



**MICROWAVE ENHANCED KNOEVENAGEL/DOEBNER REACTIONS:
GREENER CHEMISTRY APPROACHES EMPLOYING TDA-1 AS A BASE**

Ram Naresh Yadav¹, Subhendu N. Ganguli*², Arun Mandadi², and Bimal K Banik*^{2,3}

¹*Department of Chemistry, Faculty of Engineering & Technology, VBS Purvanchal University, Jaunpur-222003 (U.P) INDIA*

²*Department of Chemistry, Chemical Biology, and Biomedical Engineering, Stevens Institute of Technology, Hoboken, New Jersey, 07030, USA*

³*Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Deanship of Research, Prince Mohammad Bin Fahd University, Al Khobar 31952, Kingdom of Saudi Arabia.*

Email: bimalbanik10@gmail.com; bbanik@pmu.edu.sa

Dedicated to: Dedicated to the memory of Professor Ajoy K. Bose, former professor at Stevens Institute of Technology, Hoboken, NJ, for his pioneering contributions to beta-lactam antibiotics and microwave chemistry.

Abstract: Tris (3,6-dioxahexyl) amine was used as a novel and efficient phase transfer catalyst in the Knoevenagel/Doebner reaction for the condensation of aryl and heteroaryl aldehydes with acidic methylene compound (i.e., malonic acid), allowing for the facile synthesis of unsaturated olefine with microwave irradiation. The reaction proceeds smoothly under mild and solventless conditions, affording a high yield of olefin with (E)-geometry. This approach works with a wide range of aromatic aldehydes with electron-withdrawing and donating group and heteroaromatic aldehyde in more eco-friendly and energy-efficient than the classic reaction. Furthermore, microwave irradiation significantly reduced reaction time and resulted in high product yields.

Keywords: Acrylic acid, Microwave chemistry, Condensation reactions, Active methylene compounds, TDA-1 base

Introduction: The Knoevenagel reaction is a fundamental C-C bond forming reaction in organic synthesis that involves the condensation of carbonyl compounds with an active methylene group under mild basic conditions (i-iii). This reaction was discovered in 1898 by Emil Knoevenagel, and it has since become a powerful tool and efficient in the synthesis of lumefantrine, a potential anti-malarial drug, and coumarin derivatives, which could serve as a crucial intermediate in the synthesis of a wide range of pharmaceuticals, perfumes, and cosmetics (iv-vi). In addition, the Knoevenagel products can be used as possible dienophiles in the Diels-Alder reaction and as a Michael acceptor in the Michael addition reaction. There has been a recent resurgence of interest in the Knoevenagel/Doebner product owing to its high medicinal activity, for example, phenolic acids (PAs) and acyanothiocinnamide (i.e., tyrophostines), a well-known EGF receptor inhibitor via autophosphorylation and antiproliferative impact on human keratinocytes (vii). In

general, a weak base such as cyclic 2° amine (i.e., piperidine), amino acids (i.e., glycine, β -alanine, and L-proline), and KF are required to promote the Knoevenagel reaction under homogeneous conditions (viii-x). However, on other hand some powerful methods based on heterogeneous catalytic system has also been developed to promote the Knoevenagel condensation reaction (xi-xiv). Furthermore, in recent years, ionic liquid-based catalytic models have also proven successful in carrying out the Knoevenagel reaction for the synthesis of olefinic compounds.

The microwave-assisted reaction has recently emerged as the most powerful technique for producing biologically active compounds in a cost-effective and reproducible manner, and it has become the preferred method of scientists. This methodology has been widely described in the literature to Knoevenagel-Doebner reaction, including work of Allais et al., Yadav et al., Mitra et al., Rodrigues-Santos et al., Mobinikhaledi et al., Sandhu et al., and Goel et al., employing automated or domestic microwave reactor. Peng et al work in aqueous media using a combination of ultrasound and microwave is effectively exploited. However, while these methods have good conversion and yield, some have significant drawbacks, including decomposition of sensitive substrates or products, and some have reproducibility challenges. Many of the procedures described in the literature required a combination of solvents to complete the reaction. Microwave approaches have several advantages over traditional reactions, including simplicity of use, higher selectivity, and faster reaction rates. The solvent-free reaction strategy is gaining a lot of attention in chemical synthesis because it allows one to do the reaction in an open vessel, which reduces the high-pressure build-up in the automated microwave reactor and enables to scale up the reaction from milligrams to grams scale in dry conditions. As a result, microwave irradiation has undeniably become a reliable technique for the rapid synthesis of a wide range of biologically active compounds in

solvent-free conditions, and it is commonly employed to accelerate the rate of classical reactions.

