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A simple synthesis of 2-{2-[(arylmethylidene)amino]-indazol-3-yl}malonate esters

Lyubov I. Kuznetsova[1], Alexey O. Chagarovskiy[1,2], Irina I. Levina[3], Victor B. Rybakov[4], Olga A. Ivanova[1,4]*, Igor V. Trushkov[1,2]*

[1] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., Moscow 119991, Russia; e-mail: trush@ioc.ac.ru*

[2] *Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, 1 Samory Mashela St., Moscow 117997, Russia*

[3] *M. N. Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, 4 Kosygina St., Moscow 119334, Russia*

[4] *Lomonosov Moscow State University, 1 Build. 3 Leninskie Gory, Moscow 119991, Russia; e-mail: iv@kinet.chem.msu.ru*

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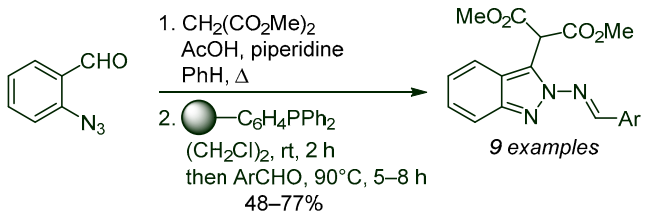


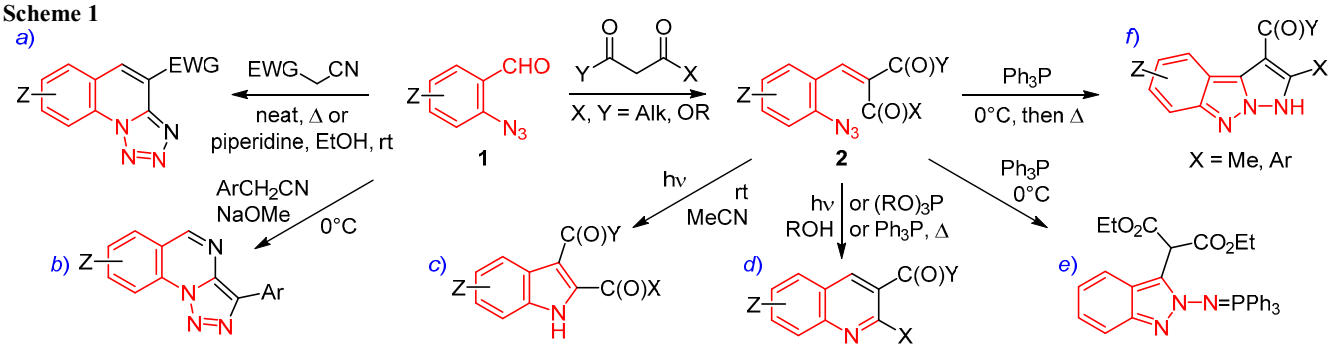
A method was developed for the synthesis of dimethyl {2-[(arylmethylidene)amino]-2*H*-indazol-3-yl}malonates on the basis of a Knoevenagel condensation between 2-azidobenzaldehyde and dimethyl malonate, followed by treatment of the obtained adduct with aromatic aldehydes in the presence of polymer-supported triphenylphosphine. It was shown that the interaction of the synthesized Schiff bases with Corey ylide provided a route for the synthesis of 2-(aziridin-1-yl)indazoles.

Keywords: aldehydes, alkenes, aziridines, indazoles, organic azides.

Polyfunctional reagents continue to attract significant interest of synthetic organic chemists, since the presence of several functional groups with a relative arrangement enables a wide range of chemical transformations in such compounds, making them convenient building blocks for the assembly of natural compounds, synthetic pharmaceutical substances, and other products with useful properties.

One of such polyfunctional reagents is 2-azidobenzaldehyde (**1**), the azide and formyl groups of which may participate in a wide range of transformations leading to a signifacant increase of structural complexity.[1] Among such transformations, diverse condensations of the aldehyde group with CH acids, followed by the involvement of the azide group in the formation of a new ring form one of the most important groups. The chemoselectivity of these reactions depends both on the nature of the CH acid and reaction conditions. Thus, suitable nitriles reacted with 2-azidobenzaldehyde (**1**), leading to the formation of either tetrazolo[1,5-*a*]quinolines (Scheme 1*a*)[2–4] or triazolo[1,5-*a*]quinazolines (Scheme 1*b*).[4,5] However, the reaction of 2-azidobenzaldehyde (**1**) with dialkyl malonates, keto esters, or 1,3-diketones produced the "classic" Knoevenagel adducts **2**, which upon irradiation were converted into either 2,3-substituted indoles (Scheme 1*c*)[6,7] or quinolines (Scheme 1*d*).[7] The latter were also formed by treatment with sodium sulfide,[3] triethyl phosphite,[8] and triphenylphosphine[9] (Scheme 1*d*). At the same time, Molina et al. reported that diethyl (2-azidobenzylidene)-malonate in the presence of triphenylphosphine was converted into an indazole derivative (Scheme 1*e*).[10] The formation of this compound was recognized to be of great practical significance, since such iminophosphoranes can be efficiently transformed not only into various

