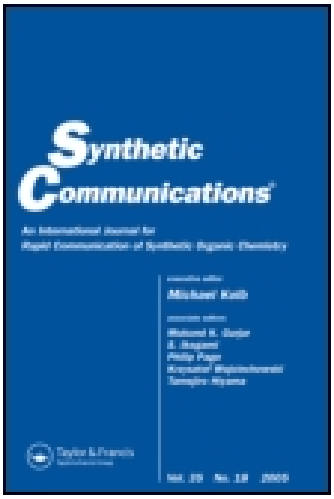

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Novel and Efficient Synthesis of 4-Indazolyl-1,3,4-trisubstituted Pyrazole Derivatives

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NOVEL AND EFFICIENT SYNTHESIS OF 4-INDAZOLYL-1,3,4-TRISUBSTITUTED PYRAZOLE DERIVATIVES

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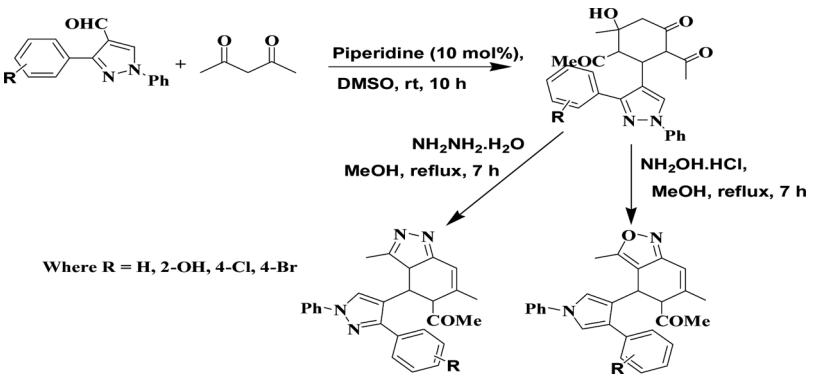
GRAPHICAL ABSTRACT



Abstract *In the present study, 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)-3aH-indazol-5-yl)methanone derivatives (**9–12**) and isoxazoleyl (**13–16**) have been synthesized by the condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (**1–4**) with acetyl acetone via Knoevenagel/Michael/aldol reactions in a sequential manner to yield intermediate cyclohexanone (**5–8**). The intermediates (**5–8**) treated with $NH_2NH_2 \cdot H_2O$/$NH_2OH \cdot HCl$ afforded 4-indazolyl-1,3,4-trisubstituted pyrazole and isoxazoleyl derivatives. All of these compounds are reported for the first time, and the structures of these compounds were confirmed by means of infrared, ^1H NMR, ^{13}C NMR, and mass spectroscopy.*

Keywords Acetyl acetone; cyclohexanone; indazolyl; isoxazoleyl

INTRODUCTION

Development of rapid access to N-heterocycles with complexity and diversity stemming from their wide occurrence in nature and broad applications in chemistry, biology, and material sciences has attracted considerable attention in the studies of chemical genetics.[1] In this respect, pyrazoles and indazoles are important synthetic

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targets in biologically active molecules, synthetic drugs, and drug candidates, and in addition, they can be used as ligands for generating metallic complexes.[2,3] The importance of these heterocyclic moieties has prompted the development of many practical synthetic routes to construct their derivatives.[4,5]

Substituted pyrazoles are rarely found in nature but serve as important synthetic targets in medicinal chemistry and pharmaceutical industries.[6] Both 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles constitute the useful structure of several commercial drugs such as celebrex,[7] Viagra,[8] acomplia, and the insecticide fipronil as well as numerous other compounds that exhibit a wide spectrum of biological and pharmacological properties such as antifungal,[9] antimicrobial,[10] antidiabetic,[11] herbicidal,[12,13] antitumor[14] and antianxiety,[15] activities and serve as active pharmacophores in celecoxib (COX-2 inhibitor)[16] and slidenafil citrate[17] (cGMP specific phosphodiesterase type 5) inhibitors. Substituted pyrazole derivatives play essential roles in biologically active compounds and therefore are an interesting template for medicinal chemistry.

