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Multifunctional molecules with interesting stereochemistry derived by the reaction of salicyl N-phenylhydrazones with dimethyl acetylenedicarboxylate

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ABSTRACT

Treatment of salicyl N-phenylhydrazones with dimethyl acetylene dicarboxylate in the presence of ^{t}BuOK at room temperature affords the uncyclised multifunctional products derived by the reaction of one molecule of phenylhydrazone with two molecules of the diester. The interesting point about the structure of the products is that the olefin diester moiety attached with the oxygen of the phenolic hydroxyl group possesses (E)-configuration while that attached with the nitrogen of the hydrazone function contains (Z)-configuration.

Key words: Salicyl N-phenylhydrazones, dimethyl acetylene dicarboxylate, ^{t}BuOK, multifunctional molecule, stereochemistry.

INTRODUCTION

Salicyl N-tosylimines has recently been utilized to produce highly functionalized chromenes [1-4] (**Scheme 1**). We were interested to these conversions of the compounds as we would like to exploit them for the transformations of the similar molecules. We treated the related compounds, salicyl N-phenylhydrazones (1) [5-11] with dimethyl acetylene dicarboxylate in the presence of ^{t}BuOK in THF at room temperature; we did not get expected chromene derivatives. Instead, we obtained uncyclised products **2** derived from one molecule of hydrazone with two molecules of the diester (**Scheme 2**).

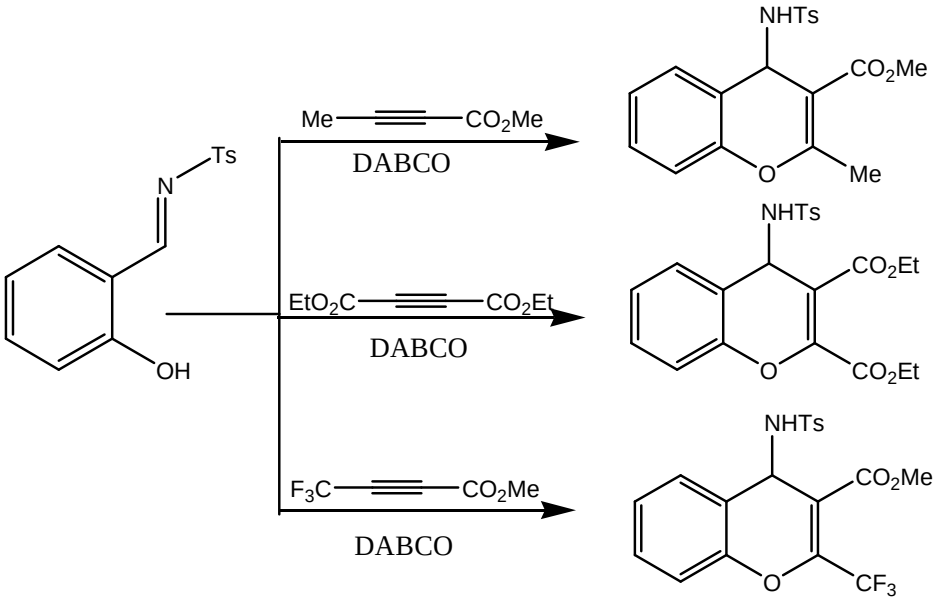
MATERIALS AND METHODS

The spectra were reported with the following instruments, IR: Perkin-Elmer RX1 FT-IR spectrophotometer; NMR: Varin Gemini 200 MHz (^{1}H) and 50 MHz (^{13}C) spectrometer; ESIMS: VG-Autospec micromass and HRESI-MS: QSTAR XL, Hybrid Ms system. Column chromatography was carried out with silica gel (BDH 100-200 mesh) and TLC with silica gel GF254 pre-coated plates.

