Arabian Journal of Chemistry (2014) xxx, xxx–xxx

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Phenylation of aminoindazole derivatives

Abdellah Miloudi [a,b,*], Douniazad El Abed [a], Gerard Boyer [c]

[a] Laboratoire de Chimie Fine, Université d'Oran, Es-Senia, BP 1523, El Mnaouer, Oran, Algeria
[b] Ecole Nationale Polytechnique d'Oran, BP 1524, El Mnaouer, Oran, Algeria
[c] Laboratoire H.I.T, Université Paul Cézanne Aix-Marseille III, Case 552, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

Received 11 March 2012; accepted 5 August 2014

KEYWORDS

Aminoindazole;
Triphenylbismuth diacetate;
Copper diacetate;
Phenylaminoindazole;
Diphenylaminoindazole

Abstract The triphenylbismuth diacetate reacted selectively with different aminoindazole derivatives in presence of copper diacetate to engender a new series of mono phenyl aminoindazole compounds in good to high yields. Moreover, the same reagent with 4-chloro-2-methyl-2H-indazol-7-amine led to a mixture of mono- and N,N-diphenylaminoindazoles. However, its combination with 2H-indazol-4-amine provided only one N,1-diphenylaminoindazole compound.

1. Introduction

Heterocycles constitute a family of substances particularly important in organic chemistry because of their presence in a large number of natural and synthetic molecules with varied useful properties. They play a major role in many areas of medicine, biology, agronomy, cosmetology, and are endowed with diverse pharmaceutical activities (anti-parasitic, anti-fungal, anti-inflammatory, psychotropic) (Yang and Knochel, 2004; Boyer et al., 2000; Barton et al., 1987; Pinhey et al., 1980). Indeed, many heterocyclic indazole therapeutic effects are reported in the literature. For example, the compound YC-1 (Fig. 1) is an activator of the soluble enzyme guanylyl cyclase (Sopkova-De Oliveria-Santos et al., 2000), whereas Rimonabant (Fig. 2) is an anorectic antiobesity drug that reduces bodyweight and improves cardiovascular and metabolic risk factors in non-diabetic overweight or obese patients (Scheen et al., 2006).

On the other hand, the N-aryl hetero aromatic molecules are interesting in stereo selective synthesis and challenging because they reveal new pathways to obtain pharmaceutical and agrochemical compounds. In the past few years, considerable importance has been attached to synthetic methods leading to indazole derivatives because of their biological properties (Caron and Vazquez, 1999; Yeu et al., 2001; Sun et al., 1997; Rodgers et al., 1996; Norman et al., 1996; Yoshida et al., 1996; Robertson et al., 1990; Keppler and Hartmann, 1994; Li et al., 2003; Collot et al., 1999; Batt et al., 2000; Cerecetto et al., 2005; Aronov and Murcko, 2004; Chem et al., 2011; Hering et al., 2006; O'Reilly et al., 2001; Ahabchane et al., 2001).

In this paper, we present a simple and efficient synthetic procedure developed to obtain mono and di-N-phenylamino indazole derivatives which were subsequently aryled by means

* Corresponding author at: Laboratoire de Chimie Fine, Université d'Oran, Es-Senia, BP 1523, El Mnaouer, Oran, Algeria. Tel.: +213 662 071 673.
E-mail address: miloudi_a@yahoo.fr (A. Miloudi).

Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2014.08.003

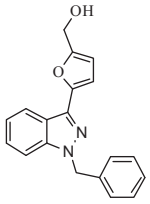


Figure 1 YC-1.

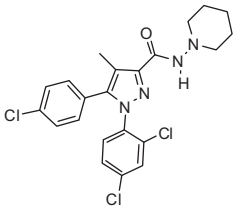


Figure 2 Rimonabant.

of the diacetate triphenylbismuth/copper diacetate system (Barton et al., 1980; Miloudi et al., 2001, 2004).