There are several reactions reported for the preparation of pyrazole derivatives. Among them, the Knorr pyrazole synthesis is considered one of the standard methods because of its generality. The reaction leads to the pyrazole derivatives via the condensation of substituted hydrazine with 1,3-dicarbonyl compounds or their derivatives.[18–21] The other method is the 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes.[19] Recently, a novel regioselective synthesis of 1,3,4-trisubstituted pyrazoles has been successfully employed.[22] As successful as these two methods are in preparing pyrazoles with various substitution patterns, both are not particularly suitable for the regioselective synthesis of 1,3,4-trisubstituted pyrazole in neutral condition.

The 4-substituted pyrazoles are pharmaceutically important, yet less represented in the literature, probably because of synthetic difficulties.[23] Recently, Liu et al. reported moderate antitumor activity of 1-aryl-5-amino-4-pyrazolecarboxylate derivatives.[24,25] Lange et al. synthesized novel 3,4-diarylpyrazolines and evaluated cannabinoid (hCB1 and hCB2) receptors.[26] Liu et al. reported 2-ethoxyethyl-5-amino-3-methyl-1-phenyl-1H-pyrazol-4-carboxylate derivatives and found anticancer, fungicidal, and herbicidal activity.[27] Furthermore, no reports were found on the synthesis of 4-substituted indazolyl and isoxazoleyl derivatives of 1,3-diphenyl-1-*H*-pyrazole compounds.

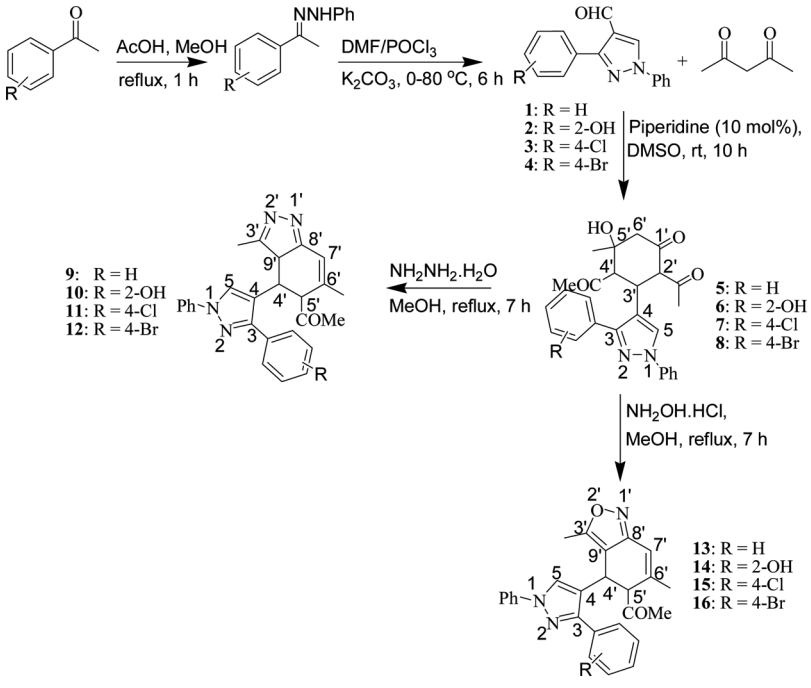
Keeping in view these points, we were prompted to synthesize functionalized 4-indazolyl substituted 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3a*H*-indazol-5-yl)methanone and 1,3-diphenyl-1*H*-pyrazole derivatives 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1-phenyl-1*H*-pyrazol-4-yl)benzo[c]isoxazole-5-yl)ethanone derivatives. To the best of our knowledge, this is the first time that this transformation has ever been documented. The reaction scope is quite broad on a range of substrates, and the functional group compatibility is excellent. Our method of preparation is simple, economical, and devoid of any toxic by-products during the reaction.

