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K_2CO_3-Catalyzed Synthesis of 2,5-Dialkyl-4,6,7-tricyano-Decorated Indoles via Carbon−Carbon Bond Cleavage

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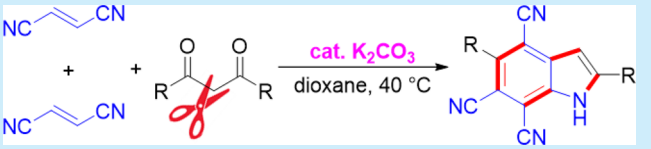
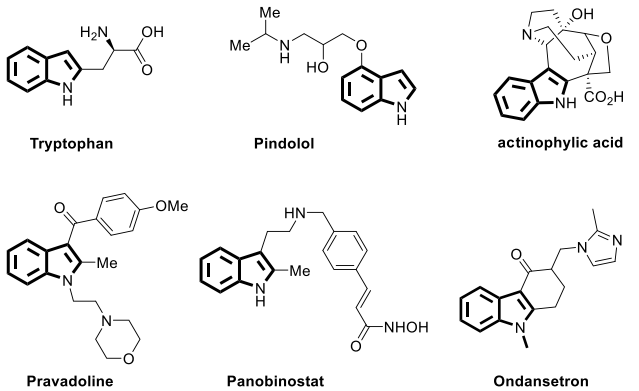
ABSTRACT: We describe a novel method to synthesize 2,5-dialkyl-4,6,7-tricyanoindole derivatives from a base-catalyzed reaction of 1,3-diketones with fumaronitrile. The reaction proceeds by the condensation of two molecules of fumaronitrile and one molecule of 1,3-diketone in a remarkable process that involves the cleavage of one $C(sp^3)-C(sp^2)$ bond in 1,3-diketones and the formation of one carbon−nitrogen bond and four carbon−carbon bonds to construct both the aryl and pyrrole rings of the indole in one step.



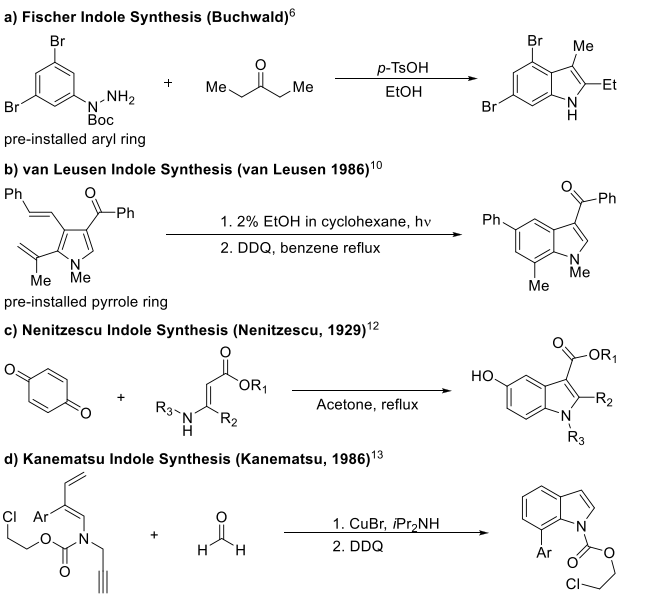
Indole scaffolds are privileged structures ubiquitously found in nature and are indispensable for the survival of every organism. For example, indoles are produced by numerous bacteria for intracellular signaling, a biological mechanism responsible for drug resistance, spore formation, and a pathogen's ability to affect its host.[1] Indole derivatives are also present in a wide array of bioactive molecules, pharmaceuticals, and materials (Scheme 1).[2] Consequently, a large number of reactions have been developed over the course of several years to synthesize a variety of indole derivatives. Among the most appealing methods are the Fischer,[3] Bartoli,[4] Larock,[5] Buchwald,[6] Wipf,[7] Bischler,[8] Leimgruber−Batcho,[9] and van Leusen[10] indole syntheses that can generate a wide range of substituted indoles (Scheme 2).

