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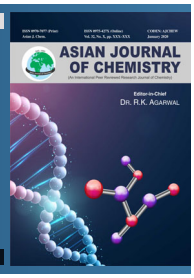

A Study on *N*-Substituted Nortropinone Synthesis using Acetone Equivalents

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Robinson's synthesis has long been a classic in organic chemistry due to its simplicity and impact in the industry. Various modifications have been made to improve the system. Among them, replacing acetone with more acidic chemical equivalents such as calcium dicarboxylic acid or ethyl dicarboxylic acetone improved the yield. In line with this trend, our group previously reported the synthesis of mono- and di-N-substituted tropinone derivatives from the one-pot reaction of 2,5-dimethoxy tetrahydrofuran and various amines with acetonedicarboxylic acid in the presence of HCl and water at room temperature. In this study, the synthesis with acetone instead of acetone-dicarboxylic acid was examined. Mono- and di-*N*-substituted nortropinones were prepared in higher yields in all cases although there were extent to which yields increased depending on the nature of substituents.

Keywords: Tropane alkaloids, Robinson's synthesis, Acetone, Substituent effects, Reaction mechanism.

INTRODUCTION

Tropane alkaloids, which contain a bicyclic tropane ring in the structure such as atropine and cocaine, have attracted much attention of medicinal chemists due to their anticholinergic or stimulating behaviours [1,2]. Aside from numerous studies trying to unravel the biosynthesis of tropane ring, many synthetic routes have been developed as well [3,4]. Authors are particularly interested in the synthesis of *N*-substituted derivatives since nitrogen is one of two important binding sites shared in atropine and cocaine. Yet, *N*-substituted tropinone derivatives have not been studied much in detail.

Robinson's tropinone synthesis, a landmark of total synthesis, is a well-known method to prepare tropinones [5,6]. It involves one-pot reaction of succinaldehyde, methylamine and acetone in aqueous solution. Various *N*-substituted nortropinones can be synthesized using different primary amines. However, this method has been revisited by many chemists because of its low yield, cumbersome purification and long reaction time, which make difficult to develop the library of compounds for drug discovery. For example, acetone was replaced by calcium dicarboxylic acid or ethyl dicarboxylic acetone because of low acidity of acetone and as the result, the product yield was improved up to 40 %. Furthermore, Schöpf modified the reaction and improved the yield by conducting the reaction at pH 7 with dicarboxylic acetone [7]. In previous studies [8-10], authors reported a convenient one-pot synthesis of mono- and di-*N*-substituted tropinone derivatives from the reaction of 2,5-dimethoxytetrahydrofuran and various amines with acetonedicarboxylic acid in the presence of HCl and water at room temperature. Achieved yield was 54 % and 48 % in the case of tropinone synthesis using acetone in lieu of acetonedicarboxylic acid.

In this study, authors explored the synthesis of mono- and di-*N*-substituted nortropinone derivatives using 2,5-dimethoxytetrahydrofuran, various amines and acetone. 8-Phenyl-8-azabicyclo[3.2.1]octan-3-one and related compounds, which have been previously synthesized using acetonedicarboxylic acid by authors were revisited. Mono- and di-*N*-substituted nortropinones were prepared in higher yields compared to previously reported yields of using acetonedicarboxylic acid.

EXPERIMENTAL

Except where explicitly stated, all chemicals were purchased from Aldrich, Fisher and TCI, and used as received. ^{1}H and ^{13}C NMR spectra were obtained with Bruker AC 2000 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Melting points were determined using an electrothermal capillary melting point apparatus and are uncorrected. Mass spectra were measured with HP 5890 GC/Mass (70 eV, EI).

Synthesis of 8-phenyl-8-azabicyclo[3,2,1]octan-3-ones : 2,5-Dimethoxytetrahydrofuran (0.05 mol) and conc. HCl (1 mL) were dissolved in acetone (10 mL). Amine (0.05 mol) in water (10 mL) was added and stirred the reaction mixture at room temperature and observed by TLC to the point of completion. The resulting solution was washed, neutralized with Na_2CO_3 solution and extracted three times with methylene chloride. Organic layers were dried with magnesium sulfate, filtered and concentrated. Products were purified into column chromatography and the corresponding compounds **1-7** were obtained.

