

Functionalization of aromatic and heteroaromatic compounds in copper-catalyzed reactions utilizing hypervalent iodonium salts

Doctoral Thesis

Zsombor Gonda

certified chemist



Eötvös University, Chemistry Doctoral School,

Program of Synthetic Chemistry, Materials Science and Biomolecular Chemistry

Head of Chemistry Doctoral School: Dr. György Inzelt, DSc

full professor

Head of Program: Dr. András Perczel, DSc

full professor

Supervisor: Dr. Zoltán Novák, PhD

assistant professor

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Introduction

One of the main goals of my doctoral research was to develop an efficient, widely applicable copper-catalyzed trifluoromethylation reaction, which can be extended to several aromatic and heterocyclic substrates. The other aim was the study of a hypervalent iodine mediated oxidative coupling reaction of diaryliodonium salts and pyrazoles for the preparation of N-arylated pyrazole derivatives.

The previously published C-H activated trifluoromethylation reactions, which usually follows radical mechanism have several disadvantages, e.g. high temperature is needed, or usually are not selective. Thus, this approach is applicable only in special cases.¹ In the case of transition metal catalyzed reactions the CF₃ source is either applied in high excess or expensive.² The most commonly used noble metals significantly increase the cost of the procedures. To decrease the cost, the need for cheaper and in greater amount of available metals is highly desired, such as copper³ or iron.⁴ Another solution to the economic problems can be the utilization of a metal free coupling reaction, but this is really challenging even nowadays. We have to consider that these types of reactions can be very sensitive of the trace transition metals occurring in the components. Recently several hypervalent iodine mediated carbon-carbon and carbon-heteroatom bond forming reactions were published, but in some cases the transformation could be carried out in the absence of transition metal catalysis.⁵

Results

1. Study of copper catalyzed trifluoromethylation of aryl iodides

According to literature a promising trifluoromethylation reagent, the potassium salt of trifluoromethyl-trimethylborate was studied in trifluoromethylation reaction. For the experiments, we have synthesized the trifluoromethyl borate salt from the proper trialkoxy borates (**Figure 1**).⁶

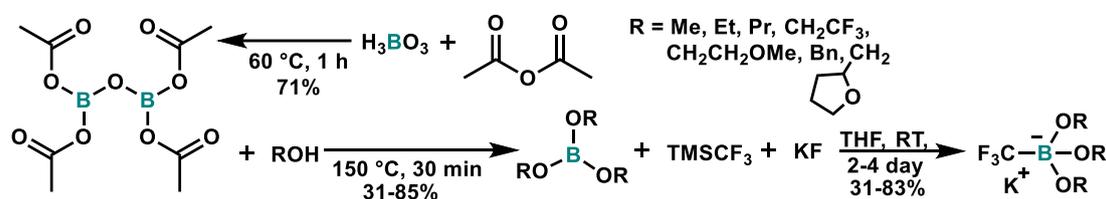


Figure 1 Synthesis of trialkoxyborates and the potassium trifluoromethyl trialkyl borates

¹ Dolbier, W. R. Jr., *Chem. Rev.* **1996**, *96*, 1557–1584.

² a) Nagib, D. J.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224–228. b) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525–7528. c) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.*, **2012**, *134*, 9034–9037.

³ Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909–1911.

⁴ Uraguchi, D.; Yamamoto, K.; Ohtsuka, Y.; Tokuhisa, K.; Yamakawa, T. *Appl. Catal., A* **2008**, *342*, 137–143.

⁵ Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B., *Chem. Eur. J.* **2013**, *19*, 10334–10342.

⁶ Knauber, T.; Arikian, F.; Röschenhaler, G.-V.; Gooßen, L. J. *Chem.–Eur. J.*, **2011**, *17*, 2689–2697.

The reactivities of the trifluoromethyl trialkyl borate salts were compared in the trifluoromethylation reaction of 1-iodonaphthalin (**Figure 2**). We have determined that increasing the length of the alkyl chain decreases the reactivity of the salt and the most active and most effective trifluoromethylation reagent was the trifluoromethyl trimethyl potassium salt.