2. Results and discussion

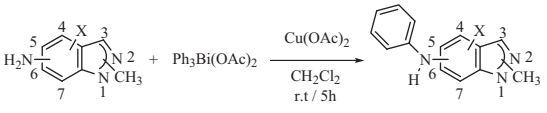
Along the course of this arylation synthesis, the amino indazole group was obtained by reduction of the corresponding nitro group with the Pd/H_2 catalyst in presence of ethanol. The amino and chloroamino indazole derivatives were obtained in good yields with $SnCl_2/HCl$ in a solution of ethanol as products functionalized in different positions (Miloudi et al., 2006).

The derivatives **1**–**12** were reacted with 1.1 equiv. of triphenylbismuth diacetate in presence of a catalytic quantity of copper diacetate (0.1 equiv) in methylene chloride (5-30 mL) at room temperature. The reaction pathway is summarized in Scheme 1.

The monophenyl compounds **1**–**9** were obtained with moderate to good yields. The phenylation of the aminoindazoles by the $Ph_3Bi(OAc)_2/Cu(OAc)_2$ system led to the corresponding monophenylated products with yields varying from 62% to 97%. The lowest yield of 49% was in each case achieved with 4-aminophenyl-7-chloro-2-methylindazolic **4** (Table 1).

It should be noted that the phenylation of the 7-amino-4-chloro-2-methylindazole **13** by the same system led to a mixture of mono and diphenylated compounds **13a** and **13b**, respectively (Scheme 2). The latter products were isolated by silica gel chromatography with a yield of 28% and 22%, respectively.

Moreover, the reaction of 4-aminoindazole **14** with triphenylbismuth diacetate led to 4-phenylamino-1-phenylindazole **14a** diphenylation product with a 23% yield (Scheme 3).



Scheme 1 Phenylation of aminoindazole **1**–**12.**

Table 1 Yields of aminophenylindazolic **1a**–**12a** obtained from the compounds **1**–**12.**

Entry	Product	NH_2	NCH_3	X	Yield (%)
1	**1a**	4-NH_2	1-CH_3	7-H	62
2	**2a**	4-NH_2	1-CH_3	7-Cl	72
3	**3a**	4-NH_2	2-CH_3	7-H	97
4	**4a**	4-NH_2	2-CH_3	7-Cl	49
5	**5a**	5-NH_2	1-CH_3	4-H	84
6	**6a**	5-NH_2	1-CH_3	4-Cl	88
7	**7a**	5-NH_2	2-CH_3	4-H	79
8	**8a**	6-NH_2	1-CH_3	7-H	74
9	**9a**	6-NH_2	2-CH_3	7-H	66
10	**10a**	7-NH_2	1-CH_3	4-H	85
11	**11a**	7-NH_2	1-CH_3	4-Cl	85
12	**12a**	7-NH_2	2-CH_3	4-H	70

The phenylation was done at two sites: the N-1 nitrogen of the azolic cycle and the amine related to C-4 of the indazole group.

3. Experimental section

3.1. Measurements

Melting points were determined by the Büchi Melting Point apparatus and were not corrected. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance 300 spectrometer operating at 300 MHz. Chemical shifts were recorded as units relative to DMSO-d6 or $CDCl_3$ as the solvent unless otherwise stated, with J values in Hertz. Combustion analyses were performed in the "Laboratoire de Microanalyse du centre National de la Recherche Scientifique", Vernaison (France). Chromatography separations were achieved on silica gel (Merck).

3.2. General procedure of N-phenylamin-indazole derivative preparation

A mixture of the appropriate amino indazole (1 equiv.), triphenylbismuth diacetate (1.1 equiv.) and copper diacetate (0.1 equiv.) in dichloromethane solution of variable volume according to the substrate was stirred at room temperature during 5 h, unless otherwise stated. After filtration of the solution, the solvent was distilled under reduced pressure to afford oil which was then purified by chromatography on silica gel with ether/pentane (1:1) eluent to supply N-phenylation products (Barton et al., 1978).

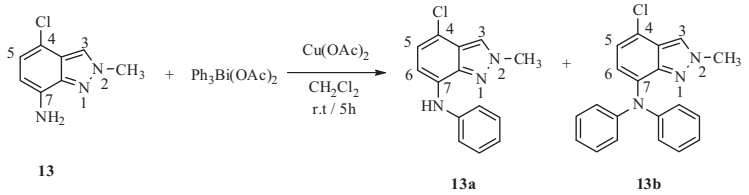
All the following compounds were obtained using the general preparation procedure described above.