8-phenyl-8-azabicyclo[3.2.1]octan-3-one (1): Yield: 55.3 %; m.p.: 99-100 ºC; R_f: 0.13 (TLC eluent; ethyl acetate: *n*-hexane = 1:10, v/v); Mass (70 eV), *m/z* (rel. int.%): 201(45), 172(10), 158(35), 144(100), 130(10), 117(10), 104(45), 77(65); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33 (t, 2H), 6.86 (m, 3H), 4.51 (s, 2H), 2.0 (dd, 2H), 2.32 (d, 2H), 2.19 (m, 2H), 1.80(m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 208.27, 145.03, 129.81, 118.39, 114.89, 54.34, 45.51, 28.4. Elemental analysis calcd. (found) %: C, 77.58 (77.50); H, 7.51 (7.54); N, 6.96 (6.91).

8-(4-Ethylphenyl)-8-azabicyclo[3.2.1]octan-3-one (2): Yield: 92 %; m.p.: 51-53 ºC; R_f: 0.30 (TLC eluent; ethyl acetate :*n*-hexane = 1:10, v/v); Mass (70 eV), *m/z* (rel. int.%): 229(5), 172(30), 132(35), 105(35), 91(35), 77(80), 68(100), 51(45); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.14 (d, 2H), 6.82 (d, 2H), 4.47 (s, 2H), 4.47 (s, 2H), 2.70 (dd, 2H), 2.56 (q, 2H), 2.28 (d, 2H), 2.18 (m, 2H), 1.46 (m, 2H), 1.22 (t, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 208.45, 142.94, 129.17, 114.97, 54.58, 45.49, 28.76, 27.80, 15.54. Elemental analysis calcd. (found) %: C, 78.56 (78.45); H, 8.35 (8.39); N, 6.11 (6.02).

8-(4-Methoxyphenyl)-8-azabicyclo[3.2.1]-octan-3-one (3): Yield: 83.7 %; m.p.: 106-107 ºC; R_f: 0.21 (TLC eluent; ethyl acetate:*n*-hexane = 1:5, v/v); Mass (70 eV), *m/z* (rel. int.%): 231(95), 216(5), 202(10), 188(20), 174(100), 158(10), 134(45), 121(10) 107(10) 92(10), 77(15); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.86 (m, 4H), 4.42 (s, 2H), 3.77 (s, 3H), 2.68 (dd, 2H), 2.27 (d, 2H), 2.17 (m, 2H), 1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 208.35, 152.46, 139.20, 116.07, 155.30, 55.57, 55.03, 45.29, 28.82. Elemental analysis calcd. (found) %: C, 72.70 (72.81); H, 7.41 (7.34); N, 6.06 (6.01).

8-(4-Acetylphenyl)-8-azabicyclo[3.2.1]octan-3-one (4): Yield: 79.3%; m.p.: 106-107 ºC; R_f: 0.2 (TLC eluent; ethyl acetate:*n*-hexane = 1:3, v/v); Mass (70 eV), *m/z* (rel. int.%): 245(45), 176(30), 162(100), 148(15), 135(20), 122(65), 109(25), 95(70), 75(30); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.80 (d, 2H), 6.64 (d, 2H), 4.20 (m, 2H), 2.64 (dd, 2H), 2.51 (s, 3H), 2.29 (d, 2H), 1.66 (m, 2H) 1.31 (m, 2H).

8-(4-Fluorophenyl)-8-azabicyclo[3.2.1]octan-3-one (5): Yield: 83.2 %; m.p.: 88-90 °C; R_f: 0.15 (TLC eluent; ethyl acetate:*n*-hexane = 1:10, v/v); Mass (70 eV), *m/z* (rel. int.%): 219(45), 176(30), 162(100), 148(15), 135(20), 122(65), 109(25), 95(70), 75(30). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.00 (m, 2H), 6.82 (m, 2H), 4.42 (S, 2H), 2.64 (dd, 2H), 2.29 (d, 2H), 2.17 (m, 2H), 1.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.39, 154.88, 141.97, 116.87, 116.58, 116.31, 116.22, 55.30, 45.64, 29.24. Elemental analysis calcd. (found) %: C, 71.21 (71.14); H, 6.44 (6.49); N, 6.39 (6.31).

