Tetrahedron Letters
journal homepage: www.elsevier.com

$AlCl_3$-promoted reaction of cycloalkanones with hydrazones: a convenient direct synthesis of 4,5,6,7-tetrahydro-1*H*-indazoles and their analogues

Rima Laroum,[a] Fabienne Berrée,[b] Thierry Roisnel,[b] Vincent Dorcet, [b] Bertrand Carboni[b*] and Abdelmadjid Debache [a*]

[a] *Laboratoire de Synthèse des Molécules d'Intérêts Biologiques, Université des Frères Mentouri-Constantine, 25000 Constantine, Algérie*
[b] *Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes), UMR 6226, F-35000 Rennes, France*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Cycloalkanones
Hydrazones
Tetrahydroindazoles
Aluminium chloride

ABSTRACT

The $AlCl_3$-promoted reactions of cycloalkanones with hydrazones are described. This approach represents a mild and operationally simple method to access 2,3-diaryl-4,5,6,7-tetrahydro-1*H*-indazoles and their analogues in good to moderate yields.

Introduction

Nitrogen-containing heterocycles represent one of the most important classes of organic compounds. They are abundant in natural products and are also the major constituents of a variety of drugs.[1] Among the vast number of pharmacologically active heterocyclic compounds, 4,5,6,7-tetrahydro-1*H*-indazoles and their analogues are of particular interest since they possess anti-inflammatory,[2] antituberculosis,[3] and antiproliferative properties,[4] or are sigma-1 receptor ligands,[5] ERα agonist/ERβ antagonists,[6] cannabinoid-1 receptor inverse agonists,[7] gamma secretase modulators[8] or interleukin-2 inducible T-cell kinase inhibitors[9] (Fig. 1). In parallel, they are also used as ligands in gold, uranium, rhodium, iridium and palladium complexes.[10]

4,5,6,7-Tetrahydro-1*H*-indazoles are generally prepared *via* the reaction of aryl hydrazines with 1,3-diketones [2b,4c,11] or α,β-unsaturated ketones,[12] an approach that is often affected by regioisomer formation. Other important strategies for the construction of the tetrahydro-indazole ring consist of base-mediated addition of hydrazones to nitroolefins[13] metal-catalyzed cyclization of β-bromo-α,β-unsaturated ketones with arylhydrazines,[14] aminohydroxylation of allylic hydrazones,[15] nitrilimine cycloaddition to enamines,[16] or iodine-mediated intramolecular amination.[17] Alternative approaches include modification of a prebuilt bicyclic subunit *via* oxidation of dihydroindazoles,[2a,18] partial reduction of indazoles,[8] Pd(II)- or photoredox-catalyzed C-3 arylation,[19] or *N*-arylation reactions in the presence of Cu(I).[20]

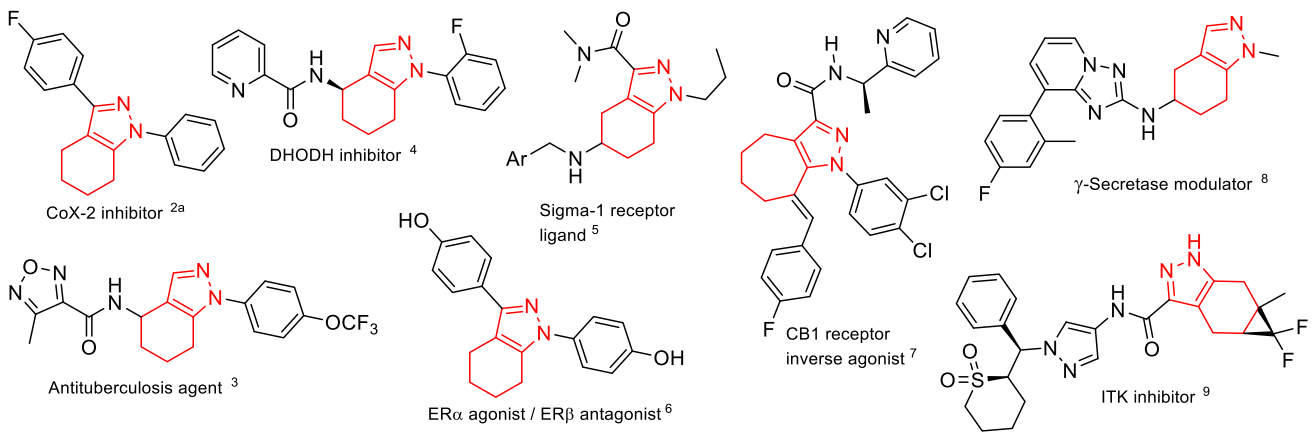
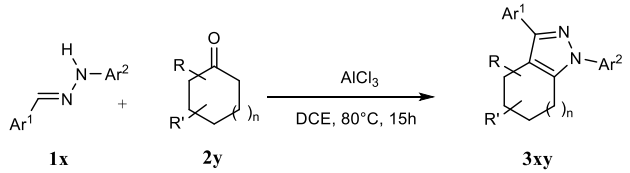


