

TPGS-750-M-Mediated Synthesis of Pyrano[2,3-c]pyrazoles in Water: A Critical Review of Reaction Design, Mechanistic Insights, Sustainability, and Catalyst Recyclability.

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Abstract

Pyrano[2,3-c] pyrazoles are synthetically valuable fused N/O-heterocycles that can be assembled efficiently through multicomponent reactions (MCRs). Their synthesis has attracted sustained interest because a single operation can combine a β -ketoester, hydrazine, malononitrile and an aldehyde to generate a densely functionalized heterocyclic framework. This review critically examines aqueous TPGS-750-M-mediated synthesis of pyrano[2,3-c]pyrazoles, using the 2024 study of Cetin and Bayden as the principal case study. The reported process employs ethyl acetoacetate, hydrazine hydrate, malononitrile and aldehydes in water containing TPGS-750-M, with an optimized condition of 2 wt% TPGS-750-M at 50 °C. The reported substrate series provides 55–99% yields within 6–22 min, while product isolation avoids column chromatography and relies on filtration and ethanol recrystallization. Catalyst-phase reuse was demonstrated for four cycles, with reported yields of 99, 96, 94 and 84%. The study illustrates the potential of designer-surfactant-enabled aqueous chemistry to reduce reliance on conventional organic reaction media. However, a critical assessment shows that the sustainability claim requires quantitative qualification because ethanol remains part of the work-up, the mechanism was proposed rather than experimentally demonstrated, and complete process metrics such as E-factor, process mass intensity, reaction mass efficiency, energy demand and life-cycle impact were not reported. The review places TPGS-750-M chemistry within the broader evolution of green pyranopyrazole synthesis and identifies opportunities in mechanistic studies, substrate expansion, closed-loop surfactant recovery, scale-up and quantitative green-chemistry assessment.

Keywords

Pyrano[2,3-c]pyrazole; TPGS-750-M; micellar catalysis; aqueous synthesis; multicomponent reaction; green chemistry; surfactant-enabled synthesis; catalyst recycling; sustainable heterocyclic chemistry.

1. Introduction

Green organic synthesis increasingly seeks to minimize hazardous reagents, volatile organic solvents, waste generation and energy consumption while maintaining high efficiency and reproducibility. Multicomponent reactions are particularly attractive because several simple reactants are incorporated into one product, often avoiding isolation of intermediates. Pyrano[2,3-c]pyrazoles represent an important class of multifunctional heterocycles commonly obtained through four-component combinations of ethyl acetoacetate, hydrazine, malononitrile and an aldehyde. The source paper reports that these compounds have been associated with anticancer, antimicrobial, anti-inflammatory, antiviral and enzyme-inhibitory activities, while also serving as useful synthetic intermediates. These biological associations should be interpreted as medicinal-chemistry potential rather than evidence of established therapeutic applications.

The central contribution considered here is the use of TPGS-750-M in water. TPGS-750-M is a water-compatible amphiphile derived from α -tocopherol and polyethylene-glycol-based functionality. In aqueous solution it forms micellar nanostructures capable of creating hydrophobic reaction domains. This provides a fundamentally different

reaction environment from conventional homogeneous aqueous catalysis: organic substrates can be concentrated or organized within or near the micellar phase while water remains the bulk medium. Foundational TPGS-750-M studies established its utility in aqueous organic synthesis, while subsequent work has explored its behavior in hydrolysis, enzymatic chemistry and other transformations.

2. Review scope and critical approach

The article was analyzed with emphasis on reaction optimization, substrate scope, product isolation, characterization, mechanistic interpretation, catalyst recycling and comparison with previously reported catalysts. The present manuscript retains the original reaction schemes and numerical comparison tables, but reframes the discussion as a critical review. Source-derived experimental values are clearly treated as reported literature results rather than as newly generated data. Additional literature is used to place the method within the broader development of sustainable pyranopyrazole synthesis and micellar chemistry.