8-(4-Chlorophenyl)-8-azabicyclo[3.2.1]octan-3-one (6): Yield: 89.2 %; m.p.: 96-97 ºC; R_f: 0.2 (TLC eluent; *n*-hexane:ethyl acetate = 9:1, v/v); Mass (70 eV), *m/z* (rel. int.%): 238.08(100), 237.07(32), 236.08(15), 148(15), 135(20), 122(65), 109(25), 95(70), 75(30); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.12 (m, 2H), 6.72 (m, 2H), 3.32 (m, 2H), 2.62 (dd, 2H), 1.66 (m, 2H), 1.31 (m, 2H).

8-Furan-2-ylmethyl-8-azabicyclo[3.2.1]octan-3-one (7): Yield: 86.3 %; R_f: 1.33 (TLC eluent; ethyl acetate:*n*-hexane = 1:3, v/v); Mass (70 eV), *m/z* (rel. int.%): 205(20), 147(20), 138(30), 94(20), 81(100), 68(20), 53(40); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40 (d, 1H), 6.34 (m, 1H), 6.25 (d, 1H), 3.37 (s, 2H), 3.54 (s, 2H), 2.71 (dd, 2H), 2.21 (dd, 2H), 2.11 (m, 2H), 1.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 209.93, 152.46, 142.22, 110.04, 108.08, 58.66, 48.04, 47.97, 47.82, 47.71, 27.54. Elemental analysis calcd. (found) %: C, 70.22 (70.14); H, 7.37 (7.31); N, 6.82 (6.69).

1,4-Di-(8-azabicyclo[3,2,1]octan-3-onyl)benzenes: 2,5-Dimethoxytetrahydrofuran (0.05 mol) and conc. HCl (1 mL) were dissolved in acetone (10 mL). Diamine (0.02 mol) in water (10 mL) was added dropwisely at 0 ºC. The reaction mixture was stirred overnight at room temperature and checked by TLC when finished. The resulting solution was washed, neutralized with a sodium bicarbonate solution and extracted three times with methylene chloride. Organic layers were dried with magnesium sulfate, filtered and concentrated. Products were purified by column chromatography to afford the corresponding compounds **8-13**.

1,4-Di-(8-azabicyclo[3.2.1]octan-3-onyl)benzene (8): Yield: 73.0 %; m.p.: 246-247 ºC; Rf: 0.45 (TLC eluent; ethyl acetate); Mass (70 eV), *m/z* (rel. Int.%): 324(100), 267(58), 214(28), 117(14), 68(15); IR (KBr, ν_{max}, cm^{-1}): 3037, 2923, 1730 (C=O), 1590; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.86 (m, 4H), 4.49 (s, 4H), 2.70 (d, 4H), 2.31 (d, 4H), 2.17 (d, 4H), 1.82 (d, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.93, 138.05, 117.18, 55.08, 55.35, 45.76, 29.20.

1,3-Di-(8-azabicyclo[3.2.1]octan-3-onyl)benzene (9): Yield: 47.0 %; m.p.: 176-178 ºC; R_f: 0.41 (TLC eluent; ethyl acetate:*n*-hexane = 1 : 2, v/v); Mass (70 eV), *m/z* (rel. Int.%): 324(100), 281(21), 267(52), 225(15), 209(52), 143(16), 117(17), 68(16); IR (KBr, ν_{max}, cm^{-1}): 3040, 2920, 1728 (C=O), 1595; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 4H), 4.49 (s, 4H), 2.73 (d, 4H), 2.31 (d, 4H), 2.18 (d, 4H), 1.80 (d, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.69, 147.06, 131.54, 106.17, 101.79, 54.90, 46.11, 29.16.

1,2-Di-(8-azabicyclo[3.2.1]octan-3-onyl)ethane (10): Yield: 39.9 %; m.p.: 140-142 ºC; R_f: 0.25 (TLC eluent; MeOH :CH_2Cl_2:*n*-hexane = 1:5:5. v/v/v); Mass (70 eV), *m/z* (rel. Int.%): 276(2), 138(100), 96(13), 4(8); IR (KBr, ν_{max}, cm^{-1}): 3030, 2920, 2905, 1725 (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.55

(s, 4H), 2.77 (s, 4H), 2.63 (dd, 4H), 2.16 (d, 4H), 1.21 (m, 4H), 1.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 209.61, 59.24, 50.25, 47.37, 27.83.