Figure 1. Selected examples of bioactive 4,5,6,7-tetrahydro-1*H*-indazoles and their analogues.

In this context, it is still relevant to develop simple and direct approaches for the synthesis of this class of heterocycles. Inspired by the work of Minunni[21] and Cecchi[22] and co-workers regarding the reaction of aldohydrazones with benzoylacetic esters, we hypothesized that a similar approach could constitute a direct access to 2,3-diaryl-4,5,6,7-tetrahydro-1*H*-indazoles and their analogues starting from cycloalkanones and aryl hydrazones *via* an acid-catalyzed process (Scheme 1).



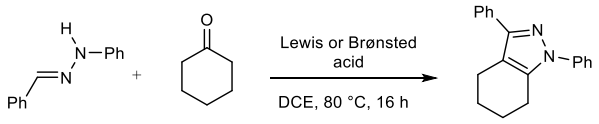
1x **2y** **3xy**

Scheme 1. Synthesis of 2,3-diaryl-4,5,6,7-tetrahydro-1*H*-indazoles.

Results and Discussion

Our investigations were initiated with phenylhydrazone **1a** and cyclohexanone **2a** as model substrates to develop optimal conditions for the formation of **3aa**, as depicted in Table 1. In the presence of $AlCl_3$ in 1,2-dichloroethane, no reaction occurred at room temperature; however, the desired product was obtained in 49% yield after heating for 15 h at 80 °C (Table 1, entry 1). Lower yields were observed with $FeCl_3$ and $Yb(OTf)_3$; the latter had the advantage of requiring only 0.1 equivalents of catalyst (Entries 2-3). The reaction failed with TsOH or $PhB(OH)_2$ (Entries 4-5). A short study of the influence of the relative amounts of **1a**, **2a** and $AlCl_3$ showed that the highest yield was obtained with a 1/1.5/2 ratio (Entries 1, 6-8).

Table 1. Optimization of the reaction conditions.