Scheme 1



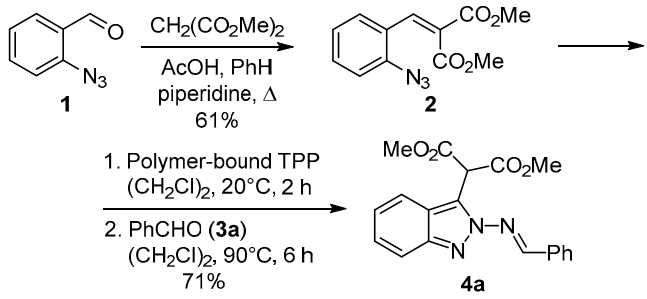
2-aminoindazole derivatives having a significant pharmacological potential,[11] but also into certain polyheterocyclic compounds that may find applications both as biologically active agents[12] and in the field of materials science. Unfortunately, Molina et al. provided only a single example for the given transformation. As recently demonstrated by the Ding research group,[13] pyrazolo[1,5-*b*]indazoles were formed from the corresponding 1,3-diketones, β-keto esters, and β-ketoamides under similar conditions (Scheme 1*f*). For these reasons, there has been a significant interest in detailed study of this remarkable transformation, including the factors directing reaction of (2-azidobenzylidene)malonates with triphenylphosphine, and in the synthesis of new 2-aminoindazole derivatives.

In the current work, we studied the interaction of dimethyl 2-(2-azidobenzylidene)malonate (**2**) with aromatic aldehydes **3a**–**i** in the presence of polymer-supported triphenylphosphine at room temperature. It was shown that the products were ({2-[(het)arylmethylidene]amino}-indazol-3-yl)malonates **4a**–**i** – a previously unknown subtype of indazole derivatives.

The most efficient method for the preparation of the starting material – 2-azidobenzaldehyde (**1**) is the reaction of 2-nitrobenzaldehyde with NaN_3 in hexamethylphosphoramide (HMPA),[14] but this solvent has been categorized as undesirable due to its carcinogenic properties. Another study published by Gribble in 1997 proposed to perform this reaction *via* moderate heating in DMF.[15] Indeed, 2-azidobenzaldehyde (**1**) was formed under those conditions in a quite high yield. A subsequent step involving the Knoevenagel reaction of 2-azidobenzaldehyde (**1**) and dimethyl malonate allowed to obtain dimethyl 2-(2-azidobenzylidene)malonate (**2**) (Scheme 2). It is important to note that this reaction must be performed using PhH as solvent, since refluxing the mixture in PhMe resulted in a spontaneous decomposition, associated with a significant heating of the reaction mixture and dangerous gas evolution.

After the synthesis of azidoalkene **2**, we studied its reaction with triphenylphosphine and benzaldehyde (**3a**), finding that the sole product of this reaction was 2-(benzylidenamino)indazole **4a** (Scheme 2), the formation of which was in agreement with the mechanism of interrupted Staudinger reaction (Scheme 1*e*),[10] but not with direct formation of iminophosphorane, which would be the reaction intermediate giving rise to quinolines (Scheme 1*d*).[9]

Scheme 2



We also found that during the synthesis of indazole **4a**, it is advantageous to use polymer-supported triphenylphosphine. Even though this approach required a longer time for achieving a complete conversion of azidoalkene, the immobilized phosphine and its transformation products could be easily removed by filtration after the completion of the reaction, not only providing for an easier experimental procedure, but also substantially improving the yield of compound **4a**, compared to the use of triphenylphosphine itself. The structure of product **4a** was confirmed on the basis of X-ray structural analysis results (Fig. 1).

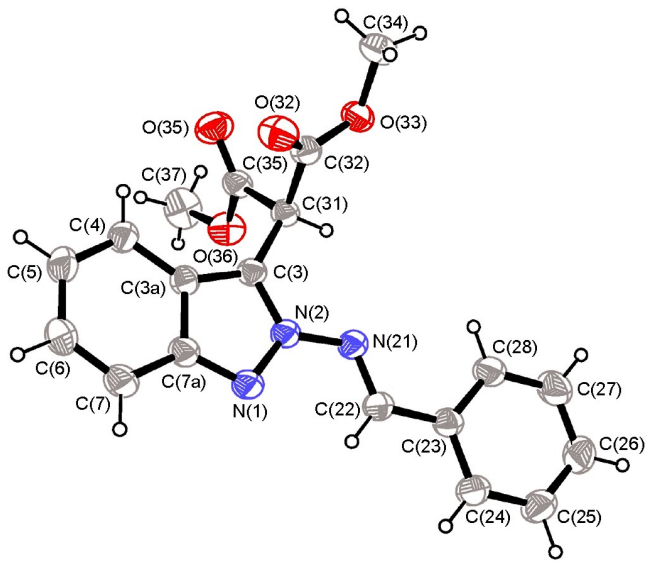


Figure 1. The molecular structure of compound **4a** with atoms represented by thermal vibration ellipsoids of 30% probability.