Herein, we report a novel catalyst, tris (3,6-dioxaheptyl) amine, as well as microwave-controlled methods for promoting Knoevenagel condensation and Doebner reaction of heteroaromatic and aromatic aldehydes with malonic acid and cyanoacetic acid in the synthesis of substituted alkene and acrylonitrile's derivatives with good to excellent yields in a shorter time.

Result and Discussion

As a model conventional strategy for these reactions, the conversion of aldehyde to an unsaturated ester, which needs heating under reflux for 2 hours with pyridine as the solvent and the base as outlined in Organic Syntheses, might be employed. Alkylidene malonic acids and derivatives are used by medicinal chemists as intermediates for compounds that have the potential to be physiologically active.

In course of our study, the microwave enhanced Knoevenagel reaction for the preparation of alkylidene malonic esters and

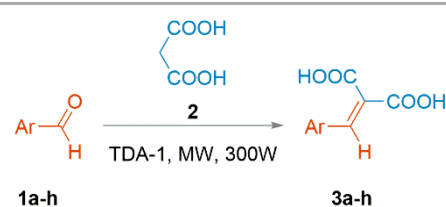


TABLE 1 TDA-1 catalyzed synthesis of arylidene malonic acid under microwave irradiation^[a]

Entry	Ar	3 a-h	Time (Min)	Yield [%] ^[b]
1	2-Furfuryl	3a	1.0	75%
2	O-C ₆ H ₄	3b	2.0	80%
3	p-C ₆ H ₄	3c	1.0	90%
4	m-BrC ₆ H ₄	3d	3.0	85%
5	O- NO ₂ C ₆ H ₄	3e	5.0	75%
6	m- NO ₂ C ₆ H ₄	3f	7.0	70%
7	p-	3g	4.0	95%

8	NO ₂ C ₆ H ₄ C ₆ H ₅	3h	5.0	90%
[a] Reactions are performed 0.1 mmol of an aldehyde and malonic acid				
[b] Isolated yield after column purification				

related compounds can be performed in a solvent-free reaction in just a few minutes.

In our procedure, a mixture of an aldehyde, an active methylene compound, and TDA-1 is irradiated for 30 seconds

at a time under low power (300W) microwave irradiation, followed by a short interval for a total of about 10 minutes; the target compound is thus obtained in high yield.

As a result, alkylidene malonic esters are synthesized using diethyl malonate as the active methylene molecule. When malonic acid is used instead of the ester, the reaction is almost as successful with diversely substituted. In a matter of minutes, malonic acid can be substituted with cyanoacetic acid to obtain the appropriate alkylidene derivatives in a high yield (Table 1).

If the target molecule is acrylic acid, two microwave-assisted approaches are possible (Doebner product). Alkylidene malonic acids can be subjected to microwave irradiation at higher power, alternatively, the starting materials (namely, the aldehyde, TDA-1, and malonic acid) can be irradiated at a higher power level for about 5-10 min - with TLC monitoring to determine when the conversion of the starting materials to the desired acrylic acid is complete.

While extending the TDA-1 assisted solvent-free Knoevenagel reaction to particularly active methylene compounds (i.e., cyanoacetic acid), it was realized that the reaction was sometimes spontaneous, requiring no external energy source (Table 2). From a mechanistic standpoint, the reaction appears to be driven by phase transfer catalysis of tris [2-(2-methoxy ethoxy) ethyl] amine, TDA-1 under the stated conditions. The reaction begins with the formation of the malonic acid anion, which is produced by removing the acidic proton from the active methylene group, forming the anionic

complex of TDA-1 and malonic acid. This complex improves the absorption of malonic acid in the liquid phase and acts as a phase transfer active catalyst for the subsequent reaction. The nucleophilic approach of the malonate anion on the carbonyl function,