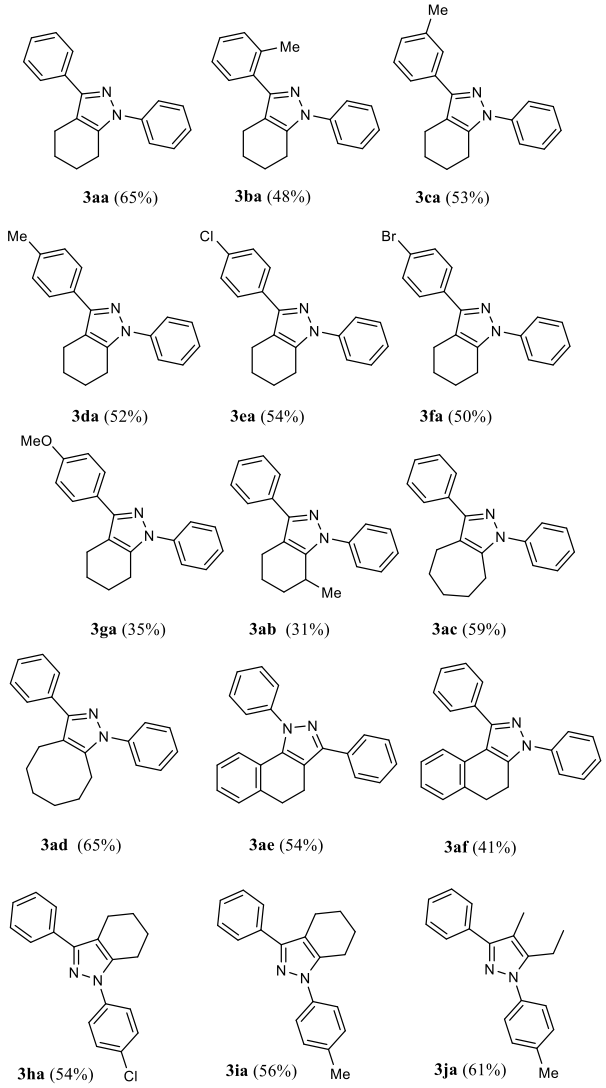


1a **2a** **3aa**

Entry	Acid	**2a** (equiv.)[a]	Acid (equiv.)[a]	Yield **3aa** (%)[b]
1	$AlCl_3$	1	1	49
2	$FeCl_3$	1	1	45
3	$Yb(OTf)_3$	1	0.1	35
4	$PhB(OH)_2$	1	1	0
5	TosOH	1	1	0
6	$AlCl_3$	1.5	2	72
7	$AlCl_3$	1	2	53
8	$AlCl_3$	2	2	45

The scope of the reaction was then evaluated under the optimized conditions. A range of arylhydrazones **1** derived from phenylhydrazine and aromatic aldehydes were first engaged in this process using cyclohexanone **2a** as a model partner (Scheme 1, Table 2). Various electron-donating or withdrawing substituents on the aromatic moiety were tolerated with no significant influence of their nature or location. The lower yield observed for **3ga** was attributed to partial demethylation due to the presence of the Lewis acid. The introduction of a substituent at the C-2 position of the cyclohexanone notably decreased the yield (**3aa** versus **3ab**) and no product was observed with a more hindered substrate such as menthone. In contrast, cycloheptanone and cyclooctanone gave 4,5,6,7-tetrahydro-1*H*-indazole analogues, as α- and β-tetralones, which afforded **3ae** and **3af**, respectively. In the latter case, a single regioisomer was formed. Finally, similar yields were obtained with hydrazones prepared from 4-methyl and chloro-substituted benzaldehydes. It is worth noting that this approach can be extended to a dialkylketone, such as 3-pentanone, while the reaction inexplicably failed with cyclopentanone.

Table 2. Scope of the $AlCl_3$-catalyzed reaction of alkanones with hydrazones.



[a] Reagents and conditions: **1a** (1 mmol), alkanone **2a** (1.5 mmol), $AlCl_3$ (2 mmol), 1,2-dichloroethane (5 mL), 80 °C, 16 h. [b] Yield was calculated using the ^1H NMR of the crude product with 1,3,5-trimethoxybenzene as an internal standard.

Compounds **3** were fully characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy with experimental data in full agreement with the proposed formula (see ESI). Additionally, the structures of compounds **3ae** and **3af** were confirmed by single crystal X-ray analysis (Fig. 2).[23]

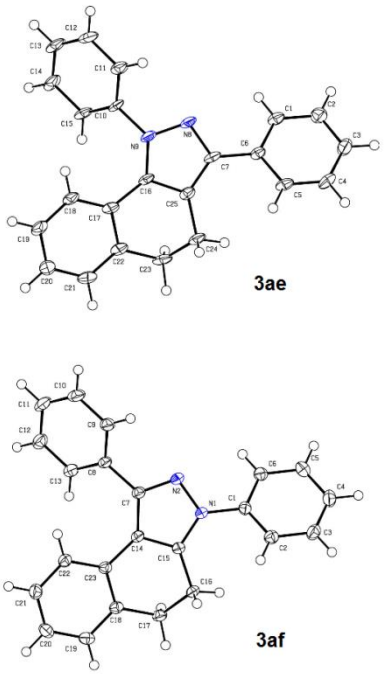
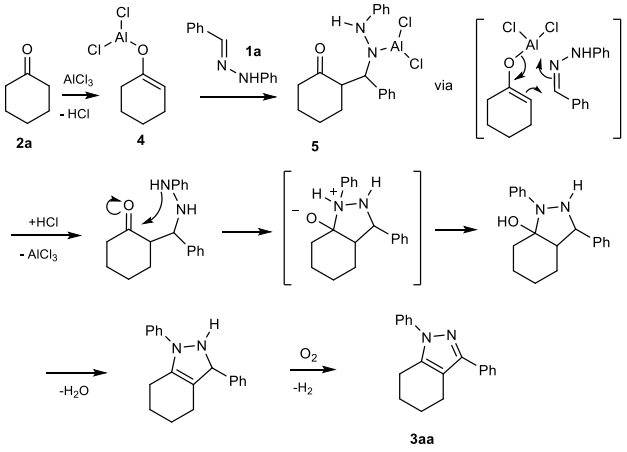