We studied the scope of applicability for this reaction and demonstrated that various aromatic aldehydes **3b–i** containing either electron-donating or electron-withdrawing groups afforded (2-{[(het)arylmethylidene]amino}indazol-3-yl)malonates **4b–i** in good yields (Scheme 3, Table 1). Aldehydes with heteroaromatic substituents also can be efficiently involved into the given process.

Scheme 3

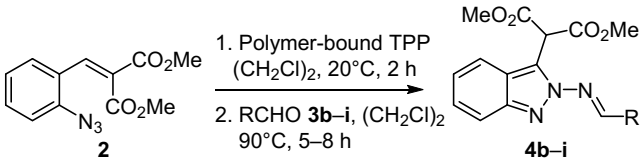


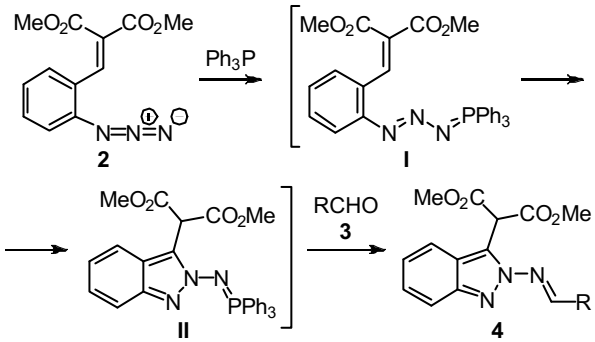
Table 1. The reaction conditions and isolated yields in the synthesis of iminoindazoles **4b–i**

Compound	R	Reaction time, h	Yield, %
4b	3-BrC_6H_4	6	75*
4c	4-MeOC_6H_4	6	48*
4d	Thiophen-2-yl	6	77*
4e	4-MeC_6H_4	5	77**
4f	4-FC_6H_4	5	71**
4g	4-O_2NC_6H_4	8	48**
4h	5-Me-furan-2-yl	5	59**
4i	5-Me-thiophen-2-yl	5	63**

* Yield after chromatographic purification.
** Yield after recrystallization from 1:1 mixture of CH_2Cl_2 – petroleum ether.

The reaction leading to the preparation of indazoles **4** can be viewed as a domino process: the initial formation of phosphazene intermediate **I** was followed by its cyclization, leading to iminophosphorane **II**. As a result of the reaction between iminophosphorane **II** and (hetero)-aromatic aldehydes **3**, the target imines **4** were obtained (Scheme 4).

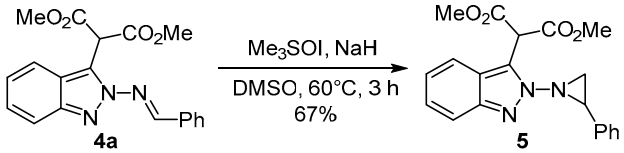
Scheme 4



Comparison of the reaction conditions that resulted in the formation of either indazoles or quinolines from 2-azidobenzylidene derivatives of malonic acid, β-keto esters, and 1,3-diketones showed that the temperature regime and the nature of phosphorus(III) reagent were the key factors determining the reaction chemoselectivity. The use of triphenylphosphine at room temperature (in this study) or at 0°C[10,13] led to the formation of indazole derivatives *via* an interrupted Staudinger reaction. On the other hand, if the reaction with triphenylphosphine was performed under heating,[9] rapid elimination of a molecular dinitrogen was observed, with the formation of iminophosphoranes according to the typical course of the Staudinger reaction.

We demonstrated the significant synthetic potential of the synthesized Schiff bases by using the example of imine **4a** as a model compound in a Corey–Chaykovsky reaction.[16] As a result of this interaction, aziridine **5** was obtained in a 67% yield (Scheme 5). The respective aziridines are polyfunctional compounds that could be subjected to further structural modifications for the purpose of assembling important biologically active molecules.

Scheme 5



The structure of product **5** was established on the basis of the data obtained from ^{1}H–^{13}C HMBC experiment. Thus, signals of the methylene group protons of the small ring appeared as double doublets at 2.70 and 3.78 ppm and exhibited cross peaks with the quaternary carbon atom of the phenyl substituent at 136.6 ppm. The signal of the methine proton of the malonate residue at 5.76 ppm correlated with the quaternary carbon atom signals of the indazole system at 120.2 and 124.6 ppm (Fig. 2).

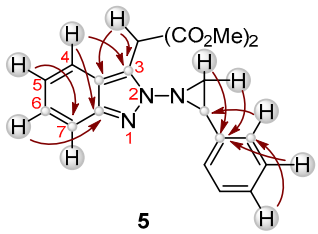


Figure 2. The characteristic correlations in ^{1}H–^{13}C HMBC spectrum of compound **5**.