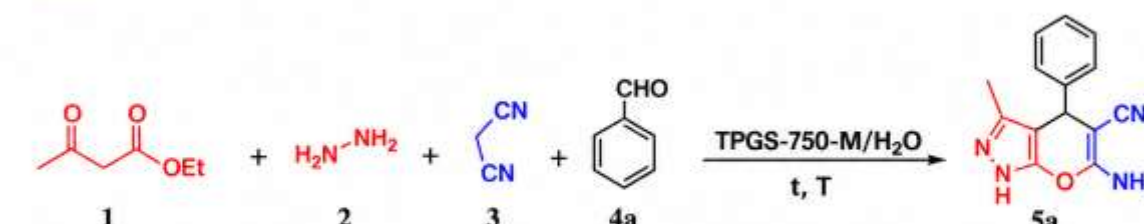
3. Synthetic significance of pyrano[2,3-c]pyrazoles

Pyrano[2,3-c]pyrazoles combine a pyrazole ring and a pyran ring and commonly contain amino and nitrile functionality. The scaffold is attractive for library synthesis because substituent diversity can be introduced primarily through variation of the aldehyde component. The MCR approach also provides a high degree of bond construction per operation. Earlier methods have employed conventional organic bases, amino acids, cyclodextrins, biomolecules, ionic liquids, natural materials, inorganic solids and nanocatalysts. The major contemporary challenge is therefore not simply to obtain high yield, but to combine yield with safer media, short reaction times, low catalyst loading, simple isolation and genuine catalyst or surfactant recovery.

4. Reaction design and optimization