1,6-Di-(8-azabicyclo[3,2,1]octan-3-onyl)-hexane (11) Yield: 53.2 %; R_f: 0.25 (TLC eluent; ethyl acetate:*n*-hexane = 1:5, v/v); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.54 (s, 4H), 2.71 (d, 4H), 2.59 (d, 4H), 2.18 (d, 4H), 2.03 (t, 4H), 1.77 (s, 8H), 1.60 (d, 4H).

1,8-Di-(8-azabicyclo[3,2,1]octan-3-onyl)octane (12): Yield: 32.2 %; R_f: 0.15 (TLC eluent; ethyl acetate:CH_2Cl_2 = 1: 1, v/v); Mass (70 eV), *m/z* (rel. Int.%): 360 (13), 303 (100), 275 (9), 245 (7), 138 (69), 96 (14), 68 (11), 55 (13); IR (KBr, ν_{max}, cm^{-1}): 3035, 2925, 2910, 1726 (C=O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.52 (s, 4H), 2.67 (d, 4H), 2.54 (t, 4H), 2.15 (d, 4H), 2.00 (d, 4H), 1.53 (d, 8H), 1.33 (s, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 210.23, 58.42, 50.08, 47.10, 29.48, 29.07, 27.88, 27.46.

1,12-Di-(8-azabicyclo[3,2,1]octan-3-onyl)-dodecane (13): Yield: 31.0 %; R_f: 0.15 (TLC eluent; MeOH:ethyl acetate = 1:1, v/v); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.61 (s, 4H), 3.31 (d, 8H), 3.17 (d, 8H), 1.91 (d, 4H), 1.65 (m, 10H), 1.25 (m, 10H).

RESULTS AND DISCUSSION

Reaction design: The synthesis of tropane alkaloids has been the subject of many different studies because of their biological significance. The tropinone synthesis reported by Robinson [11] is a simple condensation reaction between succinaldehyde, methylamine and acetone (Fig. 1). Since then, Robinson′s tropinone synthesis has become a classic in organic synthesis. Another way to prepare tropinone reported by Nicolaou *et al*. [12] is to start from cycloheptanol, oxidize with *o*-iodylbenzoic acid followed by sequential addition of methylamine. These two methods readily prepared tropinone. However, authors' aim was to synthesize *N*-substituted derivatives since nitrogen is one of two important binding sites shared in atropine and cocaine. Third approach involves the synthesis of 8,8-dimethyl-3-oxo-8-azonia-bicyclo[3.2.1]octane iodide from tropinone and subsequent alkylation to yield *N*-substituted tropinones [13]. Despite its simplicity, this method is limited to primary arylmethylamines and arylethylamines presumably due to its electrophilic addition nature. In previous studies, authors utilized Schöpf's modified version of Robinson synthesis to prepare *N*-substituted tropinones with aniline derivatives. A convenient one-pot reaction prepared the mono- and di-*N*-substituted tropinone derivatives from the reaction of 2,5-dimethoxytetrahydrofuran and various amines with acetonedicarboxylic acid in the presence of HCl and water at room temperature. During the reaction, however, acetonedicarboxylic acid in aqueous solution is anticipated to decompose to CO_2 and acetone. Therefore, authors felt it would be interesting to revisit the Robinson′s tropinone synthesis using acetone in lieu of acetone-dicarboxylic acid.

Substituent effects in mono- and di-substituted tropinones: First, a library of mono-*N*-substituted tropinones using various aniline derivatives are synthesized. Results are summarized in the Tables 1 and 2 along with the reaction conditions and the structure of products. 8-Phenyl-8-azabicyclo[3.2.1]-octan-3-one (**1a**) was synthesized from aniline in 55.3 % yield, which was a significant improvement from the results of other groups of 13.3 % and 30% [14]. To authors' surprise, however, *para*-substituents on aniline ring generally increased the reaction yield no matter the nature of the substituents. Both electron donating groups on the *para*-position were **2a** and **3a**. However, electron-withdrawing substituents also increased the yield although there were differences in extent to which yields were increased 2-actetyl substituent increased the yield in smaller scale when compared to 2-halogen p*K*a values. Aniline has p*K*a of 4.58 and other derivatives have similar or slightly higher p*K*a values (5.12 for 4-alkyl, 5.36 for 4-methoxy, 4.65 for 4-fluoro and 4.15 for 4-chloro) [15]. 4-Acetylaniline, however, has p*K*a of 1.76 and exhibited lowest increase in yield. This is presumably due to *para*-acetyl groups participating in the conjugated π-system. Next, a series of di-substituted tropinones were synthesized using various diamines. *para*-Phenylenediamine showed highest yield of 73.0 %, *meta*- phenylenediamine showed moderate 47.0 % while *ortho*-phenylenediamine did not proceed with the reaction presumably due to the steric hindrance (data not shown). Linear diamines exhibited comparable yields of around 35 % except for 1,6-di-(8-azabicyclo[3,2,1]-octan-3-onyl)hexane (**11a**) which showed highest 53.2 %.