Thus, we have developed a simple method for the preparation of substituted 2-{2-[(arylmethylidene)amino]-indazol-3-yl}malonate esters on the basis of a reaction between 2-azidobenzylidenemalonate and aromatic aldehydes in the presence of polymer-supported triphenylphosphine. The results of this work provide a contribution to understanding the effects of the reagent type and reaction conditions on the chemoselectivity in the reactions between 2-azidobenzylidene derivatives of a CH acid and phosphines.

Experimental

IR spectra were recorded on a Thermo Scientific Nicolet IR 200 FT-IR spectrometer with the spectral resolution of 4 cm^{-1}, the number of scans was 20, using a ZnSe ATR

accessory with an incidence angle of 45°. ^{1}H and ^{13}C NMR spectra (500 and 126 MHz, respectively), as well as the two-dimensional ^{1}H–^{13}C HMBC, ^{1}H–^{13}C HSQC, and ^{1}H–^{15}N HMBC experiments were acquired on a Bruker Avance-500 instrument, using the residual solvent signals as internal standard ($CDCl_3$: 7.26 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei; CD_3OD: 3.31 ppm for ^{1}H nuclei, 49.0 ppm for ^{13}C nuclei). High-resolution mass spectra with electrospray ionization were recorded on an LTQ Orbitrap Elite instrument for samples in MeCN–H_2O solutions, using HCO_2Na–HCO_2H for calibration. Elemental analysis was performed on a Fisons EA-1108 instrument.

The starting materials used in this study were commercially available reagents. The polymer-supported triphenylphosphine was a diphenylphosphinylated copolymer of styrene and divinylbenzene (CAS 39319-11-4), with the triphenylphosphine content of the polymer equivalent to 3 mmol/g.

2-Azidobenzaldehyde (1).[15] A solution of *o*-nitrobenzaldehyde (8.0 g, 53 mmol) in anhydrous DMF (106 ml) was stirred under argon atmosphere and treated by the addition of NaN_3 (6.89 g, 1.06 mmol). The reaction mixture was heated on an oil bath at 60°C for 20 h, then cooled, and poured into ice water (70 ml). The aqueous phase was extracted with EtOAc (5×30 ml), then washed with brine (5×20 ml) and H_2O (2×20 ml). Yield 4.36 g (56%). The physicochemical characteristics of the obtained azide **1** were in agreement with those described earlier.[15,17]

Dimethyl 2-(2-azidobenzylidene)malonate (2). A solution of 2-azidobenzaldehyde (**1**) (4.75 g, 32.3 mmol) and dimethyl malonate (3.69 ml, 32.3 mmol) in PhH (10 ml) was treated by the addition of glacial AcOH (0.37 ml, 6.5 mmol) and piperidine (0.13 ml, 1.3 mmol). The reaction mixture was refluxed in a flask equipped with a Dean–Stark trap until the evolution of H_2O ceased. The organic layer was washed with brine (4×10 ml) and dried with anhydrous Na_2SO_4. PhH was evaporated at reduced pressure, the residue was purified by column chromatography on silica gel using a petroleum ether – EtOAc eluent system with a gradient from 20:1 to 4:1. Yield 4.26 g (61%), yellow solid, mp 85–86°C, R_f 0.58 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 2954, 2451, 2139, 2106, 1735, 1693, 1626, 1595, 1481, 1456, 1392, 1315, 1267, 1221, 1093, 1063, 976, 933. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.75 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 7.08 (1H, ddd, ^3J = 8.4, ^3J = 8.0, ^4J = 0.6, H Ar); 7.16 (1H, dd, ^3J = 8.1, ^4J = 0.6, H Ar); 7.33 (1H, dd, ^3J = 8.0, ^4J = 1.5, H Ar); 7.40 (1H, ddd, ^3J = 8.4, ^3J = 8.1, ^4J = 1.5, H Ar); 7.95 (1H, s, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 52.5; 52.7; 118.5; 124.7; 124.8; 126.6; 128.9; 131.7; 138.1; 139.6; 164.2; 166.6. Found, *m*/*z*: 262.0823 [M+H]$^+$. $C_{12}H_{12}N_3O_4$. Calculated, *m*/*z*: 262.0822. Found, %: C 55.16; H 4.23; N 16.08. $C_{12}H_{11}N_3O_4$. Calculated, %: C 55.17; H 4.24; N 16.09.

Synthesis of compounds 4a–d (General method). A solution of azidoalkene **2** in 1,2-dichloroethane was stirred under argon atmosphere and treated with 2 equiv of polymer-supported triphenylphosphine. The obtained mixture was stirred at room temperature for 2 h, followed by the addition of the appropriate aldehyde **3a**–**d** and refluxing at 90°C for 6 h. The solid polymer was removed by filtration and washed with 1,2-dichloroethane (2×5 ml). The filtrate was concentrated at reduced pressure, the residue was purified by chromatography on alumina (petroleum ether – EtOAc eluent system, gradient from 20:1 to 4:1).

