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ARE MULTICOMPONENT STRECKER REACTIONS OF DIKETONES WITH DIAMINES UNDER HIGH PRESSURE AMENABLE TO HETEROCYCLIC SYNTHESIS?

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Abstract –Employing double Strecker strategy, two new heterocyclic compounds, 5,6,11,12-tetrahydro-6,11-dimethyldibenzo[*b,f*][1,4]diazocine-6,11-dicarbonitrile and 1,2,3,4,5,10-hexahydrophenazine-4a,10a-dicarbonitrile, were prepared in one step albeit in low yields. The reaction has proven to be very limited, but such a sterically hindered amine as *N*-methylaniline underwent Strecker reaction with benzaldehyde and TMSCN to give the corresponding α -amino nitriles.

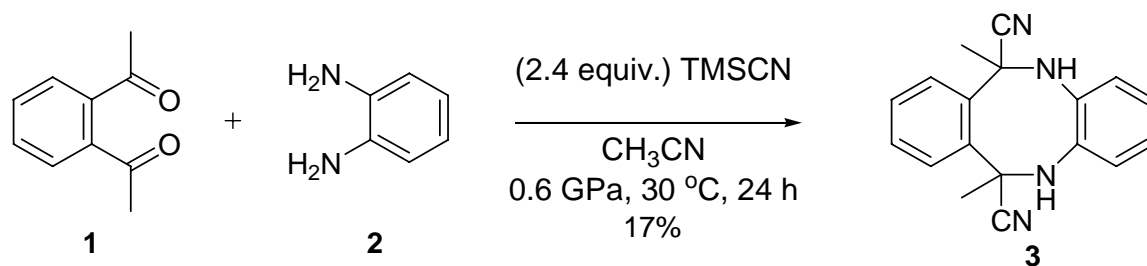
INTRODUCTION

Reactions in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the material can be found in the product are called multicomponent reactions (MCRs).¹⁻⁴ In multistep syntheses the temporal and preparative complexity increases in proportion to the number of steps in a first approximation. These aspects are reflected in many isolation and purification operations, such as crystallization, extraction, distillation, or chromatography. Besides the multistep, sequential synthesis of a target molecule, the desired product can also be obtained in one-pot reactions of three or more starting compounds, e.g. multicomponent reactions (MCRs), in many cases. Therefore, MCRs are very efficient in organic synthesis and have represented a rapid upsurge at the literature. MCRs are often amenable to synthesis of heterocyclic compounds. Notably, classical examples are illustrated by Hantzsch synthesis of 1,4-dihydropyridine and pyrrole synthesis, Radziszewski imidazole

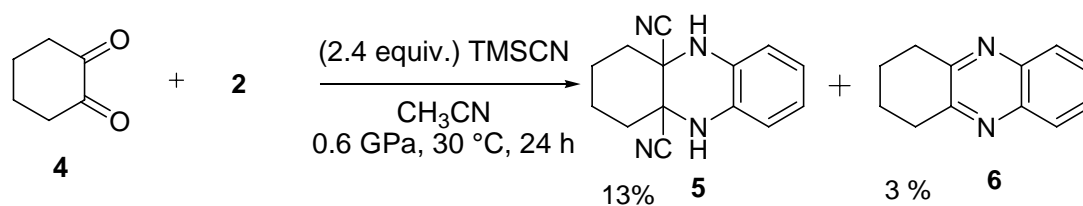
synthesis, Biginelli reaction of dihydropyrimidinone synthesis, and Bucherer-Bergs hydantoin synthesis. More recently, the tricyclic diamino ketone from octahydro-2*H*-quinolin-2-one was prepared by Scheiber and Nemes using a double Mannich condensation.⁵ Ihara and Fukumoto developed an efficient synthesis of polycyclic compounds employing the intramolecular double Michael reaction.⁶ The development of this type of synthetic method can lead to a reduction in the amount of undesired by-products, thereby contributing to the protection of the environment. However, MCRs under high pressure were hardly studied.^{7,8} Quite recently, we have developed a highly efficient method for the synthesis of acyclic α -amino nitriles in high yields employing the high-pressure-mediated three-component Strecker reactions of ketones without using any catalyst, including two types of double Strecker reactions.⁹ Encouraged by these results, it was envisioned that this strategy might be applicable to the synthesis of heterocycles using suitably substituted substrates such as diamines and 1,2-diketones. Thus, we describe results at this purpose.