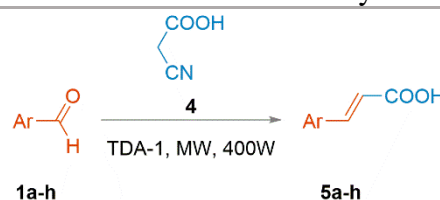


TABLE 2 TDA-1 catalyzed synthesis of acrylic acid derivatives under microwave irradiation^[a]

Entry	Ar	5 a-h	Time (Min)	Yield [%] ^[b]
1	2-Furfuryl	5a	0.5	70%
2	O-ClC ₆ H ₄	5b	1.0	70%
3	p-ClC ₆ H ₄	5c	1.0	80%
4	m-BrC ₆ H ₄	5d	2.0	85%
5	O-NO ₂ C ₆ H ₄	5e	4.0	70%
6	m-NO ₂ C ₆ H ₄	5f	6.0	65%
7	p-NO ₂ C ₆ H ₄	5g	4.0	85%
8	C ₆ H ₅	5h	5.0	90%

[a] Reactions are performed 0.1 mmol of an aldehyde and cyanoacetic acid

[b] Isolated yield after column purification

followed by base-assisted elimination of the water molecules, further aids the synthesis of the corresponding substituted olefins. It's worth noting that no reaction has been observed when the TDA-1 is omitted. In Doebner reaction at higher power under microwave condition, concerted base assisted decarboxylation has been taken place to furnish the acrylic acid derivatives.

Conclusion:

In summary, we have demonstrated here that under solvent-free conditions and in presence of TDA-1, the energy and time requirements for the widely used Knoevenagel / Doebner reactions are greatly reduced while high atom

economy is achieved because chemical waste is minimized.

Experimental Section:

General procedure for the microwave-assisted synthesis of 2-Aryl-2-methylene-malonic acid

using TDA-1 as the base:

2-Furan-2-ylmethylmalonic acid (3a):

Typical procedure: 10 mL of TDA-1, 9.6 g (0.1 mol) of furfuraldehyde, and 10.4 g (0.1 mol) of malonic acid were placed in a 250 mL Erlenmeyer flask and irradiated in a 1000 W domestic microwave oven at power level 3 (300W) for 30 seconds. After a short period (about 30 sec to 1.0 min) microwave irradiation was repeated. This cycle was continued, but the temperature of the reaction mixture was maintained below 75 °C. After completion of the reaction (as monitored by TLC), the flask was cooled in an ice bath and acidified with cold dilute HCl. The precipitated solid was filtered under vacuum, washed several times with cold water, and dried. Yield 75%; m.p. 205 °C; ¹H NMR (200MHz, CD₃OD): δ 6.61(s, 1 H), 6.98(s, 1 H), 7.47(s, 1 H), 7.71 (s, 1 H).

Synthesis of (2-Cyano-3-furan-2-yl) acrylic acid (5a):

10 mL of TDA-1, 9.6 g (0.1 mol) of furfuraldehyde, and 0.1 mol of cyanoacetic acid were placed in a 250 mL Erlenmeyer flask and irradiated in a domestic microwave oven (1000W) at 330W power. The progress of the reaction was monitored by TLC. The temperature of the reaction mixture was maintained below 75 °C. After the reaction was complete, the flask was cooled in an ice bath and acidified with cold dil HCl (30 mL). The precipitated solid was vacuum filtered, washed several times with cold water, and air-dried to obtain the title compound, as a gray crystalline solid.

Acknowledgment:

BKB acknowledges financial support from the National Institutes of Health, National Cancer Institute, Kleberg

Foundation, and Prince Mohammad Bin Fahad University, Saudi Arabia. RNY acknowledges the infrastructural support provided by the Department of Chemistry at VBS Purvanchal University during the preparation of this manuscript. The generous support of the TEQIP phase II in terms of computation assistance is also greatly appreciated.

We are also grateful to Union Mutual Foundation for its financial support. We are thankful to Dr. Mark Cardillo for the useful discussion. We thank the Stevens Institute of Technology for laboratory facilities to carry out this work.