Dimethyl {2-[(phenylmethylidene)amino]-2*H*-indazol-3-yl}malonate (4a) was obtained from a solution of compound **2** (1.0 g, 3.83 mmol) in 1,2-dichloroethane (20 ml), using polymer-supported triphenylphosphine (2.55 g, 7.65 mmol) and benzaldehyde (**3a**) (0.71 ml, 7.67 mmol). Yield 0.95 g (71%), colorless crystals, mp 126.4–127.7°C (CH_2Cl_2), R_f 0.51 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3066, 3037, 3018, 2954, 1751, 1739, 1598, 1574, 1477, 1448, 1436, 1319, 1309, 1273, 1198, 1153, 1016. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.82 (6H, s, 2OCH_3); 5.94 (1H, s, CH); 7.15–7.18 (1H, m, H Ar); 7.38–7.42 (1H, m, H Ar); 7.51–7.57 (3H, m, H Ar); 7.72–7.76 (2H, m, H Ar); 7.97–8.00 (2H, m, H Ar); 9.54 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 48.7 (CH); 53.2 (2OCH_3); 117.4 (CH Ar); 120.5 (CH Ar); 120.9 (C Ar); 122.6 (CH Ar); 122.5 (C Ar); 127.9 (CH Ar); 129.0 (4CH Ar); 132.0 (CH Ar); 132.6 (C Ar); 145.9 (C Ar); 153.6 (CH=N); 166.8 (2$\underline{C}O_2CH_3$). Found, *m*/*z*: 352.1298 [M+H]$^+$. $C_{19}H_{18}N_3O_4$. Calculated, *m*/*z*: 352.1292. Found, %: C 64.69; H 4.87; N 11.56. $C_{19}H_{17}N_3O_4$. Calculated, %: C 64.95; H 4.88; N 11.96.

Dimethyl (2-{[(3-bromophenyl)methylidene]amino}-2*H*-indazol-3-yl)malonate (4b) was obtained from a solution of compound **2** (0.50 g, 1.92 mmol) in 1,2-dichloroethane (29 ml), using polymer-supported triphenylphosphine (1.28 g, 3.84 mmol) and 3-bromobenzaldehyde (**3b**) (0.69 ml, 5.89 mmol). Yield 0.62 g (75%), colorless crystals, mp 112–113°C, R_f 0.54 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3019, 2959, 1757, 1739, 1603, 1557, 1520, 1430, 1383, 1350, 1294, 1280, 1215, 1199, 1178, 1070. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.83 (6H, s, 2OCH_3); 5.89 (1H, s, CH); 7.14 (1H, ddd, ^3J = 8.5, ^3J = 6.7, ^4J = 0.5, H Ar); 7.36–7.41 (2H, m, H Ar); 7.66 (1H, ddd, ^3J = 8.1, ^4J = 1.8, ^4J = 1.1, H Ar); 7.69 (1H, br. d, ^3J = 8.9, H Ar); 7.72 (1H, br. d, ^3J = 8.5, H Ar); 7.84 (1H, br. d, ^3J = 7.6, H Ar); 8.12 (1H, dd, ^4J = 1.8, ^4J = 1.2, H Ar); 9.46 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 48.7 (CH); 53.2 (2OCH_3); 117.5 (CH Ar); 120.6 (CH Ar); 121.0 (C Ar); 122.8 (CH Ar); 123.2 (C Ar); 125.5 (C); 127.9 (CH Ar); 128.1 (CH Ar); 130.5 (CH Ar); 131.2 (CH Ar); 134.7 (C Ar); 134.8 (CH Ar); 146.0 (C Ar); 152.1 (CH=N); 166.6 (2$\underline{C}O_2CH_3$). Found, *m*/*z*: 430.0397 [M+H]$^+$. $C_{19}H_{17}BrN_3O_4$. Calculated, *m*/*z*: 430.0397. Found, %: C 53.20; H 3.75; N 9.77. $C_{19}H_{16}BrN_3O_4$. Calculated, %: C 53.04; H 3.75; N 9.77.

Dimethyl (2-{[(4-methoxyphenyl)methylidene]amino}-2*H*-indazol-3-yl)malonate (4c) was obtained from a solution of compound **2** (0.20 g, 0.77 mmol), using polymer-supported triphenylphosphine (0.51 g, 1.53 mmol) in 1,2-dichloroethane (4 ml) and 4-methoxybenzaldehyde (**3c**) (0.17 ml, 1.53 mmol). Yield 141 mg (48%), yellowish

crystals, mp 157–159°C, R_f 0.56 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3036, 3009, 2922, 2900, 2807, 1734, 1717, 1583, 1550, 1499, 1419, 1364, 1293, 1266, 1236, 1198, 1155, 1143, 1021, 1007, 971. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.77 (6H, s, $2OCH_3$); 3.86 (3H, s, OCH_3); 5.87 (1H, s, CH); 6.98 (2H, br. d, ^3J = 8.8, H Ar); 7.08–7.11 (1H, m, H Ar); 7.31–7.35 (1H, m, H Ar); 7.65–7.68 (2H, m, H Ar); 7.87 (2H, br. d, ^3J = 8.8, H Ar); 9.42 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 48.7 (CH); 53.1 ($2OCH_3$); 55.4 (OCH_3); 114.5 (2CH Ar); 117.3 (CH Ar); 120.4 (CH Ar); 120.8 (C Ar); 122.4 (CH Ar); 124.6 (C); 125.3 (C Ar); 127.5 (CH Ar); 130.9 (2CH Ar); 145.6 (C Ar); 153.2 (CH=N); 162.8 (C Ar); 166.8 ($2\underline{C}O_2CH_3$). Found, *m*/*z*: 382.1391 $[M+H]^+$. $C_{20}H_{20}N_3O_5$. Calculated, *m*/*z*: 382.1397. Found, %: 62.62; H 5.08; N 10.90. $C_{20}H_{19}N_3O_5$. Calculated, %: C 62.99; H 5.02; N 11.02.