RESULTS AND DISCUSSION

The synthesis of target derivatives 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3a*H*-indazol-5-yl)methanone **9–12** and 1-(4,5-dihydro-3,

6-dimethyl-4-(1,3-diphenyl-1-phenyl-1*H*-pyrazol-4-yl)benzo[*c*]isoxazole-5-yl)ethanone **13–16** were synthesized as illustrated in Scheme 1. The key starting intermediates containing various substituted 1, 3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1–4** was prepared from two steps. The first one was the reaction between various substituted acetophenones with phenylhydrazine to afford hydrazone derivatves, which with Vilsmeier–Haack reagent (DMF-$POCl_3$) lead to the corresponding substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1–4** functionalized pyrazole heterocyclic ring in mild operating conditions.[28] Subsequently, acetyl acetone on condensation with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde via Knoevenagel, Michael, and intramolecular aldol reactions in solvent dimethylsulfoxide (DMSO) using piperidine (10 mol%) with stirring for 10 h in a sequential manner afforded 2,4-diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)cyclohexanone intermediates **5–8** with yields in the range of 79–66%.[29]

To synthesize the derivatives **9–12**, condensation reactions of 2,4-diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1*H*-pyrazol-4-yl) cyclohexanone derivatives **5–8** refluxed with $NH_2NH_2 \cdot H_2O$ in methanol for 7 h obtained 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3a*H*-indazol-5-yl)methanone derivatives **9–12**.[30] In an extension of this methodology, 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1-phenyl-1*H*-pyrazol-4-yl)benzo[c]isoxazole-5-yl)ethanone derivatives **13** were prepared in 66–71% yields by treatment of **5–8** with $NH_2NH_2 \cdot H_2O$ in the same manner, and the structures of **13–16** were examined by infrared (IR), ^{1}H NMR, ^{13}C NMR, and mass spectral data.



Scheme 1. Synthesis of 4-indazolyl-1,3,4-trisubstituted pyrazole and isoxazolyl derivatives.

The 2,4-diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)cyclohexanone **5** exhibited strong intensity OH broad stretching bands in the region 3440 cm^{-1} and strong C=O stretching bands in the region 1713 cm^{-1} due to the CH_3CO group, and weak stretching bands in the region 1692 cm^{-1} shows the C=O in cyclohexanone moiety. The weak bands in the region 1069 cm^{-1} show the C-N stretching vibrations in pyrazol ring. The C=O stretching bands appeared at 1741 cm^{-1} in 4-substituted indazolyl **9** and 1720 cm^{-1} in isoxazolyl derivatives **13**.

The ^{1}H NMR spectra of 2,4-diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)cyclohexanone (**5**) has the 6′-H proton at δ 3.782, dd, $J = 2.4$ Hz, coupled with 2′-H and hydroxyl proton. The 2′-H proton at δ 3.570, $J = 12$–13.8 Hz appears coupled with 3′-H proton whereas in target compound **9**, the 9′-H proton doublet at δ 1.897 with coupling constant $J = 9.9$ Hz is coupled with 4′-H proton. We concluded that there is formation of a five-member ring.

The 7′-H proton in 4-substituted indazolyl derivatives appears as a singlet at δ 4.913, but in isoxazolyl derivatives, the same proton appears as a singlet at δ 6.126, with formation of olefinic double bond due to dehydration. In isoxazoleyl derivatives **13**, 4′-H proton shows a doublet at δ 4.462, $J = 11.1$ Hz, coupled with 5′-H. It is a useful tool to confirm that there is no 9′-H proton.

In ^{13}C NMR spectrum of the cyclohexanone intermediates **5–8**, C-2 appears downfield at δ 71.0 ppm due to CH_3CO and C=O substitution, whereas in indazolyl and isoxazoleyl it shows upfield at δ 40.2 ppm. It is important to notice the absence of C=O group. The C-5 in **5–8** appears to peak in the range of δ 60.8–60.4 ppm, and in C-7 derivatives **9–16** appears as a signal at δ 121.9–107.0. This deshielding effect is due to the conjugation between five-membered heterocyclic and cyclohexene rings.