The source study combines ethyl acetoacetate, hydrazine hydrate, malononitrile and an aldehyde in aqueous TPGS-750-M. The optimization demonstrates a strong dependence on both surfactant concentration and temperature. Without TPGS-750-M, the model reaction did not produce detectable product after 120 min under the tested conditions. Water alone afforded only 15% yield after 2 h. Increasing TPGS-750-M concentration improved conversion, while moderate heating substantially shortened reaction time and increased isolated yield.

Table 1. Optimization of the reaction conditions for the synthesis of pyrano[2,3-c]pyrazole 5a



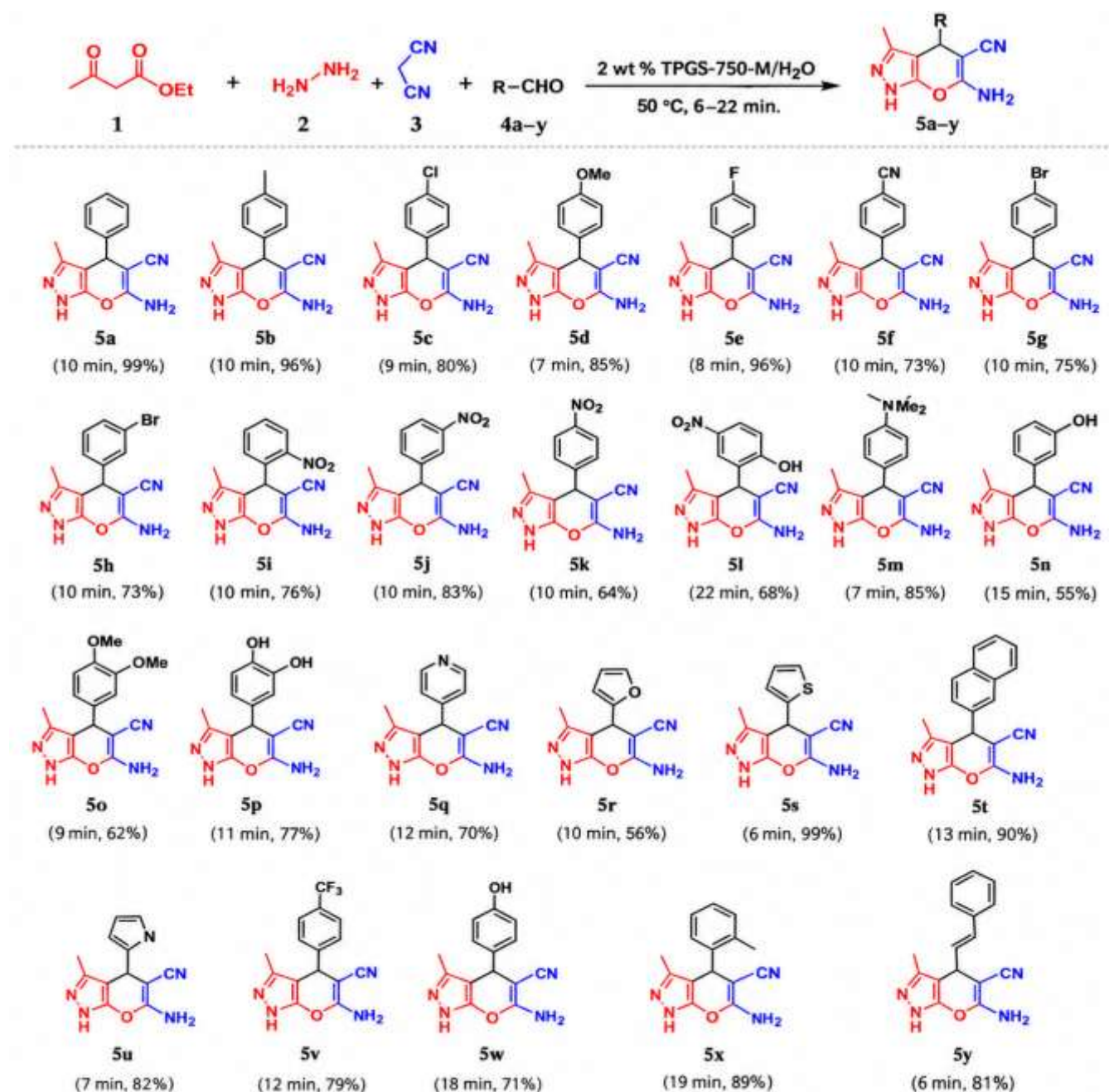
Entry	TPGS-750-M (%wt)	Temperature (°C)	Time (min)	Yield (%)
1	–	50	120	–
2	0.5	25	60	40
3	0.5	50	28	65
4	1	25	20	68
5	1	50	13	75
6	2	25	15	76
7	2	35	10	77
8	2	50	10	99
9	4	25	17	81
10	4	50	10	96