Dimethyl 2-(2-{[(thien-2-yl)methylidene]amino}-2*H*-indazol-3-yl)malonate (4d) was obtained from a solution of compound **2** (0.30 g, 1.15 mmol) in 1,2-dichloroethane (6 ml), using polymer-supported triphenylphosphine (0.76 g, 2.3 mmol) and 2-thienylcarbaldehyde (**3d**) (0.21 ml, 2.3 mmol). Yield 0.32 g (77%), yellowish crystals, mp 93–94°C, R_f 0.58 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3080, 3019, 2959, 1748, 1735, 1587, 1438, 1323, 1269, 1157, 1018. ^1H NMR spectrum ($CDCl_3$ + CD_3OD), δ, ppm (*J*, Hz): 3.81 (6H, s, $2OCH_3$); 5.84 (1H, s, CH); 7.10–7.14 (1H, m, H Ar); 7.17 (1H, dd, ^3J = 5.0, ^3J = 3.6, H thiophene); 7.33–7.37 (1H, m, H Ar); 7.58 (1H, br. d, ^3J = 5.0, H thiophene); 7.60 (1H, br. d, ^3J = 3.6, H thiophene); 7.65–7.69 (2H, m, H Ar); 9.63 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD), δ, ppm: 48.5 (CH); 53.1 ($2OCH_3$); 117.1 (CH Ar); 120.3 (CH Ar); 120.8 (C Ar); 122.5 (C Ar); 124.7 (C Ar); 127.7 (CH Ar); 128.0 (CH Ar); 131.3 (CH Ar); 134.2 (CH Ar); 137.3 (CH Ar); 145.7 (C Ar); 147.6 (CH=N); 166.7 ($2\underline{C}O_2CH_3$). Found, *m*/*z*: 358.0860 $[M+H]^+$. $C_{17}H_{16}N_3O_4S$. Calculated, *m*/*z*: 358.0856.

Synthesis of compounds 4e–i (General method). A 10-ml screw cap vial was charged with a solution of azide **2** (140 mg, 0.54 mmol) in 1,2-dichloroethane (5.4 ml), then polymer-supported triphenylphosphine (355 mg, 1.07 mmol) was added and the mixture was stirred until complete conversion of the starting azide (control by TLC) at room temperature (1–2 h), followed by the addition of the appropriate aldehyde **3e–i** (1.62 mmol). The reaction mixture was stirred in a sealed vial at 90°C for 5 h, after which the precipitate was removed by filtration and washed once with CH_2Cl_2 (10 ml). The filtrate was evaporated at reduced pressure and precipitated with petroleum ether. The obtained solid precipitate was dried and recrystallized as necessary from 1:1 mixture of CH_2Cl_2 – petroleum ether.

Dimethyl (2-{[(4-methylphenyl)methylidene]amino}-2*H*-indazol-3-yl)malonate (4e). Yield 150 mg (77%), beige crystals, mp 159–160°C, R_f 0.50 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3030, 2960, 1755, 1740, 1600, 1435, 1310, 1280, 1155, 1020, 1000, 815, 750. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 (3H, s, CH_3); 3.81 (6H, s, $2OCH_3$); 5.94 (1H, s, CH); 7.13–7.16 (1H, m, H Ar); 7.31–7.33 (2H, m, H Ar); 7.36–7.39 (1H, m, H Ar); 7.70–7.74 (2H, m, H Ar); 7.85–7.87 (2H, m, H Ar); 9.50 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.8 (CH_3); 48.8 (CH); 53.2 ($2OCH_3$); 117.4 (CH Ar); 120.6 (CH Ar); 121.0 (C Ar); 122.6 (CH Ar); 125.1 (C Ar); 127.8 (CH Ar); 129.1 (2CH Ar); 129.8 (2CH Ar); 130.0 (C Ar); 142.9 (C Ar); 145.8 (C Ar); 153.8 (CH=N); 166.9 ($2\underline{C}O_2CH_3$). Found, *m*/*z*: 366.1449 $[M+H]^+$. $C_{20}H_{20}N_3O_4$. Calculated, *m*/*z*: 366.1448.