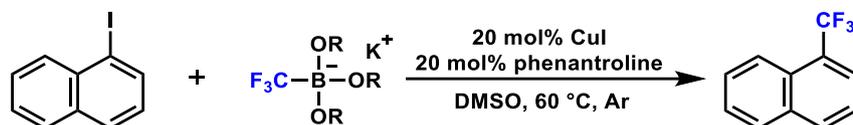


Figure 2 The reaction of trifluoromethyl trialkyl borate salt with idonaphthalin

We carried out the study of reactivity of potassium trifluoromethyl trimethyl borate in the presence of copper(I) compounds and ligands in coupling reactions. It was found that phenanthroline as ligand ensures the most effective catalytic system for the desired trifluoromethylation reaction.

During the examination of reproducibility of the reaction we found that the coupling reaction is sensitive to the presence of water. Studying the stability of the borate salts we have proved that under unsuitable storing conditions the trifluoromethyl borate salt rapidly transforms and loses its activity. The results of the comparing experiments showed that the prepared salt should be stored in freezer (-20°C) under inert gas (Ar), thus its activity can be conserved for weeks.

Solving the problems of the storage of the borate salt, we developed a novel copper-catalyzed method in which the trifluoromethylating reagent can be prepared *in situ* in the reaction mixture. Examining this possibility we have found that in dimethylsulfoxide from trifluoromethyl trimethyl silane and trimethylborate in the presence of potassium fluoride the trifluoromethyl trimethyl borate can be generated. The generation of the borate salt under the reaction conditions is not disturbed even by the catalyst or the ligand. We have found that in this case in the presence of aryl iodides the trifluoromethylation takes place faster and with higher efficiency than in the reaction performed with freshly isolated salt. We have optimized the conditions of the reaction using the *in situ* generated borate salt and found that in the model reaction, in the presence of 20-20 mol% catalyst and ligand in DMSO as solvent full conversion could be reached after 4 hours stirring at 60°C (**Figure 3**).

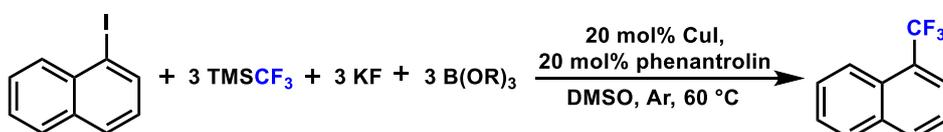


Figure 3 Trifluoromethylation with *in situ* generated borate salt

We determined that the reaction time can be further decreased with slow addition of TMSCF₃ and B(OMe)₃ and that in the case of more reactive iodo compounds 2 equivalent of the reactants is sufficient for reaching full conversion. We examined the reason for necessity of large excess of reactants and found that the potassium fluoride not only influences the decomposition of the TMSCF₃ and this way promotes the generation of the trifluoromethyl borates, but also decomposes the alkylborate. Consequently the 3 equivalent of the borate salt or the reagents for *in situ* generation are necessary because of the two rival process.

During the study of trifluoromethylation reaction in preparative scale using the *in situ* generated borate salt we have found that the transformation can be effectively done in case of aryl iodides containing both electron donating and electron withdrawing groups as well. Testing the functional group tolerance it was found that free –NH and –OH groups should be protected before the trifluoromethylation (**Figure 4**).

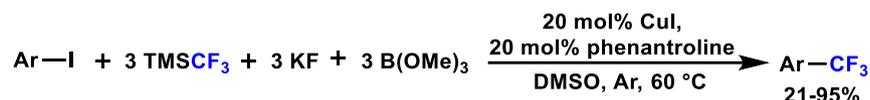


Figure 4 Synthesis of aromatic and heteroaromatic trifluoromethylated derivatives

The applicability in organic syntheses of our new method, the trifluoromethylation procedure was tested on aromatic and heteroaromatic iodides. As the result of the syntheses 28 trifluoromethylated aromatic and heteroaromatic compounds were isolated in 21-95% yield. The results were published in *Organic Letters*.

2. Study of the preparation of N-arylpirazoles

For the arylation study we have synthesized the proper diaryliodonium salts according to literature procedures.⁷

During the synthesis of diaryliodonium salts our main goal was to select reactions, which provide the best yield with the least reaction steps. Utilizing five methods we have prepared 49 different symmetrically or asymmetrically functionalized diaryliodonium salts. (**Figure 5**).