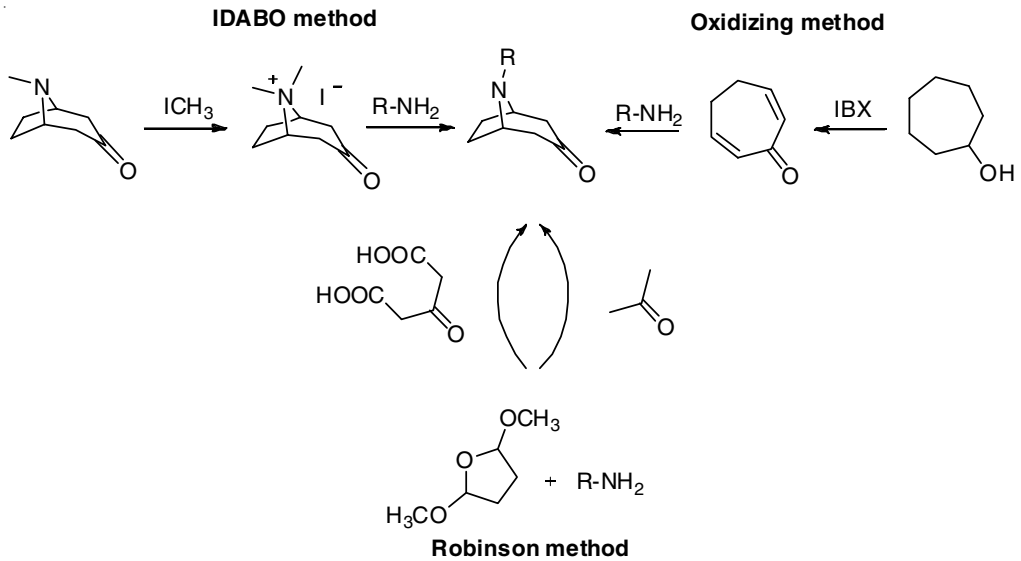
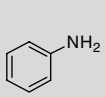
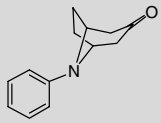
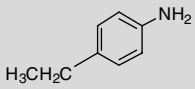
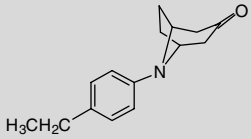
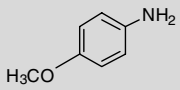
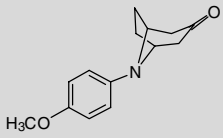
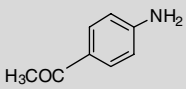
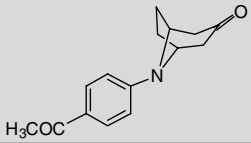
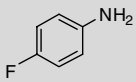
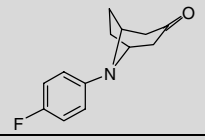
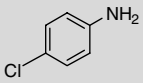
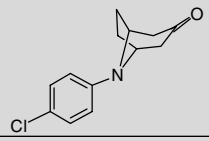
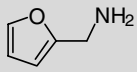
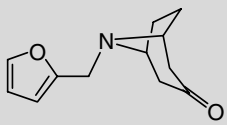


Fig. 1. Three widely accepted routes to synthesize tropinones

TABLE-1
SUMMARY OF *N*-SUBSTITUTED TROPINONE SYNTHESIS USING ACETONE OR 1,3-ACETONEDICARBOXYLIC ACID

Entry	Reactant		Reaction time (h)	Product	Yield (%)[a]
	Monoamine	Acetone equivalent			
1a		Acetone	12		55.3
1b		1,3-Acetonedicarboxylic acid			48.0[b]
2a		Acetone	12		92.0
2b		1,3-Acetonedicarboxylic acid			85.0[b]
3a		Acetone	12		83.7
3b		1,3-Acetonedicarboxylic acid			71.2[b]
4a		Acetone	24		79.3
4b		1,3-Acetonedicarboxylic acid			61.6[b]
5a		Acetone	12		83.2
5b		1,3-Acetonedicarboxylic acid			84.9[b]
6a		Acetone	12		89.2
6b		1,3-Acetonedicarboxylic acid			85.0[b]
7a		Acetone	12		86.3
7b		1,3-Acetonedicarboxylic acid			78.7[b]

