name Reactions*, 2nd ed.; Elsevier: Oxford, 2002; b) Mundy, B. P.; Ellerd, M. G.; Favalaro, F. G. *Name Reactions and Reagents in Organic Synthesis*; Wiley Interscience: Canada, 2005.
- <sup>2</sup> a) Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, 132, 478-480; b) Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, 132, 987-990; c) Blaise, E. E.; Courtot, *Bull. Soc. Chim. Fr.* **1906**, 35, 589-600.
- <sup>3</sup> a) Rathke, M. W.; Weiprt, P. *Zinc enolates: The Reformatsky and Blaise Reaction in Comprehensive Organic Reactions*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; vol. 2, pg 277-299; b) Ocamo, R.; Dolbier, Jr., W. R. *Tetrahedron*, **2004**, 60, 9325-9374.
- <sup>4</sup> Benetti, S.; Romagnoli, R. *Chem. Rev.* **1995**, 95, 1065-1114.
- <sup>5</sup> Kishi, Y.; Hannick, M. S. *J. Org. Chem.* **1983**, 48, 3833-3835.
- <sup>6</sup> Lee, A. S.; Cheng, R. Y.; Pan, O. G. *Tetrahedron Lett.* **1997**, 38, 443-446.
- <sup>7</sup> Shin, H.; Choi, B. S.; Lee, K. K.; Choi, H. W.; Chang, J. H.; Lee, K. W.; Nam, D. H.; Kim, N. S. *Synlett.* **2004**, 2629-2632.
- <sup>8</sup> The Blaise Reaction, Rao, H. S. P.; Rafi, S.; Padmavathy, K. *Lett. Org. Chem.* **2008**, 5, 527-529.
- <sup>9</sup> (a) Wang, F. D.; Yue. *Eur. J. Org. Chem.* **2005**, 2575-2579; (b) Buchanan, J. G.; Jigajinnv, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc. Perkin Trans 1*, **1987**, 2377-2384.
- <sup>10</sup> Choi, S. B.; Chang, H. J.; Choi, H.; Kim, K. Y.; Lee, K. K.; Lee, W. Y.; Lee, H. J.; Heo, T.; Nam, H. D.; Shin, H. *Org. Proc. Res. Dev.* **2005**, 9, 311-313.
- <sup>11</sup> Dondon, A.; Mass, A.; Mingnin, E. *Synlett*, **2006**, 539-542.
- <sup>12</sup> Rao, H. S. P.; Rafi, S.; Padmavathy, K. *Tetrahedron* **2008**, 64, 8037-8043.
- <sup>13</sup> Rao, H. S. P.; Padmavathy, K.; Vasantham, K.; Rafi, S. *Synthetic Commun.* **2009**, 39, 1825 - 1834.
- <sup>14</sup> H. Surya Prakash Rao,\* Nandurka Muthanna *SYNLETT* **2016**, 27, 2014-2018.
- <sup>15</sup> Murugan, R.; Scriven, E. F. V. in *Pyridines: From Lab to Production* Edited by Scriven E. F. V. 2013 Elsevier, Oxford, 1-13.
- <sup>16</sup> Anderson, T. *Liebigs Ann.* **1846**, 60, 86-103.



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<sup>17</sup>Pozharskii, A. F.; Soldatenkov A. T.; Katritzky A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, Second Ed. 2011, John Wiley & Sons, Ltd. Chichester.

<sup>18</sup>Hamama, W. S.; Waly, M.; El-Hawary, I.; Zoorob, H. H. *Synth. Commun.* **2014**, *44*, 1730–1759.

<sup>19</sup> Keller, P. A.; Abdel-Hamid, M. K.; Abdel-Megeed A. M. in *Pyridines: from lab to production* Ed. by Scriven, E. F. V. 2013 Elsevier, Oxford, 15-152.

<sup>20</sup>Kröhnke, F.; Zecher, W.; Curtze, J.; Drechsler, D.; Pfléghar, K.; Schnalke, K. E.; Weis, W. *Angew. Chem. Int. Ed. English* **1962**, *1*, 626–632.

<sup>21</sup> (a) Guareschi, I. *Mem. Reale Accad. Sci. TorinoII*, **1896**, *46*, 7, 11 & 25. (b) Guareschi, I. *Atti Accad. Sci. Torino*, **1900**, *36*, 443. (b) Baron, H.; Rernfry, F. G. P.; Thorpe, J. F. *J. Chem. Soc.* **1904**, *85*, 1726-1761.

<sup>22</sup>Hantzsch, A. *Liebigs Ann.* **1882**, *215*, 1–82.

<sup>23</sup>Chichibabin, A. E. *Russ. J. Phys. Chem.* **1905**, *37*, 1229–1253.

<sup>24</sup>Petrenko-Kritschenko, P. *J. fürPrakt. Chemie* **1912**, *85*, 1–37.