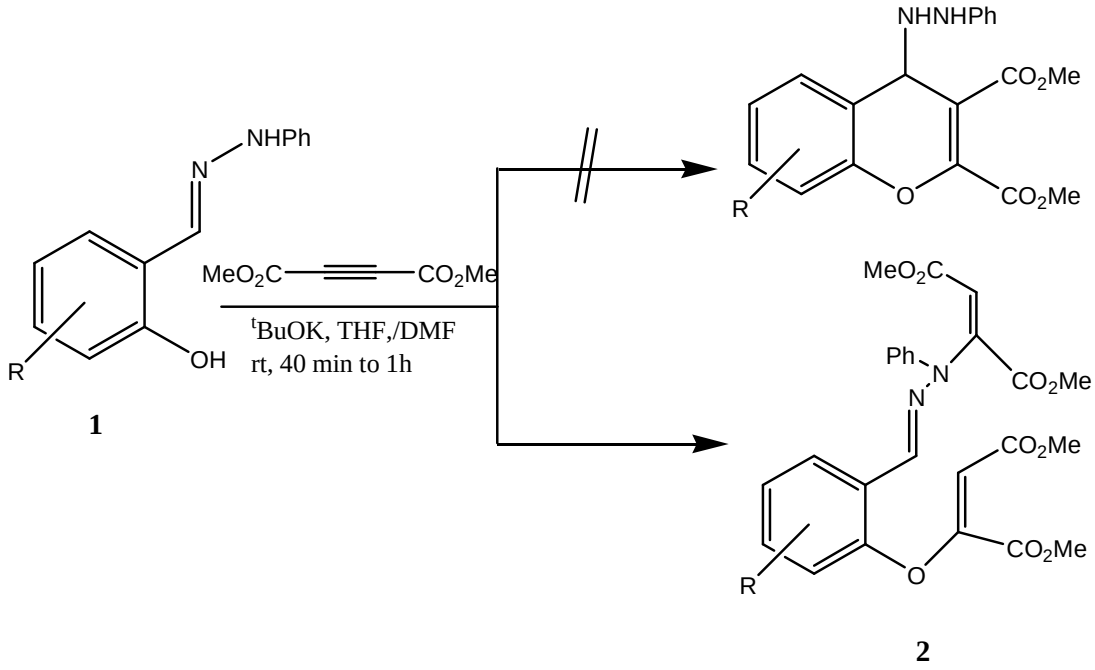
General Experimental procedure:
To a stirred solution of a salicyl N-phenyl hydrazone derivative (1.0 mmol) and ^{t}BuOK (100 mg) in THF (10 mL) dimethyl acetylenedicarboxylate (2.2 mmol) was added under N_2. The mixture was continued to stir and the reaction was monitored by TLC. After completion the solvent was evaporated under reduced pressure. Water (10 ml) was added to the residue and the mixture was extracted with EtOAc (3 x 10 mL). The extract was concentrated and the remaining gummy mass was subjected to column chromatography (silica gel, hexane-EtOAc) to obtain a pure product.

The spectral (^{1}H, ^{13}C NMR, IR and MS) data of some representative products are given below.

Compound 2a: IR: 1723, 1630, 1435, 1362, 1216 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.12 (`1 H, d, J = 8.0 Hz), 7.49 (1 H, s), 7.41-7.25 (5 H, brs), 7.21- 719 (2 H, m), 7.07 (1 H, brs), 6.98 (1 H, s), 4.89 (1H, s), 3.91 (3 H, s), 3.72 (3 H, s), 3.61 (3 H, s), 3.56 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.8, 165.4, 164.9, 162.3, 160.2, 154.1, 151.2, 135.3, 133.6, 131.4, 130.4, 129.8, 128.5, 127.0, 126.8, 126.3, 124.3, 121.3, 98.6, 53.1, 51.7, 51.1; ESIMS: m/z 514[M+Na]$^+$Anal. Calcd for $C_{25}H_{24}N_2O_9$: C, 60.48; H, 4.83; N, 5.63%, Found: C, 60.54; H, 4.80; N, 5.61%.