Scheme 1. Structures of Indole Natural Products and Pharmaceuticals



In 2011, Taber and Tirunahari[11] classified the overall process of indole synthesis in nine different types based on the art of the last bond formation. Of these nine types, seven classes of indole synthesis required fairly advanced reaction intermediates that had either the benzene or the pyrrole ring

Scheme 2. Some of the Most Common Ways to Construct Indole Rings



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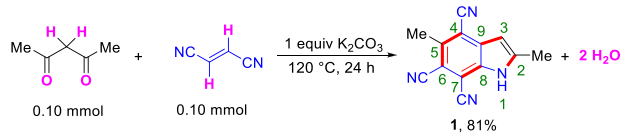
fully developed in a multistep process prior to indole formation. Nenitzescu indole synthesis (type 7) (Scheme 2c),[12] which involved the construction of both rings, derived the benzene ring from a cyclohexane or benzoquinone derivative generally after the pyrrole ring was built and required multiple steps before full-fledged indoles were created. Likewise, the Kanematsu process implemented an intramolecular Diels–Alder reaction to construct both rings of indoles (type 9) (Scheme 2d).[13] The Kanematsu strategy required the assembly of all necessary carbon and nitrogen fragments in one advanced intermediate. Herein we report a novel strategy for the synthesis of highly functionalized indoles that constructs both the benzene and the pyrrole rings in one step by a K_2CO_3-catalyzed condensation of fumaronitrile with 1,3-diketones. This unprecedented protocol synthesizes indoles by the cleavage of a C(sp^3)–C(sp^2) bond in 1,3-diketones and the simultaneous formation of five new bonds—one carbon–nitrogen bond and four carbon–carbon bonds.

During our investigation on alkene functionalization, we serendipitously discovered that fumaronitrile underwent condensation with 2,4-pentanedione in the presence of K_2CO_3 to generate 2,5-dimethylindole-4,6,7-tricarbonitrile in 81% yield based on the molar equivalence of fumaronitrile (Scheme 3). The structure of the new product was confirmed

Scheme 3. Discovery of a Novel Indole Synthesis Method



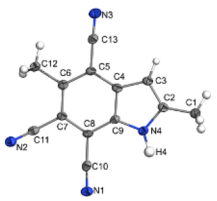
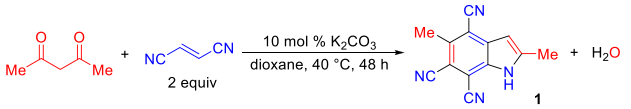


Figure 1. X-ray crystal structure of 2,5-dimethylindole-4,6,7-tricarbonitrile (**1**). Selected bond lengths (Å), angles (deg), and hydrogen bonds: N1–C10 = 1.149(3); N2–C11 = 1.141(3); N3–C13 = 1.149(3); N4–C9 = 1.371(3); N4–C2 = 1.386(3). N1–C10–C8 = 177.0(3); N2–C11–C7 = 178.1(2); N3–C13–C5 = 178.9(3); C9–N4–C2 = 108.8(2). N4···N1 = 2.996(3). N4–H4···N1 = 173(3).

by single-crystal X-ray crystallography (Figure 1). Analysis of the X-ray structure revealed that the indole product would require the insertion of two fumaronitrile molecules between carbon 2 and carbon 3 of 2,4-pentanedione with the cleavage of the 2C(sp^2)–3C(sp^3) bond, the formation of one C–N and four C–C bonds (shown in red), and the loss of two H_2O molecules. Upon C2–C3 bond cleavage, the three-carbon fragment of 2,4-pentanedione remains on the pyrrole side, whereas the remaining two-carbon acyl fragment goes to the phenyl ring. Therefore, the benzene ring of the indole **1** is constructed by five carbons from two molecules of fumaronitrile and the carbonyl carbon of the acyl fragment derived from 2,4-pentanedione. In particular, the acyl carbon forms C-5, and the four vinylic carbons of two fumaronitrile molecules generate C-4/C-9 and C-6/C-7 carbons of the phenyl ring. The phenyl C-8 is derived from the nitrile carbon of fumaronitrile that also forms the C-4/C-9 carbon diad. The remaining nitrile nitrogen at the C-8 carbon, along with two carbons of the three-carbon fragment from 2,4-pentanedione, forms the pyrrole ring.