RESULTS AND DISCUSSION

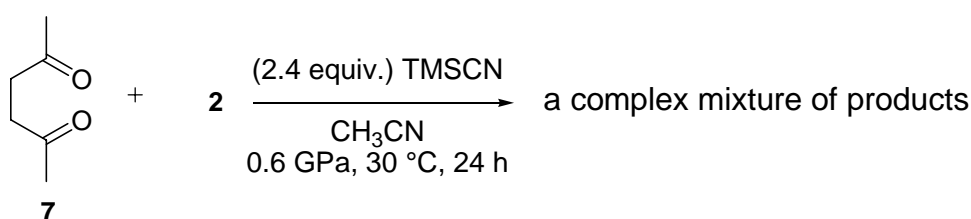
First, Strecker reaction was investigated with 1,2-diacetylbenzene (**1**), 1,2-diaminobenzene (**2**) and Me₃SiCN (TMSCN) in acetonitrile at 0.6 GPa and 30 °C for 24 h. Acetonitrile was chosen as a solvent, since it has proven in the previous work of double Strecker reaction with 1,4-diacetylbenzene, aniline, and TMSCN that acetonitrile was a choice of solvent.^{9c} Thus, 1 equivalent of **1** with **2** and TMSCN (2.4 equivalents) afforded 5,6,11,12-tetrahydro-6,11-dimethyldibenzo[*b,f*][1,4]diazocine-6,11-dicarbonitrile (**3**), albeit only in 17% yield in one step.¹⁰



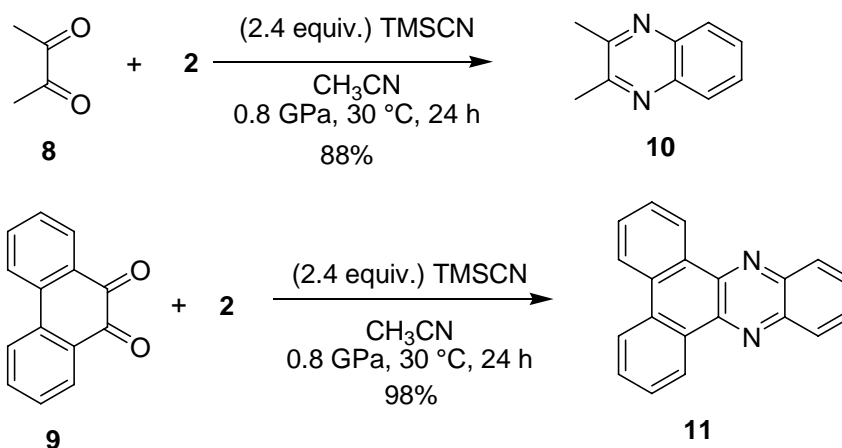
Encouraged by this result of double Strecker strategy for synthesis of novel heterocycles, a similar reaction of cyclohexane-1,2-dione (**4**) with **2** and TMSCN was investigated under high pressure conditions, producing 1,2,3,4,5,10-hexahydrophenazine-4a,10a-dicarbonitrile (**5**) in 13% yield along with the aromatized product, 1,2,3,4-tetrahydrophenazine (**6**).¹¹ It is not clear whether **6** was formed by bisdehydrocyanation of **5** or by a direct dehydrative condensation of **4** with **2** (see below).