Dimethyl (2-{[(4-fluorophenyl)methylidene]amino}-2*H*-indazol-3-yl)malonate (4f). Yield 141 mg (71%), beige crystals, mp 162–163°C, R_f 0.47 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3075, 3005, 2955, 1760, 1745, 1600, 1585, 1510, 1480, 1435, 1380, 1305, 1230, 1155, 1015, 880, 830, 750. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.81 (6H, s, $2OCH_3$); 5.90 (1H, s, CH); 7.12–7.20 (3H, m, H Ar); 7.35–7.38 (1H, m, H Ar); 7.68–7.73 (2H, m, H Ar); 7.93–7.96 (2H, m, H Ar); 9.48 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 48.8 (CH); 53.3 ($2OCH_3$); 116.4 (d, $^2J_{CF}$ = 22, 2CH Ar); 117.5 (CH Ar); 120.6 (CH Ar); 121.0 (C Ar); 122.7 (CH Ar); 125.3 (C Ar); 128.0 (CH Ar); 128.9 (d, $^4J_{CF}$ = 3, C Ar); 131.2 (d, $^3J_{CF}$ = 9, 2CH Ar); 145.9 (C Ar); 152.5 (CH=N); 165.1 (d, $^1J_{CF}$ = 254, C Ar); 166.8 ($2\underline{C}O_2CH_3$). Found, *m*/*z*: 370.1195 $[M+H]^+$ $C_{19}H_{17}FN_3O_4$. Calculated, *m*/*z*: 370.1198.

Dimethyl (2-{[(4-nitrophenyl)methylidene]amino}-2*H*-indazol-3-yl)malonate (4g). Reaction time 8 h. Yield 102 mg (48%), bright-yellow crystals, mp 201–202°C, R_f 0.28 (petroleum ether – EtOAc, 2:1). IR spectrum, ν, cm^{-1}: 3065, 2950, 2850, 1755, 1740, 1520, 1440, 1340, 1305, 1280, 1220, 1155, 845, 755. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.74 (6H, s, $2OCH_3$); 6.23 (1H, s, CH); 7.15–7.18 (1H, m, H Ar); 7.40–7.43 (1H, m, H Ar); 7.67–7.75 (2H, m, H Ar); 8.28–8.30 (2H, m, H Ar); 8.41–8.42 (2H, m, H Ar); 9.68 (1H, s, CH=N). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 47.9 (CH); 53.1 ($2OCH_3$); 117.3 (CH Ar); 120.6 (CH Ar); 120.8 (C Ar); 122.7 (CH Ar); 124.2 (2CH Ar); 126.6 (C Ar); 128.5 (CH Ar); 130.3 (2CH Ar); 138.3 (C Ar); 145.4 (C Ar); 149.3 (C Ar); 152.0 (CH=N); 166.5 ($2\underline{C}O_2CH_3$). Found, *m*/*z*: 397.1139 $[M+H]^+$. $C_{19}H_{17}N_4O_6$. Calculated, *m*/*z*: 397.1143. Found, %: C 57.48; H 4.11; N 14.25. $C_{19}H_{16}N_4O_6$. Calculated, %: C 57.58; H 4.07; N 14.14.

Dimethyl 2-(2-{[(5-methylfuran-2-yl)methylidene]-amino}-2*H*-indazol-3-yl)malonate (4h). Yield 112 mg (59%), yellow-brown crystals, mp 126–127°C, R_f 0.55 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3000, 2950, 1745, 1620, 1570, 1520, 1440, 1310, 1285, 1210, 1160, 1020, 750. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.46 (3H, d, ^4J = 0.9, CH_3); 3.80 (6H, s, $2OCH_3$); 6.00 (1H, s, CH); 6.22 (1H, dd, ^3J = 3.6, ^4J = 0.9, H furan); 6.98 (1H, d, ^3J = 3.6, H furan); 7.10–7.13 (1H, m, H Ar); 7.33–7.36 (1H, m, H Ar); 7.65–7.67 (1H, m, H Ar); 7.72–7.73 (1H, m, H Ar); 9.28 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2 (CH_3); 48.7 (CH); 53.2 ($2OCH_3$); 108.9 (CH Ar); 116.7 (CH Ar); 120.3 (CH Ar); 120.4 (CH Ar); 120.6 (C Ar); 121.9 (CH Ar); 124.2 (C Ar); 127.1 (CH Ar); 141.6 (CH=N); 145.0 (C Ar); 146.6 (C Ar);

157.3 (C Ar); 166.9 (2$\underline{C}O_2CH_3$). Found, *m*/*z*: 356.1241 $[M+H]^+$. $C_{18}H_{18}N_3O_5$. Calculated, *m*/*z*: 356.1241. Found, %: C 60.80; H 4.84; N 11.73. $C_{18}H_{17}N_3O_5$. Calculated, %: C 60.84; H 4.82; N 11.83.