Further optimization of the reaction condition with the correct stoichiometry of 2,4-pentanedione and fumaronitrile in a 1:2 molar ratio revealed that the transformation could be catalyzed by 10 mol % K_2CO_3 at 40 °C in 48 h, which afforded the indole product in 86% yield (Table 1, entry 1). The

Table 1. Optimization of Reaction Conditions[a]



entry	variation in reaction conditions	yield (%)
1	none	86 (83)
2	100 mol % K_2CO_3, 24 h	78
3	THF instead of dioxane	78
4	DMSO instead of dioxane	37
5	hexanes instead of dioxane	19
6	100 mol % $KHCO_3$, 80 °C, 24 h	80
7	100 mol % Na_2CO_3, 80 °C, 24 h	66
8	100 mol % K_3PO_4, 80 °C, 24 h	67
9	100 mol % $BaCO_3$, 80 °C, 24 h	0
10	100 mol % $CaCO_3$, 80 °C, 24 h	7
11	100 mol % Li_2CO_3, 80 °C, 24 h	0
12	100 mol % $SrCO_3$, 80 °C, 24 h	0
13	100 mol % Et_3N instead of K_2CO_3	47
14	100 mol % DBU instead of K_2CO_3	0

[a]Reactions were run on a 0.10 mmol scale in 0.5 mL of solvent. ^{1}H NMR yields are based on pyrene as an internal standard. The value in parentheses is the isolated yield from the 1.0 mmol scale reaction.

reaction also affords the indole product in THF in a comparable yield (entry 3). Other polar and nonpolar solvents like DMSO and hexanes formed the expected product in lower yield (entries 4 and 5). The indole product **1** was also formed in significant amounts, albeit at higher temperature, when K_2CO_3 was replaced with stoichiometric amounts of $KHCO_3$, Na_2CO_3, and K_3PO_4 (entries 6–8). Other bases such as $BaCO_3$, $CaCO_3$, Li_2CO_3, and $SrCO_3$ either did not form or generated the indole product **1** in trace amounts (entries 9–12). Replacing K_2CO_3 with 1 equiv of Et_3N generated product **1** in 47% (entry 13). However, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base did not form the indole product **1** (entry 14).

The optimized conditions were used to evaluate the scope of the reaction with respect to 1,3-diketones, especially considering substitution patterns and steric factors on 1,3-diketones (Scheme 4). The reaction proceeded well with symmetric 1,3-diketones containing linear, sterically accessible alkyl groups, such as Me, Et, and *i*-Bu, and afforded the substituted indole products (**1**, **2**, **4**, and **5**) in 52–83% yield. 1,3-Diketone bearing a sterically hindered *t*-Bu group generated the corresponding indole product (**3**) in only moderate yield. A symmetric 1,3-diketone with an alkene substituent can also be condensed with fumaronitrile to produce an indole (**5**) containing alkenyl side chain on both the pyrrole and benzene rings.[14]