⁷ a) Merritt, E.; Carneiro, V. M.; Silva Jr., L. F.; Olofsson, B.; *J. Org. Chem.*, **2010**, 75, 7416-7419. b) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, 73, 4602–4607. c) Bielawski, M.; Olofsson, B.; *Chem. Commun.*, **2007**, 2521–2523. d) Bielawski, M.; Zhu, M.; Olofsson, B.; *Adv. Synth. Catal.* **2007**, 349, 2610 – 2618. e) Ross, T. L., *Ph. D. Thesis*, Köln University, Germany **2005**.

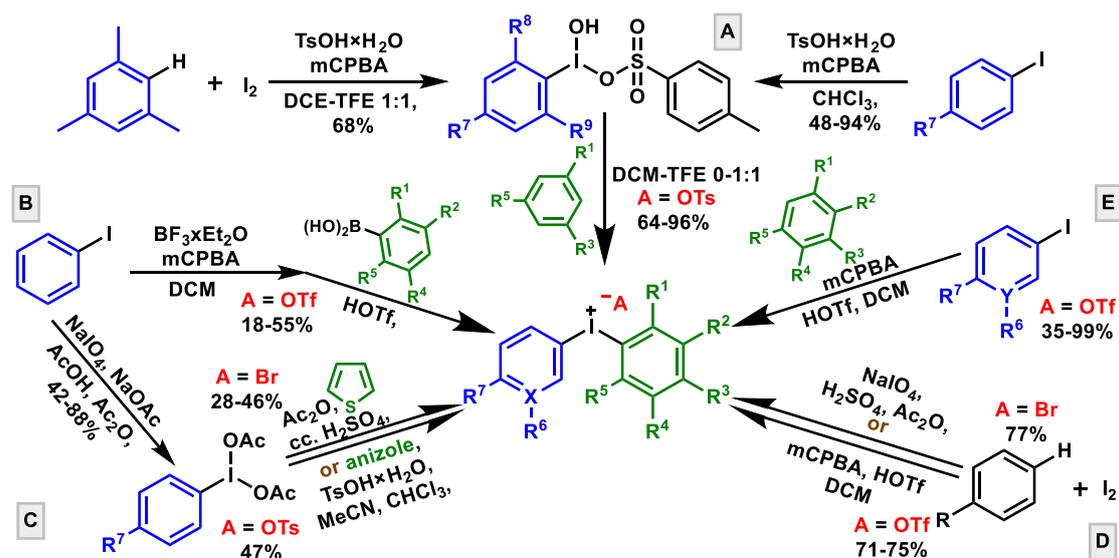


Figure 5 Methods for the preparation of diaryliodonium salts

2.1. Preparation of N-arylpiprazoles with the help of iodonium salts

Our research group has already studied the copper-catalyzed transformations alkynes in the presence of diaryliodonium salts.⁸ In these procedures not only ring-closure occurs between the nucleophilic amide group and electrophile triple bond, but the presence of diaryliodonium salt enables carboarylation of the carbon center. During my PhD work I also examined a new ring-closure reaction and the arylation reaction of N heterocyclic compounds.

In the beginning of our researches we studied the reaction of N-acetylhydrazon bearing triple bond and iodonium salts under the conditions utilized in the previously developed copper catalyzed ring-closure reactions. We observed the formation of N-arylpiprazole instead of the expected oxadiazole ring. The structure of the product was determined by NMR measurements as well (Figure 6).

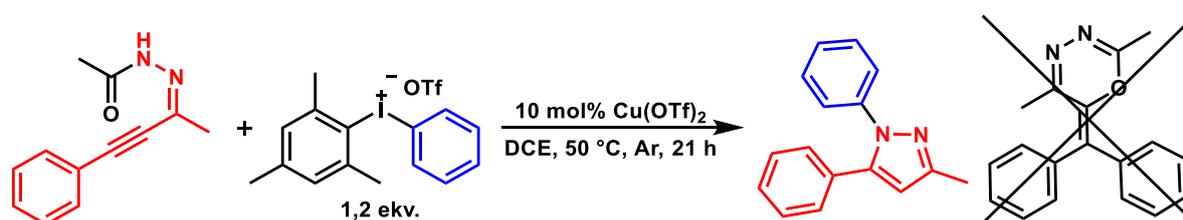


Figure 6 The test reactions executed with phenylbutynyl hydrazone

Comparison of the NMR spectra of the obtained product with literature also proved the formation of the pyrazole product. Thus, the product was not formed through 6-*exo-dig* ring-closure with the assistance of the oxygen of the acetyl group. In contrast, deacetylation took