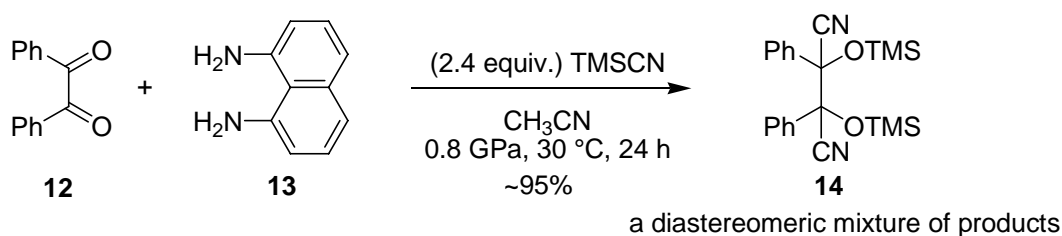
However, quite unfortunately, further attempts to prepare such novel heterocycles employing diketones and 1,2-diamines have met with failure. For example, 2,5-hexanedione (**7**) with **2** and TMSCN under same conditions only gave a complex mixture of products.



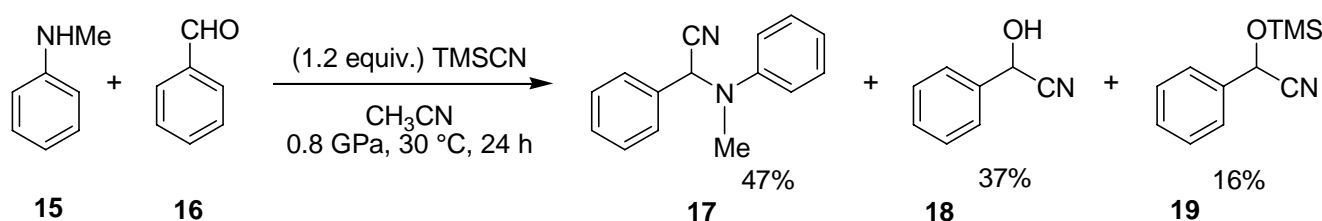
Much more disappointingly, 2,3-butanedione (**8**) and 9,10-phenanthrenequinone (**9**) with **2** and TMSCN gave very well known, yet commercially available products, 2,3-dimethylquinoxaline (**10**) and dibenzo[*a,c*]phenazine (**11**), respectively. Indeed, the reactions have proven to proceed without TMSCN at room temperature, probably due to aromatic stabilization of the products.



Furthermore, the reaction of 1,2-diphenylethanedione (**12**) with 1,8-diaminonaphthalene (**13**) also has met failure, affording a diastereomeric mixture of cyanotrimethylsilylation products (**14**).¹²



Finally, in the previous paper,^{9c} it was found that the Strecker reaction of sterically hindered *N*-methylaniline with acetone (or acetophenone) and TMSCN did not take place. Thus, it is in passing note here that *N*-methylaniline (**15**) reacted with benzaldehyde (**16**) to produce 2-(*N*-methyl-*N*-phenylamino)phenylacetonitrile (**17**) in 47% yield along with two by-products (**18** and **19**). The generality of double Strecker reaction of sterically hindered amines with aldehydes is therefore worthy of further investigation and will be a subject of future communications elsewhere.



CONCLUSION

High-pressure-mediated single and double Strecker reactions using *acyclic* diketones and aromatic amines such as aniline which do not take place without catalysts have proven successful. In contrast, a heterocyclic version of this strategy was highly limited at present; only a novel type of two heterocycles was obtained albeit in low yield *in one step*. However, it should be noted the reaction of aldehydes and ketones with TMSCN did take place in the absence of such catalysts as Lewis acids, thus this aspect is also worthy of further investigation in connection with green chemistry.^{9c} Based upon detailed mechanistic investigations on Strecker reaction under high pressure,⁹ further work is in progress by developing such new tactics as microwave techniques, supercritical methods as well as molecular modeling methods.