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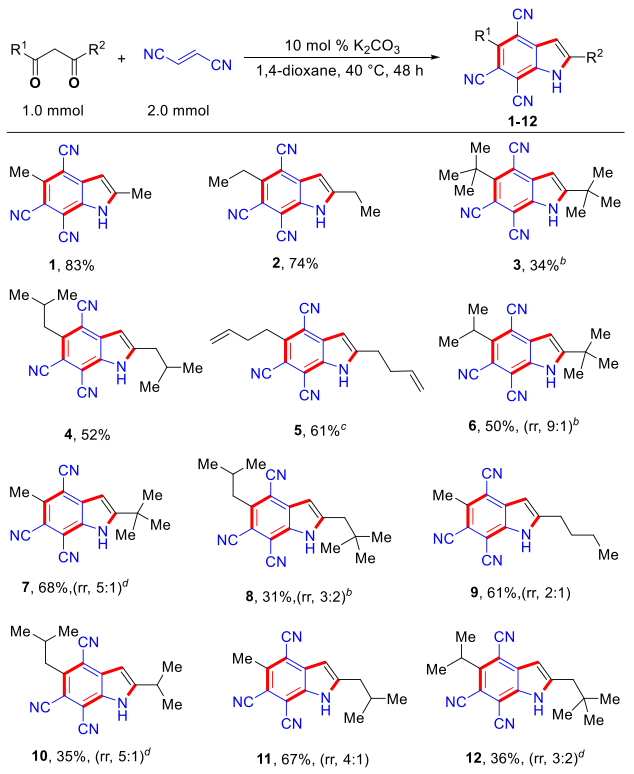
Scheme 4. Scope with Highly Decorated Indoles[a]

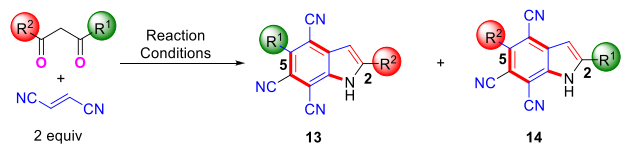


[a]Reactions were run on a 1.0 mmol scale in 5 mL of dioxane at 40 °C for 48 h. [b]20 mol % K_2CO_3, 96 h. [c]50 mol % K_2CO_3. [d]20 mol % K_2CO_3.

The current reaction can also be performed with unsymmetric 1,3-diketones, which furnish the indole products in moderate to good yield with varying degrees of regioselectivity (Scheme 4) depending on the steric encumbrance imposed by the alkyl substituents around the 1,3-dicarbonyl group. For example, unsymmetric 1,3-diketones containing a combination of two sterically prominently biased alkyl substituents, such as *i*-Pr versus *t*-Bu (**6**) and Me versus *t*-Bu (**7**), generated products with a high level of regiocontrol. Likewise, unsymmetric 1,3-diketones bearing relatively sterically indistinguishable alkyl diads, such as Me and *n*-Bu (**9**), *i*-Pr and *i*-Bu (**10**), Me and *i*-Bu (**11**), and *i*-Pr and neo-Pent (**12**), furnished the indole products with only a good to moderate degree of regioselectivity.

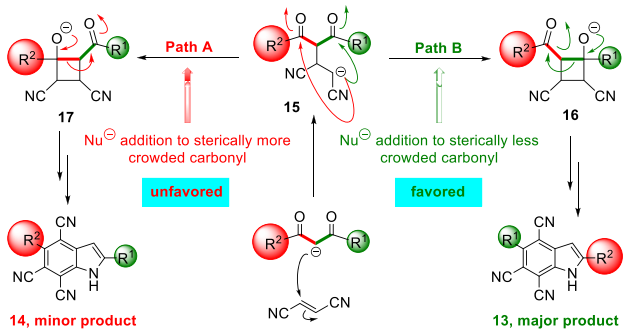
^{1}H NMR analyses and nuclear Overhauser effect (NOE) experiments of the isolated products as analytically pure major isomers (compounds **7** and **9**) revealed that the bulkier substituent (R^2, Scheme 5) in 1,3-diketone preferentially takes the second position and the smaller group occupies the fifth position of the substituted indole generated as a major product

Scheme 5. Generation of Two Regioisomers from Unsymmetrical 1,3-Diketones Bearing Sterically Biased Alkyl Groups



(**13**). The preferential occupation of the larger group at the two-position on the pyrrole ring and the smaller group at the five-position on the benzene ring for the observed regioselectivity can be explained based on the steric-induced kinetic difference at the nucleophilic 1,2-addition to the carbonyl group prior to the C−C bond cleavage step, as outlined in Scheme 6. We hypothesize that the nucleophilic