Figure 2. X-Ray crystallographic structures of 4,5,6,7-tetrahydro-1*H*-indazoles **3ae** and **3af.**

A plausible mechanism was proposed using 1-benzylidene-2-phenylhydrazine **1a** and cyclohexanone **2a** as model reactants (Scheme 2). The formation of aluminum enolate **4** is followed by the addition of hydrazone to afford hydrazinoketone **5**.[24] Cyclization provides the corresponding 2,3,4,5,6,7-tetrahydro-1*H*-indazole *via* the elimination of water. The final aromatization step results from oxidation by atmospheric oxygen, either during the reaction or upon workup.[13,25] This proposal is in agreement with the observed regioselectivity in the case of β-tetralone **3af** resulting from the more stable enolate.



Scheme 2. Proposed mechanism for the formation of **3**

Conclusion

A series of 4,5,6,7-tetrahydro-1*H*-indazoles and their analogues was synthesized *via* the reaction of cycloalkanones with hydrazones promoted by the inexpensive aluminum chloride. Although the yields are only moderate, this direct approach offers the major advantage of using commercially available or easily accessible starting materials with a wide range of structural diversity.

Acknowledgments

This work was supported by the University of Rennes 1 and the Centre National de la Recherche Scientifique (CNRS). RL gratefully acknowledges le Ministère de l'Enseignement Supérieur et de la Recherche Scientifique (Algeria) for financial support (Profas program).

Appendix A. Supplementary data

Experimental procedures for the preparation of compounds **3** and the copies of their $^{1}H/^{13}C$ NMR spectra) can be found online at ……..