3.2.1. 1-Methyl-N-phenyl-1H-indazol-4-amine (*1a*)

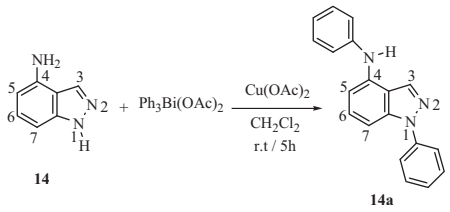
Yield 62%, m.p. 102 °C. ^1H NMR ($CDCl_3$): ppm 7.95 (s, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 7.21 (d, J = 8.2, 1H), 7.04 (t, J = 7.4, 1H), 6.90 (d, J = 7.5, 1H), 6.85 (s, 1H), 4.02 (s, 3H). ^{13}C NMR ($CDCl_3$): ppm 142.19, 141.34, 137.01, 130.22, 129.11, 127.40, 121.73, 119.21, 116.12, 104.75, 100.91, 35.40.

3.2.2. 7-Chloro-1-methyl-N-phenyl-1H-indazol-4-amine (*2a*)

Yield 72%, m.p. 85 °C. ^1H NMR ($CDCl_3$): ppm 8.15 (s, 1H), 7.53 (t, J = 7.8, 2H), 7.37 (d, J = 8.1, 1H), 7.36 (d, J = 8.1, 2H), 7.25 (t, J = 7.4, 2H), 6.98 (d, J = 8.1, 1H), 6.65 (s,



Scheme 2 Phenylation of aminoindazole **13.**



Scheme 3 Phenylation of aminoindazole **14.**

1H), 4.56 (s, 3H). ^{13}C NMR ($CDCl_3$): ppm 141.76, 136.87, 135.97, 130.22, 129.18, 128.01, 121.98, 119.24, 118.61, 105.42, 100.60, 38.58.

*3.2.3. 2-Methyl-N-phenyl-2H-indazol-4-amine (**3a**)*

Yield 97%, m.p. 193 °C. ^{1}H NMR (DMSO-d6): ppm 8.49 (s, 1H), 8.16 (s, 1H), 7.29 (d, J = 8.1, 2H), 7.27 (t, J = 8.3, 2H), 7.20 (s, 1H), 7.04 (t, J = 7.4, 1H), 6.91 (t, J = 6.80, 1H), 6.89 (d, J = 8.30, 1H), 6.83 (d, J = 7.30, 1H), 3.98 (s, 3H). ^{13}C NMR ($CDCl_3$): ppm 141.72, 141.44, 136.25, 130.16, 128.83, 127.57, 121.53, 118.93, 116.22, 104.57, 100.71, 35.13.

*3.2.4. 7-Chloro-2-methyl-N- phenyl-2H-indazol-4-amine (**4a**)*

Yield 49%, m.p. 98 °C. ^{1}H NMR ($CDCl_3$): ppm 7.70 (s, 1H), 7.25 (t, J = 8.5, 2H), 7.13 (d, J = 7.7, 1H), 7.03 (dd, J = 8.5, J = 1.2, 2H), 6.95 (t, J = 7.3, 2H), 6.64 (d, J = 7.9, 1H), 4.09 (s, 3H). ^{13}C NMR ($CDCl_3$): ppm 146.95, 142.33, 135.15, 129.22, 126.11, 123, 88, 121.68, 118.87, 117.33, 113.32, 106.33, 40.39.

*3.2.5. 1-Methyl-N-phenyl-1H-indazol-5- amine (**5a**)*

Yield 84%, m.p. 150 °C. ^{1}H NMR (DMSO-d6) ppm 8.01 (s, 1H), 7.87 (s, 1H), 7.53 (d, J = 9.0, 1H), 7.40 (s, 1H), 7.20 (d, J = 9.0, 1H), 7.17 (t, J = 6.0, 2H), 7.00 (d, J = 9.0, 2H), 6.74 (t, J = 9.0, 1H), 4.00 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 145.59, 136.90, 136.55, 131.77, 129.59, 124.58, 121.91, 119.02, 115.64, 110.76, 108.78, 35.82.