Preserved reaction scheme and Table 1: optimization of the synthesis of pyrano[2,3-c]pyrazole 5a.

The selected condition was 2 wt% TPGS-750-M in water at 50 °C, giving the model product in 99% yield in 10 min. At 4 wt% surfactant and 50 °C, the reported yield was 96% in the same reaction time. This supports the practical selection of 2 wt% rather than simply maximizing surfactant concentration.

5. Reaction scope and preserved product series

The reported aldehyde scope includes electron-donating and electron-withdrawing aromatic substituents and several heteroaromatic systems. Reaction times span 6–22 min and isolated yields range from 55 to 99%. The strongest performance was observed for several simple or appropriately substituted aromatic substrates, whereas some more highly functionalized examples gave lower yields. The data demonstrate useful tolerance but do not establish complete substrate generality across aliphatic aldehydes, highly hindered aldehydes, alternative hydrazines or alternative β -ketoesters.



Scheme 1. Preserved substrate-scope reaction and products 5a–5y. Source conditions: ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1 mmol), aldehydes (1 mmol), 2 wt% TPGS-750-M in water (2 mL), 50 °C, 6–22 min.

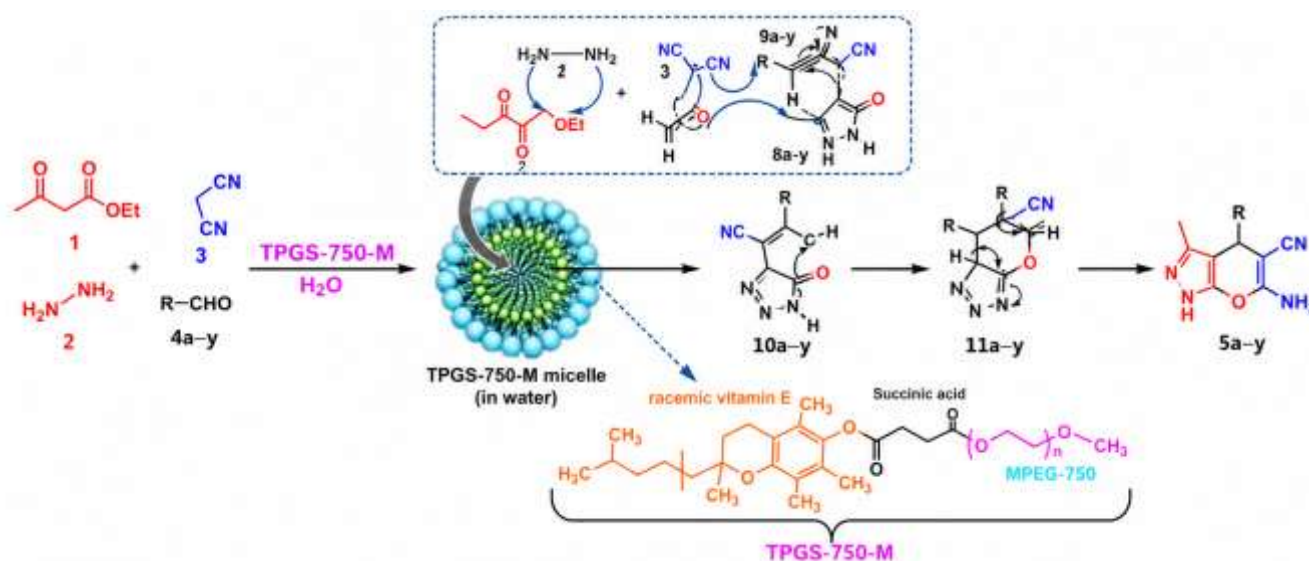
6. Product isolation and characterization

A practical advantage of the method is the absence of column chromatography. After completion, the precipitated product was filtered, washed with cold ethanol and recrystallized from ethanol. This substantially reduces silica consumption and chromatographic solvent use, but the process is not completely organic-solvent-free because ethanol is required during isolation. Future sustainability comparisons should therefore include the total amount of ethanol as well as water and any washing or recrystallization losses.

The products were characterized by ^1H NMR, ^{13}C NMR and mass spectrometry. The source paper reports a characteristic pyrazole NH signal near δ 12 ppm, an amino signal near δ 6.8 ppm and a methyl signal near δ 1.9 ppm. Representative structures were further supported by high-resolution mass spectrometry. These data provide conventional structural confirmation, although additional two-dimensional NMR or single-crystal X-ray analysis would be useful for particularly ambiguous or novel derivatives.

7. Proposed reaction mechanism

The proposed sequence begins with condensation of hydrazine hydrate and ethyl acetoacetate to form a pyrazolone-type intermediate. In parallel, the aldehyde and malononitrile undergo Knoevenagel condensation to produce an arylidenemalononitrile. A Michael addition between the two intermediates is then followed by intramolecular cyclization to furnish the pyrano[2,3-*c*]pyrazole framework. Importantly, the source authors explicitly state that the mechanism was not experimentally investigated; the sequence should therefore be presented as a plausible pathway rather than a proven catalytic cycle.



Scheme 2. Preserved proposed mechanism, showing pyrazolone formation, Knoevenagel condensation, Michael addition and cyclization in the TPGS-750-M/water system.

The major mechanistic question concerns the specific role of the micellar environment. TPGS-750-M may increase the local concentration of hydrophobic substrates, alter effective polarity at the micelle/water interface, organize reactants or influence the relative rates of the condensation and cyclization steps. These possibilities were not differentiated in the original study. Kinetic studies, control experiments with structurally different surfactants, substrate-partitioning experiments, micelle characterization under reaction conditions and computational studies could clarify the origin of the rate enhancement.

8. Catalyst comparison

The original paper compares TPGS-750-M with a broad collection of reported systems. Preserving the original table is important because it allows the proposed method to be viewed against the historical development of pyranopyrazole catalysis rather than in isolation. The comparison includes homogeneous bases and amino acids, biomolecular and natural catalysts, ionic liquids, inorganic solids and nanoparticles.