References and notes

1. (a) E. Vitaku, D.T. Smith, J.T. Njardarson, J. Med. Chem. 57 (2014) 10257–10274. (b) R. D. Taylor, M. MacCoss, A. D. G. Lawson, J. Med. Chem. 57 (2014) 5845-5859.
2. (a) Z. Sui, J. Guan, M.P. Ferro, K. McCoy, M.P. Wachter, W.V. Murray, M. Singer, M. Steber, D.M. Ritchie, D.C. Argentieri, Bioorg. Med. Chem. Lett. 10 (2000) 601–604. (b) H.H. Kim, J.G. Park, T.C. Moon, H.W. Chang, Y. Jahng, Arch. Pharm. Res. 22 (1999) 372–379. (c) M. Nagakura, T. Ota, N. Shimidzu, K. Kawamura, Y. Eto, Y. Wada, J. Med. Chem. 22 (1979) 48–52. (d) V.B. Anderson, M.N. Agnew, R.C. Allen, J.C. Wilker, H.B. Lassman, W.J. Novick Jr., J. Med. Chem. 19 (1976) 318–325.
3. S. Guo, Y. Song, Q. Huang, H. Yuan, B. Wan, Y. Wang, R. He, M.G. Beconi, S.G. Franzblau, A.P. Kozikowski, J. Med. Chem. 53 (2010) 649–659.
4. (a) M.J. Ladds, I.M. van Leeuwen, C.J. Drummond, S. Chu, A.R. Healy, G. Popova, A. Pastor Fernandez, T. Mollick, S. Darekar, S.K. Sedimbi, M. Nekulova, M.C. Sachweh, J. Campbell, M. Higgins, C. Tuck, M. Popa, M.M. Safont, P. Gelebart, Z. Fandalyuk, A.M. Thompson, R. Svensson, A.-L. Gustavsson, L. Johansson, K. Faernegaardh, U. Yngve, A. Saleh, M. Haraldsson, A.C. D'Hollander, M. Franco, Y. Zhao, M. Haakansson, B. Walse, K. Larsson, E.M. Peat, V. Pelechano, J. Lunec, B. Vojtesek, M. Carmena, W.C. Earnshaw, A.R. McCarthy, N.J. Westwood, M. Arsenian-Henriksson, D.P. Lane, R. Bhatia, E. McCormack, S. Lain, Nat. Commun. 9 (2018) 1–14. (b) K.M. Kasiotis, E.N. Tzanetou, D. Stagos, N. Fokialakis, E. Koutsotheodorou, D. Kouretas, S.A. Haroutounian, Z. Naturforsch. 70 (2015) 677–690. (c) E. Tzanetou, S. Liekens, K.M. Kasiotis, N. Fokialakis, S.A. Haroutounian, Arch. Pharm. 345 (2012) 804–811.
5. I. D. Iyamu, W. Lv, N. Malik, R. K. Mishra, G. E. Schiltz, Bioorg. Med. Chem. 27 (2019), 1824-1835.
6. X. Alexia, K. M. Kasiotis, N. Fokialakis, G. Lambrinidis, A. K. Meligova, E. Mikros, S. A. Haroutounian, M. N. Alexis, J. Steroid Biochem. Mol. Biol. 117 (2009) 159-167.
7. J.M. Matthews, J.J. McNally, P.J. Connolly, M. Xia, B. Zhu, S. Black, C. Chen, C. Hou, Y. Liang, Y. Tang, M.J. Macielag, Bioorg. Med. Chem. Lett. 26 (2016) 5346–5349.
8. K. Gerlach, S. Hobson, C. Eickmeier, U. Gross, C. Braun, P. Sieger, M. Garneau, S. Hoerer, N. Heine, Bioorg. Med. Chem. 26 (2018) 3227–3241
9. J.D. Burch, K. Barrett, Y. Chen, J. DeVoss, C. Eigenbrot, R. Goldsmith, M.H.A. Ismaili, K. Lau, Z. Lin, D.F. Ortwine, A.A. Zarrin, P.A. McEwan, J.J. Barker, C. Ellebrandt, D. Kordt, D.B. Stein, X. Wang, Y. Chen, B. Hu, X. Xu, P.-W. Yuen, Y. Zhang, Z. Pei, J. Med. Chem. 58 (2015) 3806–3816.
10. (a) S. Radisavljevic, I. Bratsos, A. Scheurer, J. Korzekwa, R. Masnikosa, A. Tot, N. Gligorijevic, S. Radulovic, A. Rilak Simovic, Dalton Trans. 47 (2018) 13696–13712. (b) J. Korzekwa, A. Scheurer, F.W. Heinemann, K. Meyer, Dalton Trans. 46 (2017) 13811–13823. (c) A. Herrera, A. Briceno, T. Gonzalez, A. Linden, F.W. Heinemann, G. Agrifoglio, J. Pastran, R. Dorta, Tetrahedron: Asymmetry. 27 (2016) 759–767. (d) I. Ilaldinov, D. Fatkulina, S. Bucharov, R. Jackstell, A. Spannenberg, M. Beller, R. Kadyrov, Tetrahedron: Asymmetry. 22 (2011) 1936–1941. (e) I.Z. Ilaldinov, D.A. Fatkulina, R. Kadyrov, Russ. J. Org. Chem. 47 (2011) 952–953. (f) M.J. Spallek, S. Stockinger, R. Goddard, O. Trapp, Adv. Synth. Catal. 354 (2012) 1466–1480.
11. (a) S.S. Rahmatzadeh, B. Karami, S. Khodabakhshi, J. Chin. Chem. Soc. 62 (2015) 17–20. (b) M. Curini, O. Rosati, V. Campagna, F. Montanari,