*3.2.6. 4-Chloro-1-methyl-N-phenyl-1H-indazol-5-amine (**6a**)*

Yield 88%, m.p. 107 °C. ^{1}H NMR (DMSO-d6): ppm 7.99 (s, 1H), 7.75 (s, 1H), 7.59 (d, J = 8.9, 1H), 7.37 (d, J = 8.9, 1H), 7.15 (t, J = 7.5, 2H), 6.80 (d, J = 8.5, 2H), 6.73 (t, J = 7.9, 1H), 4.05 (s, 3H). ^{13}C NMR ($CDCl_3$): ppm 149.50, 137.41, 132.36, 130.13, 129.00, 124.15, 123.41, 118.85, 116.39, 115.01, 109.49, 35.78.

*3.2.7. 2-Methyl-N-phenyl-2H-indazol-5-amine (**7a**)*

Yield 79%, m.p. 144 °C. ^{1}H NMR (DMSO-d6): ppm 8.06 (s, 1H), 7.97 (s, 1H), 7.51 (s, 1H), 7.26 (d, J = 9.0, 1H), 7.19 (t, J = 7.6, 2H), 7.03 (d, J = 9.0, 1H), 7.02 (d, J = 7.4, 2H), 6.74 (t, J = 7.4, 1H), 4.09 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 145.10, 144.78, 136.55, 129.04, 122.28, 118.64, 117.63(2C), 115.65, 112.84, 103.87, 39.76.

*3.2.8. 1-Methyl-N-phenyl-1H-indazol-6-amine (**8a**)*

Yield 74%, m.p. 143 °C. ^{1}H NMR (DMSO-d6): ppm 8.37 (s, 1H), 7.82 (s, 1H), 7.57 (s, 1H), 7.27 (t, J = 7.7, 1H), 7.18 (d, J = 7.7, 1H), 7.12 (s, 1H), 6.88 (d, J = 8.6, 1H), 6.87 (t, J = 7.7, 1H), 3.90 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 143.10, 142.42, 140.97, 132.18, 129.31, 121.44, 120.16, 118.12, 117.35, 114.28, 92.97, 35.12. Anal. calcd for $C_{14}H_{13}N_3$. C: 75.34, H: 5.83, N: 18.83. Found. C: 75.14, H: 5.96, N: 18.65.

*3.2.9. 2-Methyl-N-phenyl-2H-indazol-6-amine (**9a**)*

Yield 66%, m.p. 144 °C. ^{1}H NMR (DMSO-d6): ppm 8.15 (s, 1H), 8.13 (s, 1H), 7.54 (d, J = 8.9, 1H), 7.23 (t, J = 7.5, 2H), 7.11 (s, 1H), 7.09 (d, J = 7.5, 2H), 6.81 (d, J = 7.4, 1H), 6.80 (t, J = 7.3, 1H), 4.04 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 149.26, 143.72, 140.66, 129.13, 124.25, 120.94, 119.50, 117.19, 117.06, 116.76, 98.27, 39.50. Anal. calcd for $C_{14}H_{13}N_3$. C: 75.34, H: 5.83, N: 18.83. Found. C: 75.21, H: 5.98, N: 18.95.

*3.2.10. 1-Methyl-N-phenyl-1H-indazol-7-amine (**10a**)*

Yield 85%, m.p. 130 °C. ^{1}H NMR (DMSO-d6): ppm 8.07 (s, 1H), 7.78 (d, J = 7.7, 2H), 7.57 (d, J = 8.7, 2H), 7.21 (t, J = 7.8, 2H), 7.13 (d, J = 7.8, 1H), 6.88 (t, J = 8.0, 1H), 6.75 (t, J = 7.4, 1H), 4.00 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 147.50, 137.47, 135.20, 129.40, 124.25, 122.43, 122.20, 121.44, 121.25, 120.46, 115.15, 38.25.