Table 2. Used catalysts for the synthesis of pyrano[2,3-c]pyrazole

No.	Catalyst	Reaction condition	Time (min)	Yield (%)	References
1	Piperidine	H ₂ O, r.t	5–10	89	[36]
2	Glycine	H ₂ O, r.t	20	94	[37]
3	L-proline	[Bmim]BF ₄ , 50 °C	5	94	[38]
4	Maltose	solvent-free, 100 °C	10	98	[39]
5	Per-6-amino-beta-cyclodextrin	solvent-free, r.t	10	99	[40]
6	Bovine Serum Albumin	H ₂ O-ethanol (7:3), r.t	120	88	[41]
7	Montmorillonite K-10	H ₂ O, rt	300	88	[42]
8	Ionic liquid	solvent-free, r.t	30	85	[43]
9	Lemon Juice	H ₂ O-ethanol (9:1), 90 °C	45	94	[44]
10	Iso-nicotinic acid	solvent free, 85 °C	10	90	[45]
11	Bael fruit	H ₂ O, r.t	5	93	[46]
12	Heteropoly acid	solvent free, 60 °C	10	96	[47]
13	Mg/Al hydrotalcite	ethanol, r.t	240	86	[48]
14	Nano MgO	acetonitrile, r.t	10	97	[49]
15	Nano ZrO ₂	H ₂ O-ethanol (1:6), r.t	5	95	[25]
16	Nano ZnS	grinding, r.t	10	94	[25]
17	Nano ZnO	H ₂ O, 100 °C	35	89	[50]
18	Graphite oxide	25 °C	20	92	[51]
19	Nano TiO ₂	H ₂ O, r.t	30	90	[52]
20	Nano Fe ₃ O ₄	solvent free, r.t	7	96	[53]
21	Nano MgFeCrO ₄	ethanol, 78 °C	10	90	[54]
22	Nano SiO ₂	H ₂ O, 80 °C	30	94	[55]
23	γ-Alumina	H ₂ O, r.t	120	93	[56]
24	Magnetized water	H ₂ O, r.t	120	60	[57]
25	Potassium t-butoxide	H ₂ O, r.t	120	64	[58]
26	TPGS-750-M	H₂O, 50 °C	10	94	Our work

Preserved Table 2 : comparison of catalysts and reaction conditions reported for pyrano[2,3-c]pyrazole synthesis.

The comparison indicates that TPGS-750-M combines short reaction time, water compatibility and high yield. However, 'superiority' should not be inferred from yield and reaction time alone. Catalyst synthesis, catalyst loading, solvent volume, product concentration, purification, energy consumption and recovery must be compared on a common basis. For example, a solvent-free reaction using a readily available catalyst may have a lower process mass than an aqueous micellar reaction despite a similar isolated yield.

9. Recyclability of TPGS-750-M

The source study recovered the TPGS-750-M-containing aqueous phase after product filtration and regenerated the reaction medium by treatment with excess water. The recovered material was reused in subsequent model reactions. The reported yields were 99% for the fresh system, followed by 96%, 94% and 84% over three successive reuse runs. This demonstrates meaningful reuse over four cycles, but the progressive decrease in yield shows that complete retention of activity was not achieved.

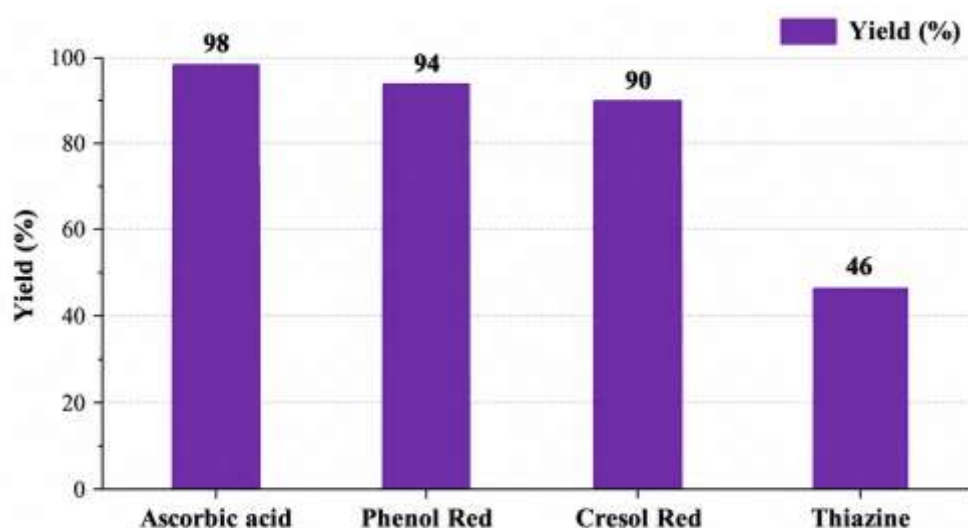


Fig. 2. Preserved recyclability profile of the TPGS-750-M system.