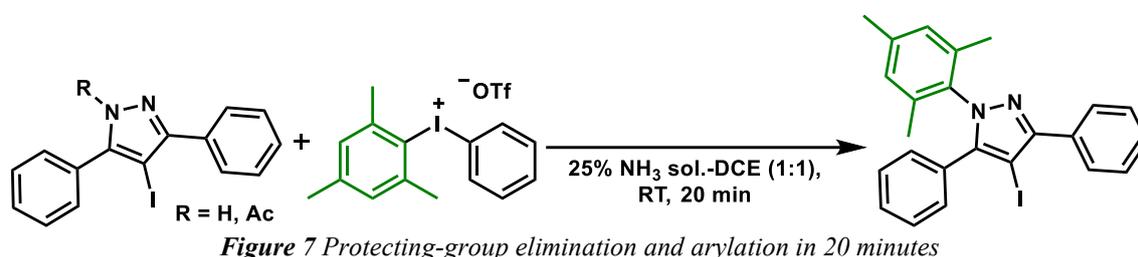
⁸ a) Sinai, Á.; Mészáros, Á.; Gáti, T.; Kudar, V.; Palló, A.; Novák, Z. *Org. Lett.*, **2013**, *15*, 5654–5657. b) Székely, A.; Sinai, Á.; Tóth, E. B.; Novák, Z. *Synthesis*, **2014**, *14*, 1871–1880. c) Sinai, Á.; Vangel, D.; Gáti, T.; Bombicz, P.; Novák, Z. *Org. Lett.* **2015**, *17*, 4136–4139. d) Aradi, K.; Novák, Z. *Adv. Synt. Catal.*, **2015**, *357*, 371–376.

place through *5-endo-dig* ring-closure similarly to the indole syntheses triggered by the diaryliodonium salts.

The study of the effect exerted by the functional groups located on different positions of the aromatic groups of the iodonium salt determined the outcome of the transformation. Only *meta*- and *para*-substituted phenyl ring of the aryl(mesityl)iodonium salts enables the N arylation. In case of *ortho*-substituted aryl(mesityl)iodonium triflates no product was obtained and the starting material remained unchanged. Moreover, we could reach only with 43% yield the desired product in the iodonium salt mediated transformation.

We developed more effective procedure for the preparation of *N*-arylpirazoles with iodonium salts modifying the reaction conditions and the work-up of the reaction mixture. We found that the addition of aqueous ammonia solution significantly increases the yield. Further optimization of the reaction parameters of the ring-closure reaction revealed that the reaction performed under slightly basic conditions does not require the presence of copper catalyst.

Changing the parameters of the reaction significantly modifies the selectivity. The results show that the selectivity of the phenyl(mesityl)iodonium salt is just the opposite of the selectivity of the previously recognized copper-mediated arylation reaction.



After the study of ring-closure mediated arylation reaction we have turned our attention to the possibility of *N*-arylation of pyrazole derivatives. We have found that the most suitable solvents for the *N*-arylation of NH or *N*-acyl-pyrazoles are the ones, which can not be mixed with water (toluene, DCM, DCE). As a base, not only ammonia, but other inorganic bases in appropriate concentrations (1 M NaOH, 1 M ^tBuOK, 25 w/w% K₂CO₃ solvent) can also be utilized (**Figure 7**).

The possible radical mechanism of the reaction was tested by tetramethylpiperidine-oxide (TEMPO). The radical path was excluded, because in the presence of TEMPO we have not observed considerable decline in the conversion compared to the transformation performed in the absence of radical scavenger.