Scheme 1



Scheme 2

Compound 2b: IR: 1727, 1637, 1438, 1213, 1128 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ8.07 (1H, d, J = 2.0 Hz), 7.41 (1H, s), 7.39-7.28 (3H, m), 7.21 (2H, dd, J = 8.0, 2.0 Hz), 7.60 (1H, t, J = 8.0 Hz), 7.02 (1H, s), 7.01 (1H, d, J = 8.0 Hz), 4.91 (1H, s), 3.90 (3H, s), 3.70 (3H, s), 3.62 (3H, s), 3.59 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.3, 163.8, 163.7, 162.5, 160.3, 148.4, 142.9, 138.2, 132.3, 131.5, 129.0, 126.2, 126.0, 124.1, 122.6, 118.9, 98.9, 52.8, 51.2, 51.0; ESIMS: m/z 533, 531 $[M+H]^+$, 555, 553 $[M+Na]^+$; Anal. Calcd for $C_{25}H_{23}ClN_2O_9$: C, 56.55; H, 4.23; N, 5.36%, Found: C, 56.55; H, 4.28; N, 5.33%.

Compound 2c: IR: 1728, 1639, 1437, 1364, 1255 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.21 (1H, d, J = 2.0 Hz), 7.42 (1H, dd, J = 8.0, 2.0 Hz), 739 (1H, s), 7.33 (2H, d, J = 8.0 Hz), 7.20 (2H. dd, J = 8.0, 2.0 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.03 (1H, s), 6.94 (1H, d, J = 8.0 Hz), 4.91 (1H, s), 3.90 (3H, s), 3.69 (3H, s), 3.61(3H, s), 3.59 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.0, 164.2, 164.0, 163.1, 161.0, 149.8, 143.5, 139.2, 133.1, 129.9, 129.7, 126.5, 124.8, 123.5, 120.8, 119.1, 99.2, 53.2, 52.1, 52.0; ESIMS: m/z 577, 575 $[M+H]^+$, 599, 597 $[M+Na]^+$; Anal. Calcd for $C_{25}H_{23}BrN_2O_9$: C, 52.17; H, 4.01; N, 4.87%, Found: C, 52.19; H, 4.09; N, 4.83%.

Compound 2d: IR: 1727, 1639, 1460, 13641259 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.67 (1H, dd, J = 8.0, 2.0 Hz), 7.49 (1H, s), 7.33-7.16(5H, m), 7.03 (1H, t, J = 7.0 Hz), 6.98 (1H, s), 6.90(1H, dd, J = 8.0, 2.0 Hz), 4.82 (1H, s), 3.88 (3H, s), 3.83 (3H, s), 3.67 (3H,s), 3.61(3H, s), 3.52 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.8, 164.2, 164.0, 162.9, 160.1, 151.3, 143.5, 139.1, 131.5, 129.2, 127.1, 125.1, 124.2, 119.2, 118.0, 112.6, 97.4, 56.2, 53.2, 51.4, 51.1; ESIMS: m/z 527 $[M+H]^+$, 549 $[M+Na]^+$; Anal. Calcd for $C_{26}H_{26}N_2O_{10}$; C, 59.32; H, 4.99; N, 5.39%, Found: C, 59.45; H, 4.28; N, 5.33%.

Compound 2e: IR: 1734, 1641, 1584, 1438, 1246 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (1H, d, J = 2.0 Hz), 7.40-7.28 (4H, m), 7.19 (2H, d, J = 8.0 Hz), 7.12 (1H, s), 7.04 (1H, t, J = 7.0 Hz), 4.72 (1H, s), 3.90 (3H, s), 3.71 (3H, s), 3.62 (3H, s), 3.57(3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.3, 163.8, 163.2, 162.1, 162.2, 160.5, 150.8, 143.6, 138.3, 133.1, 131.2, 130.6, 130.0, 129.6, 127.8, 125.0, 124.2, 121.5, 118.4, 98.5, 53.2, 53.0, 52.1, 51,8; ESIMS: m/z 569, 567, 565 $[M+H]^+$; Anal. Calcd for C, 53.10; H, 3.98; N, 4.96%, Found: C, 53.15; H, 4.01; N, 4.87%.