Scheme 6. Proposed Regioselectivity-Determining Step



enolate **15** generated after the conjugate addition of the 1,3-diketonate to fumaronitrile attacks its intramolecular carbonyl carbon bearing a small alkyl group R^1 much faster than the carbonyl carbon masked by a sterically bulky alkyl group R^2. The attack at the more accessible COR^1 generates a cyclobutane intermediate **16**, which undergoes a C−C bond cleavage event between the carbonyl carbon of the parent COR^1 and the methine carbon on the original diketone backbone, eventually leading to the formation of the major product. Likewise, the minor product is formed after the C−C bond cleavage between the parent COR^2 and the methine carbons in the cyclobutane intermediate **17** generated upon the nucleophilic attack at the sterically hindered COR^2 group.

After examining the scope and regioselectivity of the reaction, we delved into proposing a plausible mechanism (Scheme 7). The overall mechanism proceeds via a series of protonation−deprotonation involving addition, cyclization, and dehydration steps. Initially, the 1,3-diketone enolate adds to fumaronitrile by conjugate addition[15] to produce a carbanion, which then adds to the carbonyl group to generate a four-membered intermediate (steps **a** and **b**). The cyclobutane intermediate undergoes a retro aldol condensation,[16] triggering the cleavage of the C−C bond, which forms a 1,5-diketone enolate (step **c**). The 1,5-diketone enolate undergoes protonation/deprotonation to generate an ene-ketenimine enolate, which then adds a second molecule of fumaronitrile (steps **d** and **e**). The carbanion generated thereafter cyclizes onto the carbonyl group proximal to a cyano group, a process that is now followed by a sequence of protonation, dehydration, and aromatization to construct the benzene ring of indole as an aniline intermediate (steps **f**−**h**). The aniline further undergoes N−H deprotonation, which triggers cyclization onto the exocyclic carbonyl group followed by a second protonation, deprotonation, and dehydration sequence to form the pyrrole ring of indole (steps **i**−**k**).

We have observed key reaction intermediates, which provide strong support for the proposed mechanism outlined in Scheme 6. GCMS analysis of a sample obtained from the early termination of the reaction revealed that the reaction mixture contained three key reaction intermediates **18**−**20** along with the final indole product **1** (Figure 2). These intermediates **18**−

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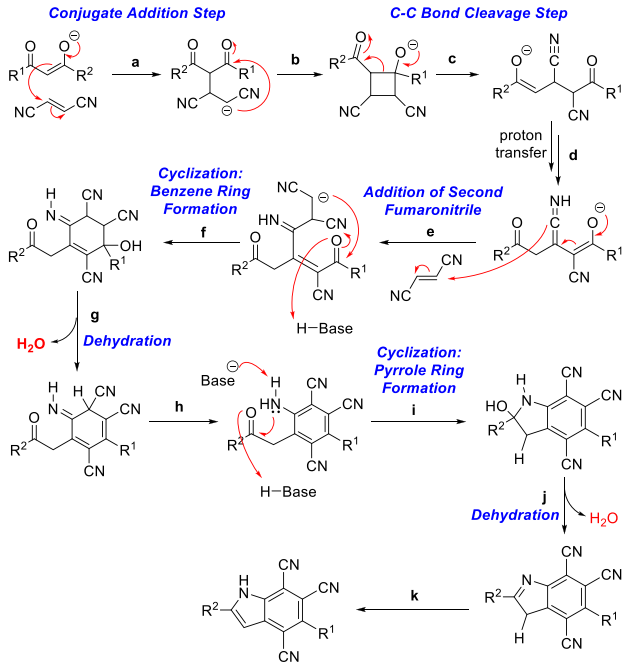
Scheme 7. Proposed Mechanism