The factors determining the selectivity of the reaction were studied by utilizing several diaryliodonium salts. According to the results we could conclude that the selectivity of the arylation reaction is considerably influenced by the electronic and steric properties of the aromatic rings of the diaryliodonium salts. We have found that the aromatic ring connecting to the pirazole is the one on the iodonium salt, which contains more *ortho*-substituents. However, if one of the aryl groups is an adequately electron rich anisole, trimethoxybenzene or thiophen, then this is a suitable “no to be transferred” group. This is beneficial in case of heterocyclic iodonium salts, because the preparation of their symmetrical variation is difficult or not possible.

We carried out the arylation reactions with the iodonium salts, which promised high selectivity in the transformation on preparative scale. In case of 3,5-diphenyl-pirazole 80-90% yields were reached in room temperature after 20 minutes to 4 hours. (**Figure 8, A**). Other symmetrically substituted pirazoles were tested in the reactions as well. Amongst them, not only the *N*-mesityl-derivatives were prepared after 20 minutes reaction time with 56-96% yield (**Figure 8, B**), but wherever it was possible the 1,3,5-triaryl pirazoles were also prepared as well (**Figure 8, C**). Utilizing the novel arylation method we prepared 32 *N*-arylpirazole derivatives, containing large number of new derivatives.

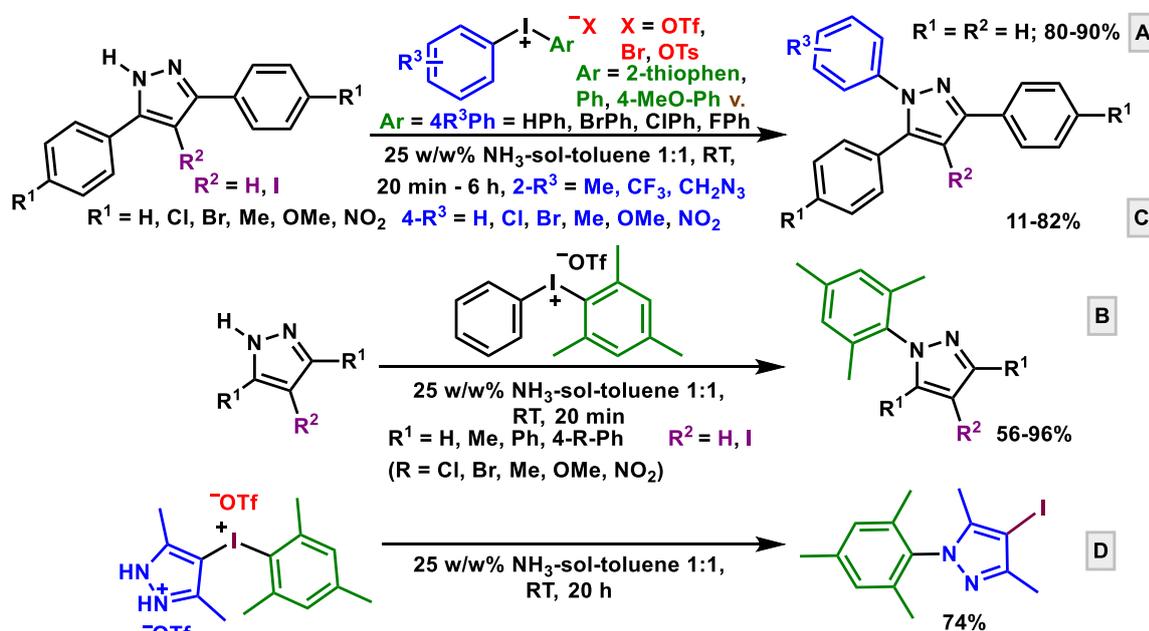


Figure 8 Preparation of *N*-arylpirazoles

It was also shown that the iodonium salt containing pirazolyl moiety can react in an intramolecular fashion (**Figure 8, D**) and provides the appropriate *N*-mesityl-3,5-dimethyl-4-iodopirazole in good yield without the formation of aryl iodide side product. We have published the results of this topic in the journal *Chemistry - A European Journal*.