G. Cravotto, M. Boccalini, Synlett. (2005) 2927–2930. (c) D.V. Sevenard, O.G. Khomutov, M.I. Kodess, K.I. Pashkevich, I. Loop, E. Lork, G.-V. Roschenthaler, Can. J. Chem. 79 (2001) 183–194. (e) C. Ainsworth, Org. Synth. 39 (1959), 27-30.
12. (a) M.M. Gar, A.V. Eremeev, K.Yu. Suponitsky, S.V. Popkov, Russ. Chem. Bull. 63 (2014) 1142–1147. (b) A. Nakhai, J. Bergman, Tetrahedron. 65 (2009) 2298–2306. (c) G.A. Nishiguchi, A.L. Rodriguez, J.A. Katzenellenbogen, Bioorg. Med. Chem. Lett. 12 (2002) 947–950.
13. (a) X. Deng, N.S. Mani, J. Org. Chem. 73 (2008) 2412–2415. (b) X. Deng, N.S. Mani, Org. Lett. 10 (2008) 1307–1310.
14. (a) H.K. Lee, C.S. Cho, Synth. Commun. 43 (2013) 915–921. (b) H.K. Lee, C.S. Cho, Appl. Organomet. Chem. 26 (2012) 570–575.
15. Y.-C. Chen, M.-K. Zhu, T.-P. Loh, Org. Lett. 17 (2015) 2712–2715.
16. K. Tshiamala, S. Kitane, J. Vebrel, B. Laude, Bull. Soc. Chim. Belg. 95 (1986) 1083–1098. (b) S. Kitane, T. Kabula, J. Vebrel, B. Laude, Tetrahedron Lett. 22 (1981) 1217–1218. (c) M.E. Kuehne, J. Weaver, P. Franz, J. Org. Chem. 29 (1964) 1582–1586.
17. W. Wei, Z. Wang, X. Yang, W. Yu, J. Chang, Adv. Synth. Catal. 359 (2017) 3378–3387.
18. G. A. Nishiguchi, A. L. Rodriguez, J. A. Katzenellenbogen, Bioorg. Med. Chem. Lett. 12 (2002) 947–950.
19. N.A. Romero, K.A. Margrey, N.E. Tay, D.A. Nicewicz, Science 349 (2015) 1326–1330.
20. S.E. Ward, M. Harries, L. Aldegheri, N.E. Austin, S. Ballantine, E. Ballini, D.M. Bradley, B.D. Bax, B.P. Clarke, A.J. Harris, S.A. Harrison, R.A. Melarange, C. Mookherjee, J. Mosley, G. Dal Negro, B. Oliosi, K.J. Smith, K.M. Thewlis, P.M. Woollard, S.P. Yusaf, J. Med. Chem. 54 (2011) 78–94.
21. (a) G. Minunni, G. Lazzarini, S. D'Urso, Gazz. Chim. Ital. 55 (1925) 502-539. (b) G. Minunni, S. D'Urso, T.G. Troia, A. Carnevale, G. Arezzi, C. Vizzini, Gazz. Chim. Ital. 58 (1928) 691-712.
22. L. Cecchi, F. Melani, G. Palazzino, G. Filacchioni, G. C. Porretta, Farmaco 39 (1984) 888-900. (b) L. Cecchi, F. Melani, G. Palazzino, G. Filacchioni, Farmaco 39 (1984) 953-962.
23. CCDC 1922242 and 1922243 contains the crystallographic data for compounds **3ae** and **3af**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac. uk/data_request/cif.
24. For a similar mechanistic hypothesis in the case of β-ketoesters, see: K. S. Hariprasad, K. V. Prasada, B. C. Raju, RSC Adv. 6 (2016) 108654-108661.
25. A. Citterio, M. Ramperti, E. Vismara, J. Heterocyclic Chern. 18, (1981) 763-765

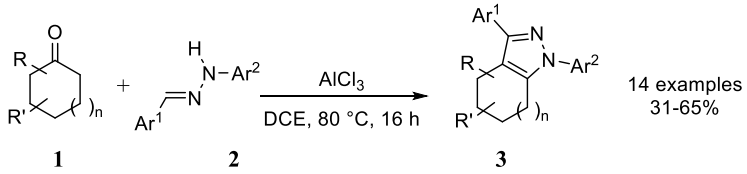
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

$AlCl_3$-promoted reaction of cycloalkanones with arylhydrazones: a convenient direct synthesis of 4,5,6,7-tetrahydro-1*H*-indazoles and their analogues

Leave this area blank for abstract info.

Rima Laroum, Fabienne Berrée, Thierry Roisnel, Vincent Dorcet, Bertrand Carboni and Abdelmadjid Debache



1 **2** **3**