The phrase '100% reusability' should therefore be used carefully. The experimental evidence supports recovery and reuse, not indefinite recyclability or 100% retention of catalytic performance. A stronger future study should report surfactant recovery percentage, recovered mass, surfactant concentration after each cycle, product carryover, possible leaching into the isolated product and chemical integrity of the recovered amphiphile.

10. Critical green-chemistry assessment

The method addresses several principles of greener synthesis: water is used as the reaction medium, reaction times are short, catalyst/surfactant reuse is demonstrated, and chromatographic purification is avoided. These are substantial practical benefits. Nevertheless, green claims should be supported by quantitative metrics rather than by solvent selection alone.

Criterion	Assessment of the reported study	What should be added
Reaction yield	55–99% reported for the substrate series	Report isolated mass and, where possible, selectivity.
Reaction medium	Water with TPGS-750-M	Report concentration, water volume and total solvent intensity.
Work-up	Filtration and ethanol recrystallization	Include ethanol in solvent and process-mass calculations.
Recycling	Four cycles reported; yield declines to 84%	Quantify recovery mass and surfactant integrity.
Energy	50 °C and short reaction times	Estimate energy per gram or mole of product.
Waste	No chromatography	Calculate PMI, E-factor and RME.
Environmental profile	Not quantitatively established	Assess toxicity, biodegradation and life-cycle impacts.
Scale-up	1 mmol experimental examples	Demonstrate gram-scale and higher-concentration operation.

12. Position within the broader literature

The TPGS-750-M approach belongs to a broader progression from classical homogeneous bases toward solvent-free, aqueous, biological, ionic-liquid, nanocatalytic and organocatalytic pyranopyrazole synthesis. Earlier literature demonstrated fast reactions using piperidine, glycine, L-proline and cyclodextrin systems, while later studies expanded the field through heterogeneous and magnetic materials. More recent reports have increasingly emphasized metal-free catalysis, gram-scale synthesis, catalyst recycling, mechanistic analysis and quantitative green metrics. This trend suggests that the next important contribution should integrate reaction efficiency with rigorous process-level sustainability.

13. Future research opportunities

- Establish the micellar origin of rate enhancement using kinetic and physical-chemical studies.
- Compare TPGS-750-M directly with conventional nonionic surfactants and other designer amphiphiles.
- Expand the reaction to aliphatic, heteroaromatic and sterically demanding aldehydes.
- Investigate alternative β -ketoesters and hydrazine derivatives.
- Demonstrate gram-scale or multigram-scale synthesis at increased substrate concentration.
- Quantify TPGS-750-M recovery and characterize the recovered surfactant after each cycle.
- Develop closed-loop reuse of the aqueous micellar phase with minimal reconditioning.
- Report PMI, E-factor, RME, solvent intensity and energy demand.
- Compare the process under standardized conditions with catalyst-free and metal-free alternatives.
- Investigate continuous-flow or intensified micellar processing.

14. Conclusions

Aqueous TPGS-750-M-mediated multicomponent synthesis provides an attractive route to pyrano[2,3-*c*]pyrazoles because it combines a water-based reaction environment with rapid multicomponent bond construction, high reported yields, simple product isolation and demonstrated reuse of the surfactant-containing phase. The source study establishes an optimized model reaction at 2 wt% TPGS-750-M and 50 °C, with a broad aldehyde series giving 55–99% yields in 6–22 min.

From a critical review perspective, however, the method should be described as a promising greener approach rather than as an unequivocally sustainable process. The proposed mechanism remains unverified, ethanol is used in isolation, the recycling experiment shows declining performance, and quantitative process-level green metrics are absent. The greatest opportunity for future work is therefore to combine the demonstrated synthetic efficiency with mechanistic evidence, closed-loop surfactant recovery, scale-up and rigorous sustainability accounting. Such developments could establish aqueous micellar chemistry as a more general platform for sustainable multicomponent heterocycle synthesis.

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