Reference:

- i Tietze, Lutz F., and U. B. *The Knoevenagel Reaction.* *Comprehensive Organic Synthesis 2*; 1992.
- ii Endemann, H. *Berichte Der Deutschen Chemischen Gesellschaft. J. Am. Chem. Soc.* **1880**, 2 (8), 366–371. <https://doi.org/10.1021/ja02139a003>.
- iii Jones, G. The Knoevenagel Condensation. *Org. React.* **1967**, 15.
- iv Yu, N., Aramini, J. M., Germann, M. W., & Huang, Z. Reactions of Salicylaldehydes with Alkyl Cyanoacetates on the Surface of Solid Catalysts: Syntheses of 4H-Chromene Derivatives. *Tetrahedron Lett.* **2000**, 41 (36), 6993–6996.
- v Lyall, R. M.; Zilberstein, A.; Gazit, A.; Gilon, C.; Levitzki, A.; Schlessinger, J. Tyrphostins Inhibit Epidermal Growth Factor (EGF)-Receptor Tyrosine Kinase Activity in Living Cells and EGF-Stimulated Cell Proliferation. *J. Biol. Chem.* **1989**, 264 (24), 14503–14509. [https://doi.org/10.1016/s0021-9258\(18\)71707-9](https://doi.org/10.1016/s0021-9258(18)71707-9).
- vi Yadav, J. S.; Bhunia, D. C.; Singh, V. K.; Srihari, P. Solvent-Free NbCl₅ Catalyzed Condensation of 1,3-Dicarbonyl Compounds and Aldehydes: A Facile Synthesis of

- Trisubstituted Alkenes. *Tetrahedron Lett.* **2009**, 50 (21), 2470–2473. <https://doi.org/10.1016/j.tetlet.2009.03.015>.
- vii Mouterde, L. M. M.; Allais, F. Microwave-Assisted Knoevenagel-Doebner Reaction: An Efficient Method for Naturally Occurring Phenolic Acids Synthesis. *Front. Chem.* **2018**, 6, 426. <https://doi.org/10.3389/fchem.2018.00426>.
- viii Rand, L.; Swisher, J. V.; Cronin, C. J. Reactions Catalyzed by Potassium Fluoride. III. The Knoevenagel Reaction. *J. Org. Chem.* **1962**, 27 (10), 3505–3507. <https://doi.org/10.1021/jo01057a024>.
- ix Wada, S.; Suzuki, H. Calcite and Fluorite as Catalyst for the Knoevenagel Condensation of Malononitrile and Methyl Cyanoacetate under Solvent-Free Conditions. *Tetrahedron Lett.* **2003**, 44 (2), 399–401. [https://doi.org/10.1016/S0040-4039\(02\)02431-0](https://doi.org/10.1016/S0040-4039(02)02431-0).
- x Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomekli, A. A Straightforward Method for the Synthesis of Alkylidene and Arylidene Malonates through Proline-Catalyzed Knoevenagel Condensation. *Synth. Commun.* **2003**, 33 (9), 1587–1594. <https://doi.org/10.1081/SCC-120018782>.
- xi Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. Knoevenagel Condensation in the Heterogeneous Phase Using AlPO₄-Al₂O₃ as a New Catalyst. *J. Org. Chem.* **1984**, 49 (26), 5195–5197. <https://doi.org/10.1021/jo00200a036>.
- xii Mondal, J.; Modak, A.; Bhaumik, A. Highly Efficient Mesoporous Base Catalyzed Knoevenagel Condensation of Different Aromatic Aldehydes with Malononitrile and Subsequent Noncatalytic Diels-Alder Reactions. *J. Mol. Catal. A Chem.* **2011**, 335 (1–2), 236–241. <https://doi.org/10.1016/j.molcata.2010.11.039>.
- xiii Zuo, W. X.; Hua, R.; Qiu, X. ReBr(CO)₅-Catalyzed Knoevenagel Condensation. *Synth. Commun.* **2004**, 34 (17), 3219–3225. <https://doi.org/10.1081/SCC-200028628>.
- xiv Rodriguez, I.; Iborra, S.; Corma, A.; Rey, F.; Jordá, J. L. MCM-41-Quaternary Organic Tetraalkylammonium Hydroxide Composites as Strong and Stable Bronsted Base Catalysts. *Chem. Commun.* **1999**, No. 7, 593–594. <https://doi.org/10.1039/a900384c>.

Received on February 20, 2024.