Considering first the cyclohexanone derivatives, the large coupling constants J_{2-3} ($J = 12.3$ Hz) and J_{3-4} ($J = 12.3$ Hz) are clearly indicative of *trans* diaxial protons. The large substituents at the neighboring carbon C-3 then must occupy the preferred equatorial positions. The hydroxyl proton was observed to be a doublet, $J = 2.4$ Hz, coupled to the axial proton 6_{Ha}, the resonance of which appeared as a doublet of doublets. This is one of the few instances known of long-range coupling to hydroxyl group (Fig. 1).[31] Addition of deuterium oxide caused the disappearance of the hydroxyl doublet and concurrent simplification of the 6_{Ha} pattern. It is suggested that strong hydrogen bonding of the hydroxyl proton with the neighboring 6_{Ha} and carbomethoxy function holds the hydroxyl proton in a conformation favorable for long-range coupling.

The plausible mechanism of target molecules for the formation of cyclohexanone derivatives **D** during the reaction of aldehyde and β-keto ester or ketone has already been reported by Enders et al.[32] It involves the Knoevenagel condensation of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with acetyl acetone to give a Knoevenagel product **A**, which undergoes a Michael addition of an active methylene compound via its enol form **B** to give an intermediate **C**. The latter undergoes intramolecular aldol condensation in the presence of a base to give an intermediate cyclized 2,4-diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)cyclohexanone **D**, which on treatment with $NH_2NH_2 \cdot H_2O/NH_2OH \cdot HCl$ afforded 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3a*H*-indazol-5-yl)methanone **E** and 1-(4,5-dihydro-3,6-dimethyl-4-(1,3-diphenyl-1-phenyl-1*H*-pyrazol-4-yl)benzo[c]isoxazole-5-yl) ethanone **F** derivatives.

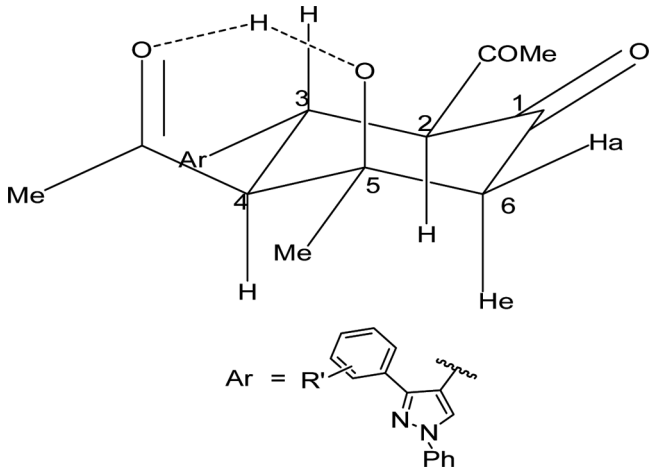


Figure 1. Conformational studies of cyclohexanone derivatives.

CONCLUSIONS

In conclusion, we have demonstrated a simple, convenient, efficient method for the preparation of functionalized 4-indazolyl and isoxazolyl substituted of 1,3,4-trisubstituted pyrazole derivatives via domino Knoevenagel, Michael and intramolecular aldol reactions to give cyclohexanone derivatives, followed by treatment with $NH_2NH_2 \cdot H_2O/NH_2OH \cdot HCl$. The procedure offers several advantages such as easy workup process, excellent yield of products, operational simplicity, and minimum environmental impact, making the technology practical, easy to perform, and facile.