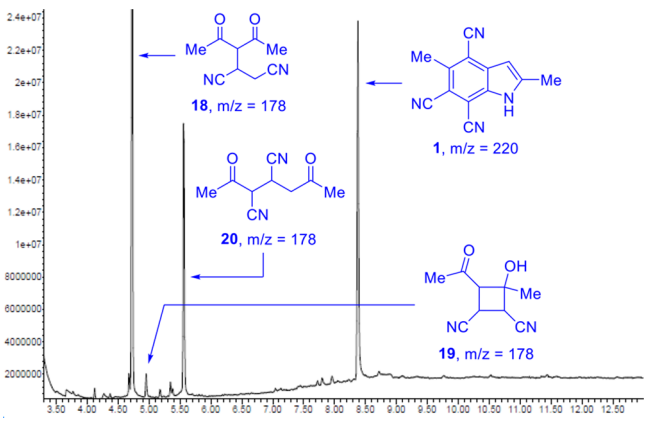
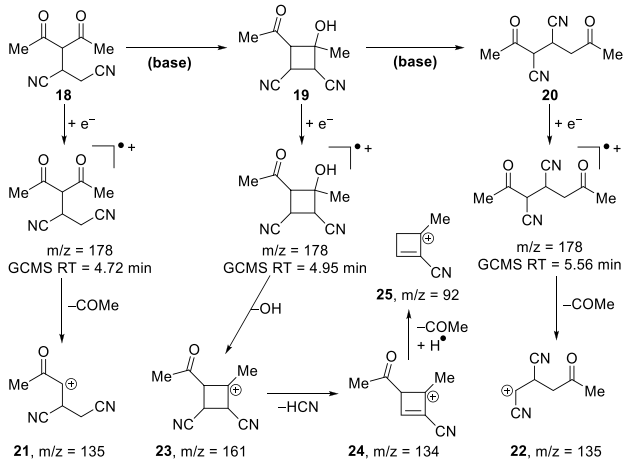


Figure 2. GC trace and intermediates confirmed by GCMS.

20 and product **1** appear at 4.72, 4.95, 5.56, and 8.38 min retention times and correspond to *m*/*z* 178, 178, 178 and 207, respectively. The cyclobutane intermediate **19** (*m*/*z* 178) has a unique fragmentation pattern that is different from those of the intermediates **18** and **20** with identical *m*/*z* values (Scheme 8). The cyclobutane intermediate **19** fragments into new molecular ions **23**–**25**, which correspond to *m*/*z* 161, 134 and 92, respectively, after sequentially losing OH, HCN, and COMe. The molecular ions (*m*/*z* 178) and the fragmentation patterns (*m*/*z* 135 with the loss of COMe) of intermediates **18** and **20** are identical. Therefore, the structures of the isomeric intermediates **18** and **20** could not be discerned from one another, and the assignment is tentative.[17] Multiple attempts to isolate and characterize the intermediates **18**–**20** were unsuccessful.

In conclusion we report a novel, base-catalyzed protocol for the synthesis of highly functionalized indole derivatives from 1,3-diketones and fumaronitrile. The reaction involves the simultaneous cleavage of one C–C bond and formation of one C–N and four C–C bonds to construct both the aryl and pyrrole rings of the indole in one step. The proposed

Scheme 8. Key Intermediates and Their Mass Fragmentation Patterns Confirmed by GCMS



mechanism, which involves a series of conjugate addition, retro-aldol reaction, protonation, deprotonation, cyclization, and dehydration, is supported by the observation and characterization of three reaction intermediates upon the analysis of reaction samples by GCMS and studies of their mass fragmentations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01057.

Experimental procedures, compound characterizations, NMR spectra, GC and GCMS traces, and crystallographic data (PDF)

Accession Codes

CCDC 1983223 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(17) The structures of the isomeric intermediates **18** and **20** were tentatively assigned based on the assumption that intermediate **20** with more carbons on a linear segment is likely to have a higher boiling point and therefore appear at a longer retention time (5.67 min) than intermediate **18** with more branched carbons (4.72 min).

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