EXPERIMENTAL

General Procedure

All high-pressure reactions were performed in a piston-cylinder type apparatus (Hikari Koatsu HR-15-B3). All melting points were measured on Yanagimoto MP-S3 micro-melting point apparatus and were uncorrected. The NMR spectra were recorded on a JEOL LA 400 (400 MHz for ¹H NMR spectral analysis and 100 MHz for ¹³C NMR spectral analysis). All NMR spectra were taken in CDCl₃ solution and were reported in part per millions (δ) downfield from TMS as an internal standard. IR spectra were measured with a JASCO FT/IR-460 plus Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm⁻¹). TLC was conducted by using Merck Kieselgel 60F-254 plates (0.25 mm). For column chromatography, Fuji Silicia BW-300 and, for flash chromatography, Merck Kieselgel (230-400 mesh) was employed.

Typical experimental procedure: A mixture of diketone (**1**, 1.0 mmol), diamine (**2**, 1.0 mmol), and TMSCN (2.4 mmol) in MeCN (*ca.* 1.5 mL) was placed in a Teflon reaction vessel, and the mixture was allowed to react at 0.6 GPa and 30 °C for 24 h. After the mixture was cooled and the pressure was released, the mixture was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (elution with hexane-AcOEt, from 4:1 to 1:1) to afford the pure product.

5,6,11,12-Tetrahydro-6,11-dimethyldibenzo[*b,f*][1,4]diazocine-6,11-dicarbonitrile (3**):** colorless solid; R_f 0.28 (hexane/AcOEt, 1:1); mp 165-168 °C (Et₂O, decomp); FTIR (KBr) ν 3496, 3393, 2217, 1612, 1499, 1460; ¹H NMR: 1.80 (6H, s), 3.98 (2H, br s), 6.84 (1H, dd, $J = 8.0, 1.2$ Hz), 6.91 (1H, dt, $J = 8.0, 1.2$ Hz), 7.24 (1H, dt, $J = 8.0, 1.2$ Hz), 7.47 (2H, m), 7.55 (2H, m), 8.17 (1H, dd, $J = 8.0, 1.2$ Hz); ¹³C NMR: 24.6 (×2), 63.9 (×2), 115.6 (×2), 119.1(5), 119.2(3), 122.5 (×2), 129.6, 130.0, 130.4 (×2), 139.7 (×2), 147.6 (×2); *Anal.* Calcd for C₁₈H₁₆N₄•4/7H₂O C, 72.39; H, 5.79; N, 18.76. Found: C, 72.11; H, 5.49; N, 18.36.

1,2,3,4,5,10-Hexahydrophenazine-4a,10a-dicarbonitrile (5**):** colorless solid; R_f 0.42 (hexane/AcOEt, 2:1); mp 230-240 °C (hexane-Et₂O, sublimed); FTIR (KBr) ν 3344, 2233, 1603, 1509, 1469; ¹H NMR: 1.84-2.02 (6H, m), 2.27 (2H, dm, $J = 12.2$ Hz), 4.20 (2H, br s), 6.68 (2H, m), 6.82 (2H, m); ¹³C NMR: 21.5 (×2), 32.8 (×2), 57.3 (×2), 116.1 (×2), 117.7 (×2), 121.6 (×2), 129.0 (×2); *Anal.* Calcd for C₁₄H₁₄N₄: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.38; H, 5.99; N, 23.56.

1,2,3,4-Tetrahydrophenazine (6**):** yellowish solid; R_f 0.36 (hexane/AcOEt, 2:1); mp 90-92 °C (AcOEt; lit.,¹³ 90-92 °C); FTIR (KBr) ν 1559, 1483, 1427, 769; ¹H NMR: 2.05 (4H, m), 3.17 (4H, m), 7.67 (2H, m), 7.97 (2H, m); ¹³C NMR: 22.8 (×2), 33.2 (×2), 128.3 (×2), 128.9 (×2), 141.2 (×2), 154.2 (×2).