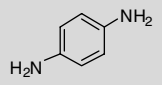
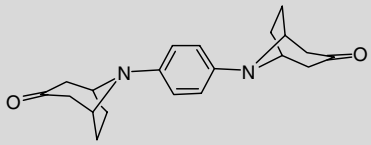
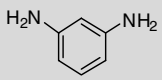
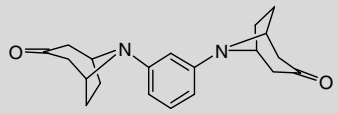
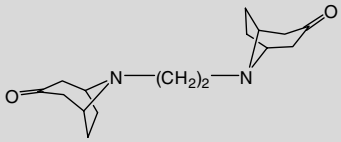
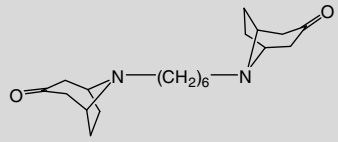
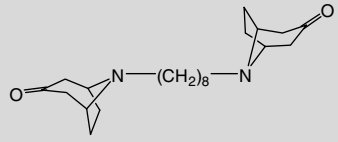
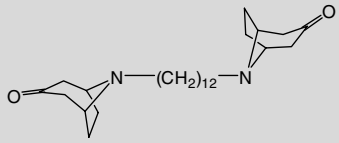
[a]Isolated yield; [b]Previously published.

Acetone *versus* acetonedicarboxylic acid and reaction mechanism: Lastly, the yields obtained using acetone were compared to the previously published yields obtained using 1,3-acetonedicarboxylic acid about 10 %, which was a surprise. It is widely accepted that low acidity of acetone results in low yield in the conventional Robinson synthesis unless activated by strong base to deprotonate α-hydrogen [16,17]. Therefore, numerous studies replaced acetone with more acidic equivalents such as acetonedicarboxylic acid, acetone silyl enol ethers and metal enol complexes of (acetonedicarboxylato)copper to improve the yields [18,19]. Authors contemplated on the results and found a difference from other studies. After the initial acidification, the reaction temperature is generally increased above the room temperature to facilitate thermal decarboxylation to obtain the final product [20]. Use of acetone does not require this unnecessary step and hence the reaction can proceed in the room temperature and within shorter amount of time (less than a day). Therefore, when two reactions are compared in the same low temperature and same period of time, acetone presumably resulted in higher yield. Reaction mechanism is proposed in Fig. 2. Nucleophilic addition of alkylamine to the aldehyde and loss of water proceeds to the formation of intermediate amino alcohol, which in acidic conditions produces a pyrolidine derivative iminium cation. Intermolecular Mannich reaction between the iminium cation and enol form of acetone takes place followed by intramolecular Mannich reaction between enolate and imine to afford tropinone.

Conclusion

In conclusion, Robinson′s tropinone synthesis was revisited. Mono- and di-*N*-substituted nortropinone derivatives were synthesized using 2,5-dimethoxytetrahydrofuran, various amines with acetone, and results were compared to those of previously results. The yields obtained using acetone were increased in general compared to the yields obtained using 1,3-acetonedicarboxylic acid although there were extent to which yields were increased depending on the nature of the substituents. Authors proposed that such increase is due to the removal of unnecessary thermal decarboxylation required to obtain the final product. Detailed mechanistic research depending on the reaction temperature could be of an interesting future research topic.