EXPERIMENTAL

All chemicals and reagents used in the current study were of analytical grade. Melting points were determined with a digital thermometer and were uncorrected. The IR absorption spectra were scanned on Perkin-Elmer Spectrum, BX II FTIR spectrometer using potassium bromide (KBr) pellets, and the wave numbers are given in cm^{-1}. All the ^1H NMR spectra were recorded on a Bruker DPX300 model spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard, the chemical shifts are reported in δ units, and the coupling constants (*J*) are reported in hertz. Multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet) and mass spectra were recorded. Thin-layer chromatography (TLC) was performed on silica-gel sheets (silica gel 60 F_{254}, Merck) and visualized in ultraviolet light (254 nm). Column chromatography was performed using silica gel (100–200 mesh), eluting with ethyl acetate and petroleum ether solvent.

Procedure for the Preparation of 2,4-Diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)cyclohexanone (5–8)

To a magnetically stirred solution of acetyl acetone (2 mmol) and different substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (1 mmol) **1–4** in dimethylsulfoxide

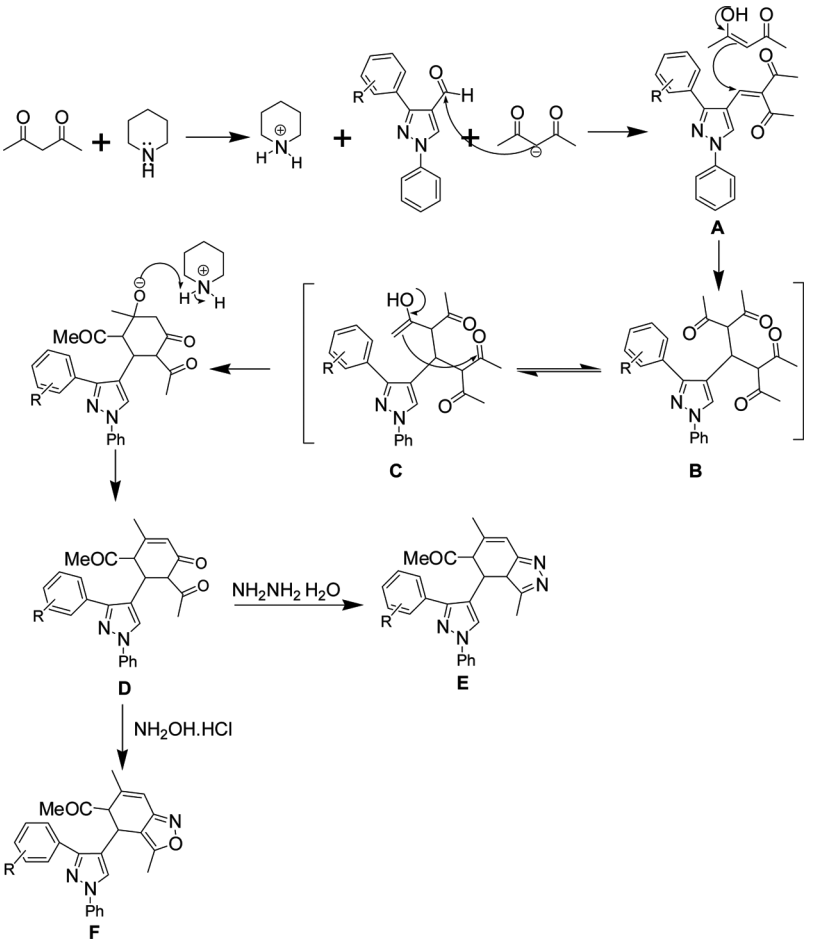


Figure 2. Plausible mechanisms.

(10 mL), 20 mol% of piperidine was added to the reaction mixture and refluxed 10 h. The progress of reaction checked by (TLC). After completion, the reaction mixture was quenched with ice water, acidified with diluted. HCl, extracted with chloroform, dried over sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography over SiO_2 (100–200 mesh) using ethylacetate–petroleum ether as an eluent to give the desired product.