Dimethyl 2-(2-{[(5-methylthiophen-2-yl)methylidene]-amino}-2*H*-indazol-3-yl)malonate (4i). Yield 126 mg (63%), beige crystals, mp 138–139°C, R_f 0.52 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 3040, 2950, 1750, 1730, 1580, 1490, 1440, 1380, 1295, 1270, 1155, 1015, 805, 750. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.57 (3H, d, ^4J = 0.9, CH_3); 3.81 (6H, s, 2OCH_3); 5.84 (1H, s, CH); 6.83 (1H, dd, ^3J = 3.5, ^4J = 0.9, H thiophene); 7.11–7.14 (1H, m, H Ar); 7.34–7.37 (1H, m, H Ar); 7.41 (1H, d, ^3J = 3.5, H thiophene); 7.66–7.70 (2H, m, H Ar); 9.54 (1H, s, CH=N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.1 (CH_3); 48.7 (CH); 53.3 (2OCH_3); 117.3 (CH, Ar); 120.5 (CH Ar); 121.0 (C Ar); 122.6 (CH Ar); 124.7 (C Ar); 126.8 (CH Ar); 127.7 (CH Ar); 135.2 (CH Ar); 135.4 (C Ar); 145.7 (C Ar); 147.5 (C Ar); 147.9 (CH=N); 166.8 (2$\underline{C}O_2CH_3$). Found, *m*/*z*: 372.1015 $[M+H]^+$. $C_{18}H_{18}N_3O_4S$. Calculated, *m*/*z*: 372.1013. Found, %: C 58.10; H 4.66; N 10.94. $C_{18}H_{17}N_3O_4S$. Calculated, %: C 58.21; H 4.61; N 11.31

Dimethyl 2-[2-(2-phenylaziridin-1-yl)-2*H*-indazol-3-yl]-malonate (5). NaH (60% suspension in mineral oil, 114 mg, 2.85 mmol) and trimethylsulfoxonium iodide (626 mg, 2.85 mmol) were added successively to anhydrous DMSO (2.6 ml). The reaction mixture was stirred under argon atmosphere at room temperature for 40 min, followed by the addition of compound **4a** (400 mg, 1.24 mmol). The reaction mixture was further stirred at 60°C for 3 h, then poured into cold saturated NH_4Cl solution (2.5 ml) and extracted with EtOAc (5×2 ml). The combined organic layer was washed with H_2O (7×2 ml) and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure, the residue was purified by column chromatography on silica gel (eluent petroleum ether – EtOAc, 4:1). Yield 279 mg (67%), white foam, mp 126–127°C, R_f 0.45 (petroleum ether – EtOAc, 4:1). IR spectrum, ν, cm^{-1}: 2952, 1756, 1743, 1435, 1381, 1313, 1275, 1255, 1220, 1197, 1154, 1029, 988. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD), δ, ppm (*J*, Hz): 2.70 (1H, dd, ^3J = 5.6, ^2J = 1.5, CH_2); 3.65 (3H, s, OCH_3); 3.68 (3H, s, OCH_3); 3.78 (1H, dd, ^3J = 8.1, ^2J = 1.5, CH_2); 3.98 (1H, dd, ^3J = 8.1, ^3J = 5.6, CH); 5.76 (1H, s, CH); 7.14 (1H, ddd, ^3J = 7.6, ^3J = 6.7, ^4J = 0.9, H-5); 7.32–7.42 (6H, m, H-6, 5H Ph); 7.60–7.63 (1H, m, H-4); 7.65–7.67 (1H, m, H-7). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD), δ, ppm: 40.1 (CH_2); 45.8 (CH); 48.7 ($\underline{C}H(CO_2CH_3)_2$); 52.92 ($OCH_3$); 52.94 ($OCH_3$); 117.2 (7-CH Ar); 119.6 (4-CH Ar); 120.2 (C-3a Ar); 122.1 (5-CH Ar); 124.6 (C-3 Ar); 126.2 (6-CH); 126.4 (3,5-CH Ph); 127.9 (4-CH Ph); 128.5 (2,6-CH Ph); 136.6 (C Ph); 144.4 (C-7a Ar); 166.6 ($\underline{C}O_2CH_3$); 166.7 ($\underline{C}O_2CH_3$). Found, *m*/*z*: 388.1277 $[M+Na]^+$. $C_{20}H_{19}N_3NaO_4$. Calculated, *m*/*z*: 388.1268.

X-ray structural analysis of compound 4a. Crystals of compound **4a**, suitable for X-ray structural analysis, were obtained from a solution in petroleum ether – EtOAc mixture by slow evaporation of solvents at room temperature. The X-ray structural analysis was performed on a STOE STADIVARI PILATUS 100K single crystal diffractometer. The structure was solved by direct methods. All calculations were performed by using the SHELXT and SHELXL-15 program sets.[18] The tables of atomic coordinates, bond lengths, valence and torsion angles, and the anisotropic temperature parameters for compound **4a** were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1585803).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds, as well as ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra of compounds **4a** and **5** and ^{1}H–^{15}N HMBC spectrum of compound **5** is available at the journal website at http://link.springer.com/journal/10593.

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*The X-ray structural analysis of compound **4a** was performed on a STOE STADIVARI PILATUS 100K single crystal X-ray diffractometer, purchased within the framework of Moscow State University modernization program.*

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