Papers related to the topic of the PhD Thesis

- 1) "Efficient Copper-Catalyzed Trifluoromethylation of Aromatic and Heteroaromatic Iodides: The Beneficial Anchoring Effect of Borates" Zsombor Gonda, Szabolcs Kovács, Csaba Wéber, Tamás Gáti, Attila Mészáros, András Kotschy, Zoltán Novák *Org. Lett.*, **2014**, *16*, 4268-4271. doi: 10.1021/ol501967c
- 2) "Transition-Metal-Free *N*-Arylation of Pyrazoles with Diaryliodonium Salts" Zsombor Gonda, Zoltán Novák, *Chemistry A European Journal*, **2015**, *21*, 16801–16806. DOI: 10.1002/chem.201502995

Other Papers

- 3) "Iron-surfactant nanocomposite-catalyzed benzylic oxidation in water" Fruzsina Szabó, Bálint Pethő, Zsombor Gonda, Zoltán Novák *RSC Advances* **2013**, Advance Article DOI: 10.1039/C3RA22856H
- 4) "Evaluation of bis-triphenylphosphano-copper(I)-butyrate ($C_3H_7COOCu(PPh_3)_2$) as catalyst for the synthesis of 1-(D-glycopyranosyl)-4-substituted-1,2,3-triazoles" Éva Bokor, Csaba Koppány, Zsombor Gonda, Zoltán Novák, László Somsák, *Carbohydr. Res.*, **2012**, *351*, 42-48.
- 5) "Efficient synthesis of deuterated 1,2,3-triazoles" Zsombor Gonda, Krisztián Lőrincz, Zoltán Novák, *Tetrahedron Letters*, **2010**. DOI: 10.1016/j.tetlet.2010.09.097
- 6) "Dramatic Impact of ppb levels of Palladium on the "Copper-Catalyzed" Sonogashira Coupling" Zsombor Gonda, Gergely L. Tolnai, Zoltán Novák, *Chemistry A European Journal*, **2010**, DOI: 10.1002/chem.201001880
- 7) "Highly active copper catalysts for azide-alkyne cycloaddition" Zsombor Gonda, Zoltán Novák, *Dalton Transactions*, **2009**, DOI: 10.1039/b920790m

Oral presentations

- 1) „Pirazolszármazékok hatékony, fém nélküli oxidatív *N*-arilezése” Gonda Zsombor, Novák Zoltán, MTA Heterociklusos és Elemorganikus Kémiai Munkabizottsági ülés, 2014. May 21-23. Balatonszemes, szóbeli
- 2) „Réz-katalizátorok szintézise és alkalmazása cikloaddíciós reakcióban” Gonda Zsombor, Novák Zoltán, MTA Heterociklusos Kémiai Munkabizottsági ülés, 2009. May 20-22. Balatonszemes.

Poster presentations

- 1) „Efficient Transition-metal-free *N*-arylation of Pyrazoles with diaryliodonium salts” Gonda Zsombor, Novák Zoltán, BDSHC, Balatonalmádi, 2015. June

- 2) „In Situ Generated Trifluoromethyl Alkylborate Salts - a Simply Method for Copper Catalyzed Trifluoromethylation of Aromatic and Heteroaromatic Iodide” Gonda Zsombor, Kovács Szabolcs, Králl Péter, Wéber Csaba, Gáti Tamás, Mészáros Attila, Kotschy András, Novák Zoltán, ICOS, Budapest, 2014. July.
- 3) „Copper catalyzed trifluoromethylation of aromatic and heteroaromatic iodides with in situ generated borate salts” Gonda Zsombor, Wéber Csaba, Gáti Tamás, Mészáros Attila, Kotschy András, Novák Zoltán, BDSHC, Olmütz, Czech Republic 2013. September.
- 4) „Iron catalyzed benzylic oxidations” Gonda Zsombor, Szabó Fruzsina, Pethő Bálint, Novák Zoltán, EuCheMs, Prague, 2012. September,
- 5) „Sonogashira coupling reactions with trace amount of palladium” Gonda Zsombor, Tolnai Gergely, Vanessa Cox, Balogh Ádám, Novák Zoltán, ESOC, Crete, Greece, 2011. July
- 6) „Réz-katalizált cikloaddíció vizsgálata” Gonda Zsombor, Novák Zoltán, Magyar Kémikusok Egyesülete Vegyészkonferencia Hajdúszoboszló, 2008. June.