Compound 2f: IR: 1727, 1641, 1532, 1438, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.92 (1H, d, J = 2.0 Hz), 8.16 (1H, dd, J = 8.0, 2.0 Hz), 7.47 (1H, s), 7.38 (2H, t, J = 8.0 Hz), 7.22 (2H, dd, J = 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 7.11 (1H, t, J = 8.0 Hz), 7.05(1H, s), 5.05 (1H, s), 3.89 (3H, s), 3.71 (3H, s), 3.62 (3H, s), 3.56 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.7, 164.2, 162.3, 159.6, 158.4, 155.9, 154.2, 146.1, 143.2, 139.5, 129.4, 128.7, 126.5, 124.6, 124.2, 122.0, 119.1, 112.1, 53.2, 51.9, 51.8; ESIMS: m/z 542 $[M+H]^+$, 564 $[M+Na]^+$; Anal. Calcd for C, 56.53; H, 4.23; N, 7.82%, Found: C, 55.45; H, 4.25; N, 7.76%.

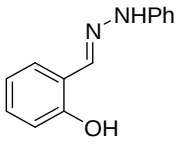
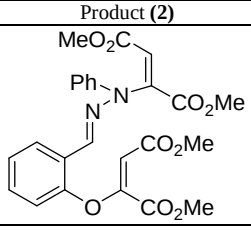
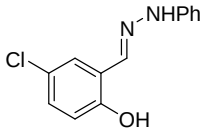
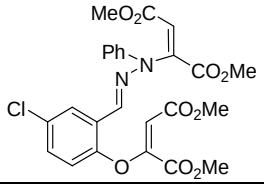
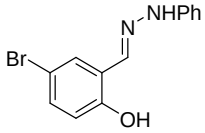
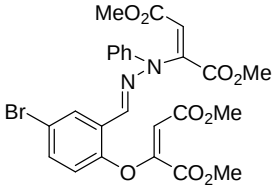
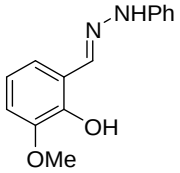
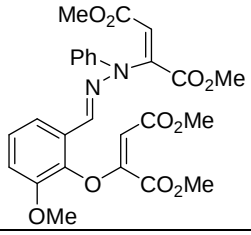
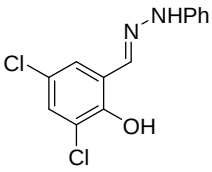
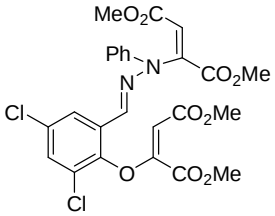
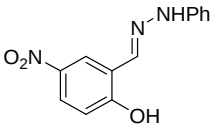
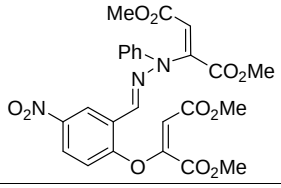
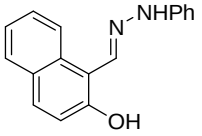
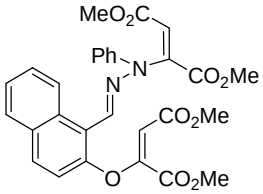
Compound 2g: IR: 1732, 1634, 1588, 1440, 1248 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.31 (1H, d, J = 8.0 Hz), 7.90 (1H, s), 7.84 (2H, d, J = 8.0 Hz), 7.70-7.51 (2H, m), 7.39-7.19 (5H, m), 7.11(1H, s), 7.05 (1H, t, J = 8.0 Hz), 4.92 (1H, s), 3.91 (1H, s), 3.72 (3H, s), 3.62 (3H, s), 3.53 (3H,s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5, 165.2, 164.3, 162.1, 160.5, 154.0, 151.7, 136.4, 133.2, 132.4, 131.5, 129.2, 129.0, 127.9, 127.2, 126.5, 126.1, 124.2, 119.9, 119.1, 99.2, 53.2,52.8, 52.7, 51.9; ESIMS: m/z 547 $[M+H]^+$, 569 $[M+Na]^+$; Anal. Calcd for C, 63.74; H, 4.76; N, 5.13%, Found: C, 63.68; H, 4.69; N, 5.18%.