TABLE-2
SUMMARY OF N-SUBSTITUTED TROPINONE SYNTHESIS USING ACETONE OR 1,3-ACETONEDICARBOXYLIC ACID

Entry	Reactant		Reaction time (h)	Product	Yield (%)[a]
	Monoamine	Acetone equivalent			
8a		Acetone	22		73.0
8b		1,3-Acetonedicarboxylic acid			69.0[b]
9a		Acetone	31		47.0
9b		1,3-Acetonedicarboxylic acid			38.0[b]
10a	$H_2N-(CH_2)_2-NH_2$	Acetone	24		39.9
10b		1,3-Acetonedicarboxylic acid			27.5[b]
11a	$H_2N-(CH_2)_6-NH_2$	Acetone	21		53.2
11b		1,3-Acetonedicarboxylic acid			46.3[b]
12a	$H_2N-(CH_2)_8-NH_2$	Acetone	67		32.2
12b		1,3-Acetonedicarboxylic acid			35.0[b]
13a	$H_2N-(CH_2)_{12}-NH_2$	Acetone	22		31.0
13b		1,3-Acetonedicarboxylic acid			22.3[b]

[a]Isolated yield; [b]Previously published

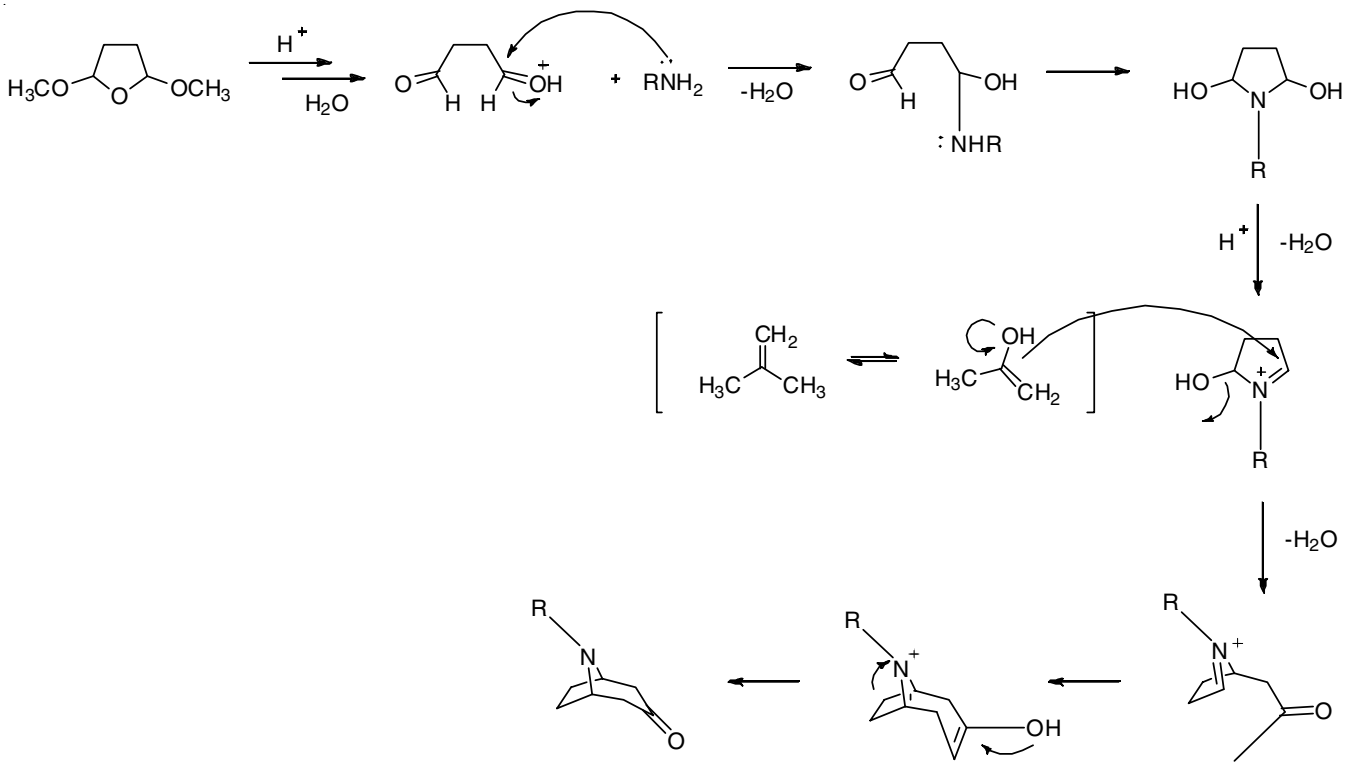


Fig. 2. Reaction mechanism of tropinone synthesis using 2,5-dimethoxytetrahydrofuran and various amines with acetone in the presence of HCl and water at room temperature

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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