*3.2.11. 4-Chloro-1-methyl-N-phenyl-1H-indazol-7-amine (**11a**)*

Yield 85%, m.p. 80 °C. ^{1}H NMR (DMSO-d6): ppm 8.06 (s, 1H), 7.15 (t, J = 7.4, 2H), 7.12 (d, J = 5.3, 1H), 7.08 (d, J = 8.0, 1H), 6.77 (d, J = 7.8, 2H), 6.73 (t, J = 7.4, 1H), 4.10 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 147.04, 145.56, 136.88, 129.44, 124.80, 124.71, 122.06, 121.00, 120.99, 120.27, 115.15, 38.25.

*3.2.12. 2-Methyl-N-phenyl-2H-indazol-7-amine (**12a**)*

Yield 70%, m.p. 128–130 °C. ^{1}H NMR (DMSO-d6): ppm 8.40 (s, 1H), 7.54 (d, J = 8.0, 1H), 7.16–7.20 (m, 5H), 7.04 (d, J = 7.8, 1H), 6.85 (t, J = 8.3, 1H), 4.12 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 147.04, 145.21, 136.88, 129.32, 124.80, 122.59, 122.40, 122.06, 121.00, 120.66, 119.04, 40.02.

*3.2.13. 4-Chloro-2-methyl-N-phenyl-2H-indazol-7-amine (**13a**) and (**13b**)*

Yield of **13a** is 28%, m.p. 125 °C. ^{1}H NMR (DMSO-d6): ppm 8.43 (s, 1H), 7.20 (t, J = 7.6, 2H), 7.04 (d, J = 7.8, 1H), 6.91

(t, J = 7.9, 1H), 6.94 (d, J = 7.2, 2H), 6.85 (d, J = 7.7, 1H), 4.03 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 147.35, 145.01, 134.98, 129.08, 124.81, 123.43, 123.00, 122.36, 122.20, 120.46, 120.27, 40.35; and yield of **13b** is 22%, m.p. 130 °C. ^{1}H NMR (DMSO-d6): ppm 8.43 (s, 1H), 7.70 (d, J = 8.9, 2H), 7.39 (t, J = 8.9, 2H), 7.22 (t, J = 7.9, 1H), 7.19 (d, J = 7.6, 2H), 7.04 (d, J = 7.8, 1H), 6.94 (t, J = 7.9, 4H), 6.85 (d, J = 7.7, 1H), 4.03 (s, 3H). ^{13}C NMR (DMSO-d6): ppm 150.71, 147.52, 145.18, 135.17, 129.62, 129.25, 125.90, 125.00, 123.57, 123.25, 122.55, 122.35, 121.99, 121.18, 120.62, 40.51.

*3.2.14. N,1-Diphenyl-1H-indazol-4-amine (**14a**)*

Yield 23%, m.p. 170 °C. ^{1}H NMR (DMSO-d6): ppm 8.48 (s, 1H), 7.76 (d, J = 7.9, 2H), 7.59 (t, J = 7.2, 2H), 7.40 (t, J = 7.0, 2H), 7.33 (d, J = 8.3, 2H), 7.29 (d, J = 8.1, 1H), 7.27 (d, J = 8.3, 1H), 7.24 (t, J = 8.3, 1H), 6.97 (t, J = 7.0, 1H), 6.92 (t, J = 8.3, 1H). ^{13}C NMR (DMSO-d6): ppm 142.49, 140.11, 139.96, 137.93, 134.22, 129.77, 129.61, 129.39, 126.59, 122.31, 121.49, 119.29, 116.99, 104.29, 101.27.

4. Conclusion

We may conclude that pentavalent triphenylbismuth diacetate appears to be a promising reagent for a novel source of C-N bond formation with high efficiency on the primary amines of indazole derivatives to provide the mono- and/or diphenylated compounds with good yields. Moreover, it should be noted that the efficiency of this arylating agent is improved by the presence of the copper diacetate catalyst.