Table 1: Reaction of salicyl N-phenyl hydrazone with dimethyl acetylenedicarboxylate using different bases

Entry	Base	Isolated Yield (%)
1	K_2CO_3	Trace
2	KOH	45
3	NaOH	41
4	tBuOK	85
5	Pyridine	73
6	LiOH	57
7	N-methyl piperidine	76

Reaction conditions: *hydrazone (1.0 mmol), diester (2.2 mmol), and base (100 mg) in THF under N_2, r.t, 40 min to 1 h.*

Table 2. Synthesis of multifunctional compounds (2)

Entry	Hydrazone **(1)**	Product **(2)**	Time (min)	Isolated Yield (%)
a			40	85
b			45	81
c			47	83
d			50	78
e			54	82
f			60	73
g			55	75

†The structures of the products were established from their spectral (IR, ^{1}H, ^{13}C and ESIMS) and analytical data.

RESULTS AND DISCUSSION

Initially salicyl N-phenylhydrazone was treated at room temperature with dimethyl acetylene dicarboxylate using various bases such as K_2CO_3, KOH, NaOH, ^{t}BuOK, Pyridine, LiOH, N-methyl pyperidine (**Table 1**). Considering the reaction time (1 h) and yield (85%) ^{t}BuOK was evaluated as the best catalyst. It was subsequently used to prepare a series of tetraester 2 from various salicyl N-phenylhydrazones 1 (**Table 2**). The hydrazones contained both electron-donating and electron-withdrawing groups in their aromatic rings. Different functional groups such as halogens, ethers, nitro and ester groups remained intact. The conversion was complete within 40 min to 1 h and the products were formed in high yields (73-85%). N-phenylhydrazone derived from 2-hydroxy-1-napthaldehyde also under-went the conversion smoothly (**Table 2**, entry **g**).

The products were formed by interaction of one molecule of salicyl N-phenylhydrazones with two molecules of dimethyl acetylene dicarboxylate. The structure of these products are interesting as they are multifunctional having ether, ester, C=C, C=N and PhN- functionalities. The imine system of the molecules has not at all been disturbed. More importantly, one of the olefinic diester moiety attached with the oxygen of the phenolic hydroxyl group is in (E)-configuration while the other olefinic double bond attached with the nitrogen of the hydrazone portion is in (Z)-configuration. The structures of the products were settled with the aid of spectroscopic (IR, ^{1}H, ^{13}C and ES-MS) and analytical data. The stereo configuration of the product can be rationalized as follows. In the presence of ^{t}BuOK the oxygen of the phenolic hydroxyl group of salicyl N-phenylhydrazones (**1**) attacks first triple bond of dimethyl acetylene dicarboxylate and the resultant olefinic diester moiety appears with stable (E)-form. However, next the nitrogen of the -NHPh function of **1** attacks the triple bond of the substrate diester to generate the olefinic diester moiety with less stereo-hindered (Z)-form.

CONCLUSION

In conclusion, we have demonstrated that the reaction of salicyl N-phenylhydrazones with dimethyl acetylene dicarboxylate in THF in the presence of ^{t}BuOK furnished the multifunctional molecules with interesting stereochemistry. Both (E) - and (Z) - olefinic double bonds are present in each molecule.

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