2,3-Dimethylquinoxaline (10**):** colorless solid; R_f 0.32 (hexane/AcOEt, 1:1); mp 103-106 °C (MeCN; lit.,¹⁴ 104-105 °C); FTIR (KBr) ν 1569, 1491, 1398, 1165, 763; ¹H NMR: 2.74 (6H, s), 7.67 (2H, m), 7.98 (2H, m); ¹³C NMR: 23.2 (×2), 128.3 (×2), 128.8 (×2), 141.0 (×2), 153.4 (×2).

Dibenzo[*a,c*]phenazine (11**):** yellowish solid; R_f 0.46 (hexane/AcOEt, 4:1); mp 228-231 °C (MeCN; lit.,¹⁵ 227-228 °C); FTIR (KBr) ν 1605, 1499, 1358, 768, 724; ¹H NMR: 7.70-7.79 (4H, m), 7.83 (2H, dd, $J = 6.5, 3.4$ Hz), 8.30 (2H, dd, $J = 6.5, 3.4$ Hz), 8.52 (2H, d, $J = 8.0$ Hz), 9.37 (2H, d, $J = 7.8$ Hz); ¹³C NMR: 122.9 (×2), 126.2 (×2), 127.9 (×2), 129.4 (×2), 129.7 (×2), 130.3 (×4), 132.0 (×2), 142.1 (×2), 142.4 (×2).

2,3-Diphenyl-2,3-bis(trimethylsilyloxy)succinonitrile (14**):**¹² a diastereomeric mixture; R_f 0.42 (hexane/AcOEt, 4:1); FTIR (KBr) ν 2238, 1491, 1449, 1255, 1142, 855; ¹H NMR: -0.04 (9H, s), 0.22 (9H,

s), 7.01 (2H, d, $J = 7.6$ Hz), 7.16 (2H, t, $J = 7.6$ Hz), 7.29 (1H, t, $J = 7.6$ Hz), 7.42-7.49 (4H, m), 7.70-7.74 (1H, m); ^{13}C NMR: 0.2 ($\times 3$), 0.6 ($\times 3$), 81.1, 81.4, 117.8, 118.9, 127.2 ($\times 2$), 127.5 ($\times 2$), 127.7 ($\times 2$), 127.8 ($\times 2$), 129.5, 129.8, 134.1, 136.1.

2-(*N*-Methyl-*N*-phenylamino)phenylacetonitrile (17): colorless oil; R_f 0.49 (hexane/AcOEt, 4:1); FTIR (neat) ν 2231, 1599, 1499, 1451; ^1H NMR: 2.75 (3H, s), 5.86 (1H, s), 6.98 (1H, t, $J = 7.3$ Hz), 7.04 (2H, d, $J = 7.8$ Hz), 7.34 (2H, m), 7.41-7.47 (3H, m), 7.55-7.58 (2H, m); ^{13}C NMR: 34.6, 58.6, 116.1, 116.7 ($\times 2$), 121.2 ($\times 2$), 127.2 ($\times 2$), 129.0, 129.1, 129.5 ($\times 2$), 133.4, 149.1.

2-Hydroxy-2-phenylacetonitrile (18):¹⁶ colorless oil; R_f 0.18 (hexane/AcOEt, 4:1); FTIR (neat) ν 3416, 2251, 1495, 1455, 1193, 1040, 1026; ^1H NMR: 2.89 (1H, br s), 5.54 (1H, s), 7.43-7.47 (3H, m), 7.52-7.55 (2H, m); ^{13}C NMR: 63.7, 118.7, 126.7 ($\times 2$), 129.2 ($\times 2$), 129.9, 135.2.

2-Phenyl-2-(trimethylsilyloxy)acetonitrile (19):¹⁷ colorless oil; R_f 0.58 (hexane/AcOEt, 4:1); FTIR (neat) ν 2240, 1495, 1455, 1255, 1196, 1097, 1072; ^1H NMR: 0.23 (9H, s), 5.50 (1H, s), 7.38-7.49 (5H, m); ^{13}C NMR: -0.3 ($\times 3$), 63.7, 119.2, 126.3 ($\times 2$), 128.9 ($\times 2$), 129.3, 136.2.

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