2,4-Diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1*H*-4-yl)cyclohexanone (5)

Faint white; yield: 79%; mp = 146–148 °C; IR υ_{max} (KBr, cm^{-1}) 3440, 3060, 2966, 2884, 1713, 1692, 1600, 1538, 1503, 1449, 1415, 1069, 964, 855, 776, 651; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.706 (m, 10 H), 7.636 (s, 1H), 3.782 (dd,

$J = 2.43$ Hz, 2H), 3.778 (d, $J = 2.4$ Hz, 1H), 3.570 (d, $J = 2.4$ Hz, 1H), 3.216 (t, 1H), 2.036 (s, 3H), 2.018 (s, 1H), 1.909 (s, 3H), 1.233 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 209.8, 208.5, 203.2, 150.2, 139.7, 133.3, 129.6, 129.5, 128.8, 127.4, 126.3, 120.4, 117.7, 71.2, 60.9, 60.7, 53.3, 29.5, 28.8, 24.3, 9.4. Anal. calc. for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27; O, 14.33%. Found: C, 72.64; H, 6.79; N, 6.25; O, 14.31%

Procedure for the Preparation of Derivatives 9–16

The mixture of 2,4-diacetyl-5-hydroxy-5-methyl-3-(1,3-diphenyl-1H-pyrazol-4-yl)cyclohexanone (1 mmol) **5–8** and the requisite $NH_2NH_2 \cdot H_2O/NH_2OH \cdot HCl$ (4 mmol) in methanol (15 mL) was refluxed for 7 h. The reaction was monitored by TLC. After completion, the reaction mixture was quenched in ice water, extracted with chloroform, dried over sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography to give the desired product.

1-(4,5-Dihydro-3,6-dimethyl-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3a*H*-indazol-5-yl) Methanone (9)

Faint white; yield: 73%; mp = 100–102 °C; IR υ_{max} (KBr, cm^{-1}) 3622, 3058, 2924, 2854, 1741, 1696, 1643, 1598, 1500, 1448, 1062, 959, 758, 692; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.710 (m, 10 H), 7.225 (s, 1H), 4.913 (s, 1H), 3.506 (d, $J = 13.8$ Hz, 1H), 3.013 (t, 1H), 2.223 (s, 3H), 2.060 (t, 3H), 1.951 (s, 3H), 1.897 (d, $J = 9.9$ Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 203.5, 164.6, 150.3, 139.6, 133.4, 129.6, 129.3, 128.6, 127.5, 126.4, 123.3, 120.4, 117.8, 107.3, 58.4, 40.5, 29.6, 27.7, 20.8, 16.3. Anal. calc. for $C_{26}H_{26}N_4O_2$: C, 76.07; H, 6.38; N, 13.65; O, 3.90%. Found: C, 76.10; H, 6.40; N, 13.67; O, 3.87%.

1-(4,5-Dihydro-3,6-dimethyl-4-(1,3-diphenyl-1-phenyl-1*H*-pyrazol-4-yl)benzo[c] isoxazole-5-yl) Ethanone (13)

Faint white; yield: 71%; mp = 85–87 °C; IR υ_{max} (KBr, cm^{-1}) 2999, 2876, 1720, 1668, 1614, 1479, 1373, 1024, 991, 873, 778, 648; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.708 (m, 10H), 7.612 (s, 1H), 6.126 (s, 1H), 4.462 (d, $J = 11.1$ Hz, 1H), 3.345 (d, $J = 10.6$ Hz, 1H), 2.185 (s, 3H), 2.047 (s, 3H), 1.873 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 203.5, 158.9, 150.4, 141.7, 139.8, 133.4, 129.7, 129.6, 128.8, 127.7, 126.5, 123.3, 121.9, 120.5, 117.6, 100.7, 74.3, 62.8, 29.7, 29.4, 20.5. Anal. calc. for $C_{27}H_{27}N_3O_2$: C, 76.21; H, 6.40; N, 9.87; O, 7.52%. Found: C,76.23; H, 6.42; N, 9.85; O, 7.50%.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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