References

Ahabchane, N.H., Ibrahimi, S., Salem, M., Essassi, E.M., Amzazi, S., Benjouad, A., 2001. Acad. Sci. Paris Chimie 4, 917.
Aronov, A., Murcko, M., 2004. J. Med. Chem. 47, 5616.
Barton, D.H., Kitchin, J.-P., Motherwell, W.B., 1978. J. Chem. Soc. Chem. Commun., 1099.
Barton, D.H.R., Lester, D.J., Motherwell, W.B., Barros Popula, M.T., 1980. J. Chem. Soc. Chem. Commun., 246.
Barton, D.H.R., Bhatnagar, N.Y., Finet, J.-P., Khamsi, J., 1987. Tetrahedron Lett. 28 (27), 3111.
Batt, D.G., Petraitis, J.J., Houghton, G.C., Modi, D.P., Cain, G.A., Corjay, M.H., Mousa, S.A., Bouchard, P.J., Forsythe, M.S., Harlow, P.P., Barbera, F.A., Spitz, S.M., Wexler, R.R., Jadhave, P.K., 2000. J. Med. Chem. 43, 41.
Boyer, G., Chatel, F., Galy, J.-P., 2000. Arkivoc 1, 563.
Caron, S., Vazquez, E., 1999. Synthesis, 588 (references cited therein).
Cerecetto, H., Gerpe, A., Gonzalez, M., Aran, V.J., De Ocariz, C.O., 2005. Mini Rev. Med. Chem. 5, 869.
Chem, W., Li, P., Wang, L., 2011. Tetrahedron 67 (2), 318.
Collot, V., Dallemagne, P., Bovy, P.R., Rault, S., 1999. Tetrahedron 55, 6917.
Hering, K.W., Artz, J.D., Pearson, H.W., Marletta, M.A., 2006. Bioorg. Med. Chem. Lett. 16, 618.
Keppler, B.K., Hartmann, M., 1994. Met. Based Drugs 1, 145.
Li, X., Chu, S., Feher, V.A., Khalili, M., Nie, Z., Margosiak, S., Nikulin, V., Levin, J., Sprankle, K.G., Tedder, M.E., Almassy, R., Appelt, K., Yager, K.M., 2003. J. Med. Chem. 46, 5663.
Miloudi, A., El Abed, D., Boyer, G., Galy, J -P., Finet, J.-P., 2001. Main Group Met. Chem. 24 (11), 767.
Miloudi, A., El Abed, D., Boyer, G., Finet, J.-P., Galy, J.-P., Siri, D., 2004. Eur. J. Org. Chem., 1509.
Miloudi, A., El Abed, D., Boyer, G., Finet, J.-P., Galy, J.-P., 2006. Heterocycle 68 (12), 2595.
Norman, M.H., Navas, F., Thompson, J.B., Rigdon, G.C., 1996. J. Med. Chem. 39, 4692.
O'Reilly, D.A., McLaughlin, B.E., Marks, G.S., Brien, J.F., Nakatsu, K., 2001. Can. J. Physiol. Pharmacol. 79 (1), 43.
Pinhey, J.T., Rowe, B.A., 1980. Aust. J. Chem. 33, 113.
Robertson, D.W., Bloomquist, W., Cohen, M.L., Reid, L.R., Schenck, K., Wong, D.T., 1990. J. Med. Chem. 33, 3176.
Rodgers, J.D., Johnson, B.L., Wang, H., Greenberg, R.A., Erickson-Viitanen, S., Klabe, R.M., Cordova, B.C., Rayner, M.M., Lam, G.N., Chang, C.-H., 1996. Bioorg. Med. Chem. Lett. 6, 2919.
Scheen, A.J., Finer, N., Hollander, P., Jensen, M.D., Van Gaal, L.F., 2006. Lancet 368, 1660.
Sopkova-De Oliveria-Santos, J., Collot, V., Bureau, I., Rault, S., 2000. Acta Crystallogr. C, 1035–1036.
Sun, J.-H., Teleha, C.A., Yan, J.-S., Rodgers, J.D., Nugiel, D.A., 1997. J. Org. Chem. 62, 5627.
Yang, X., Knochel, P., 2004. Synlett N13, 2303.
Yeu, J.-P., Yeh, J.-T., Chen, T.-Y., Uang, B.-J., 2001. Synthesis, 1775 (references cited therein).
Yoshida, T., Matsuura, N., Yamamoto, K., Doi, M., Shimada, K., Morie, T., Kato, S., 1996. Heterocycles 43, 2701.

Please cite this article in press as: Miloudi, A. et al., Phenylation of aminoindazole derivatives. Arabian Journal of Chemistry (2014), http://dx.doi.org/10.1016/j.arabjc.2014.08.003